CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-350

CHEMISTRY REVIEW(S)

Onglyza
(saxagliptin) tablets
NDA 22-350

Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls

Applicant: Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000

Indication: Saxagliptin is an orally active reversible dipeptidyl peptidase-IV (DPP-IV) inhibitor proposed for the treatment of type 2 diabetes.

Presentation: Onglyza (saxagliptin) tablets are film coated tablets containing 2.5 mg or 5 mg, ——— . Both strengths will be available in 30 count (95 ml) and 500 count (200 ml) white opaque ——————— bottles with desiccant. The 5 mg tablets will be additionally available in aluminum/ aluminum blisters. b(4)

EER Status: Acceptable, 26-FEB-09

Consults: Methods Validation – Revalidation by Agency was not requested
EA – Categorical exclusion granted under 21 CFR §25.31(c)

Original Submission: 30-JUN-08

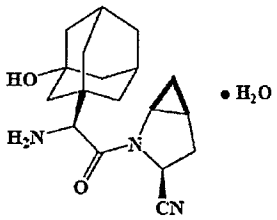
Post-Approval Agreements: None

Background for CMC Section of Application

The CMC portion of this NDA was submitted as part of the ONDQA CMC Pilot Program to explore science and risk based approaches to assuring product quality. A Comprehensive Quality Overall Summary was provided in Module 2 and an expanded pharmaceutical development section was submitted in Module 3, Section P.2. The applicant applied several Quality by Design (QbD) principles in the pharmaceutical development and manufacturing approaches.

Drug Substance:

The drug substance for Onglyza is saxagliptin in ——— monohydrate form. The formal chemical name is (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo [3.3.1.13,7]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate. The molecular structure is provided as follows: b(4)



The molecular formula is: $C_{18}H_{25}N_3O_2 \cdot H_2O$ with a calculated molecular weight of 333.43. Saxagliptin has been chemically and structurally characterized using:

b(4)

Saxagliptin drug substance will be manufactured at the BMS facility in Swords, Ireland using a commercial process from starting materials.

The NDA contained expanded information for the synthesis and process development of saxagliptin, using Quality by Design approaches. The approach included identification the critical quality attributes of the drug substance, identification of critical and "key" process parameters, and the implementation of process controls for producing drug substance of the desired quality. Several statistically designed experiments (DoEs) were utilized in the drug substance process development. The application included a design space for drug substance, allowing for increased flexibility for manufacturing. Drug substance quality is assured through manufacturing process controls combined with conventional end-product testing, including appearance, color, identification, and assay and impurities/degradants by High Performance Liquid Chromatography (HPLC).

b(4)

Based on the 32-month primary stability data for saxagliptin drug substance from Process C and the 12-month primary stability data for saxagliptin drug substance from Process D stored at 5°C (±3°C), a period for the drug substance is granted with the following label statements:

b(4)

b(4)

Conclusion: Drug substance is satisfactory

Drug product

Onglyza (saxagliptin) tablets is an immediate release tablet, with the following description:

- 2.5 mg tablet, containing 2.79 mg saxagliptin hydrochloride (anhydrous): round, biconvex yellow tablet printed with "2.5" on one side and "4214" on the other side, with a tablet weight of 236mg
- 5 mg tablet, containing 5.58 mg saxagliptin hydrochloride (anhydrous): round, biconvex pink tablet printed with "5' on one side and "4215" on the other side, with a tablet weight of 239 mg

Based on tablet dimension measurements, saxagliptin film coated tablets, 2.5 mg, and saxagliptin film coated tablets, 5 mg, are expected to have an average thickness of 4.2 mm and average diameter of 8.2 mm. b(4)

The saxagliptin film coated tablets contain the following excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium state, yellow (2.5 mg), pink (5 mg tablet), b(4) No novel excipients are used in the manufacture of saxagliptin film coated tablets. The drug loading for both strengths is relatively low at less than

The drug product is manufactured by a coating process in a

b(4)

b(4)

The enhanced pharmaceutical development provided in the application included use of risk assessment and DoEs to evaluate the criticality of process parameters and support development of the control strategy and design space. In addition, experimental data was leveraged to develop a mechanistic model of the coating operation used to predict process performance. Drug product quality is assured through manufacturing process controls combined with conventional end-product

testing, including identification, dissolution, water content, uniformity of dosage units, and assay and impurities/degradants by HPLC. b(4)

Saxagliptin film coated tablets will be packaged and marketed as 30 and 90 count in 95 mL and 500 count in 200 mL white, opaque, [redacted] bottles, with a two piece child resistant closure having an aluminum foil induction seal. Each bottle contains a cotton coil and one 2g pouch containing silica gel (desiccant) and activated carbon. 5 mg saxagliptin film coated tablets will also be packaged and marketed in aluminum/aluminum (alu/alu) blisters. b(4)

Based on provided stability data, the 2.5 mg strength saxagliptin tablets are granted a 36 month stability period for 30 and 90 count bottles containing desiccant. The 5 mg strength saxagliptin tablets are granted a 36 month stability period for 30, 90 and 500 count bottles containing desiccant, and 36 month stability period when stored in aluminum/aluminum blisters. Both the 2.5 mg and 5 mg strengths contain the following labeling statement: "Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Conclusion: Drug product is satisfactory.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

The analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the biopharmaceutical industry; revalidation by Agency laboratories will not be requested.

The application includes design space for both drug product and drug substance.

A comparability protocol for extensive changes that could be made with reduced reporting requirements was originally submitted in the application but was later withdrawn. The applicant expressed interest in submitting a revised version of the comparability protocol as a supplement at a later date following additional discussion and clarification from the Agency.

Overall Conclusion: From a CMC perspective, the application is recommended for **approval.**

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Acting Director, DPA I/ONDQA

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