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.

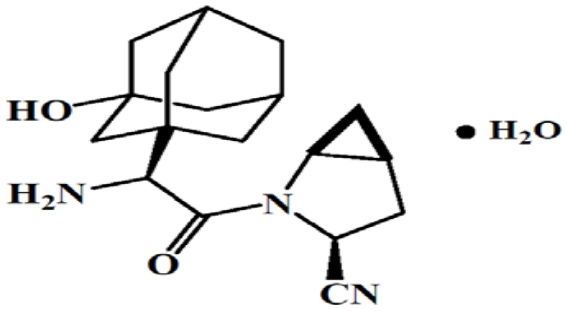
Establishments Evaluation Report (EER) Status: Acceptable

Consults:		
	EA –	Acceptable
	Statistics –	N/A
	Methods Validation –	Not recommended
	Biopharm–	Acceptable
	Microbiology –	Acceptable
	Pharm Toxicology –	N/A

Original Submission: December 30, 2009

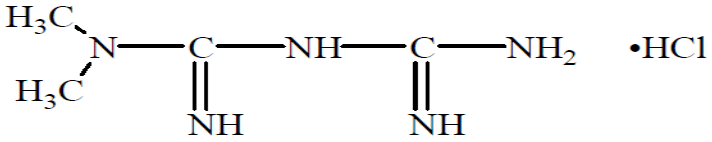
Re-submissions: N/A
Post-Approval CMC Agreements: None at this time.

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 (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: (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3 hydroxytricyclo [3.3.1.1$_{3,7}$]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate.
Molecular Weight: 333.43 (315.41 anhydrous) g/mol
Chemical Formula: $C_{18}H_{25}N_3O_2 \bullet H_2O$

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: $C_4H_{12}ClN_5$

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)

(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

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