CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200678Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	October 28, 2010
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	200678
Applicant	Bristol-Myers Squibb
Date of Submission	December 29, 2009
PDUFA Goal Date	October 29, 2010
Proprietary Name / Established (USAN) names	Kombiglyze XR (saxagliptin/metformin XR fixed-dose combination product)
Dosage forms / Strength	2.5/1000 mg, 5/500 mg, 5/1000 mg
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate
Recommended:	*Approval*

Cross Discipline Team Leader Review Template

1. Introduction

This memorandum reviews a new drug application (NDA) for the saxagliptin-metformin extended-release (metformin XR) fixed dose-combination (FDC) tablet. This NDA was submitted by Bristol-Myers Squibb (BMS), which has an alliance with AstraZeneca for commercializing saxagliptin-related products. This is a 505(b)(1) application because BMS has the right of reference for both the saxagliptin (NDA 22350) and metformin XR (Glucophage XR NDA 21202) components of the FDC product.

The sponsor has conducted a typical development program for the FDC. Specifically, there is a series of clinical pharmacology studies that attempt to bridge the FDC to co-administration of the individual components. In addition, the sponsor is relying on efficacy data from two phase 3 trials conducted as part of the saxagliptin NDA (a saxagliptin add-on to metformin trial in patients with inadequate glycemic control on metformin alone and a saxagliptin plus metformin co-administration trial in patients naïve to anti-diabetic medication). The sponsor is relying on safety data from these two trials as well as safety data from recently completed and ongoing trials that involve co-administration of saxagliptin and metformin. Note that the FDC product contains metformin XR and is proposed for once daily dosing with the evening meal. In contrast, most of the supporting clinical data are derived from once daily saxagliptin co-administered with twice-daily metformin immediate-release (metformin IR). Other components of the development program include a chemistry/manufacturing/controls package to support the FDC formulation as well as a standard bridging non-clinical toxicology program. This memorandum will focus on the adequacy of all these findings to support approvability of the FDC product.

2. Background

Saxagliptin is a dipeptidyl-peptidase 4 (DPP-4) inhibitor approved in July 2009 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The recommended dose of saxagliptin is 2.5 mg or 5 mg once daily regardless of meals. The maximum recommended dose is 2.5 mg once daily for patients with moderate or severe renal impairment and for patients on strong CYP3A4/5 inhibitors. Adverse events of interest for saxagliptin and/or other DPP-4 inhibitors include pancreatitis, hypersensitivity reactions (e.g., angioedema, anaphylaxis), skin lesions (some DPP-4 inhibitors cause necrotic skin lesions in monkeys – saxagliptin does so but with large safety margins), infections (chemokines are substrates of DPP-4 and DPP-4 is also expressed on a subset of T-cells and natural killer cells; saxagliptin can cause mild lymphopenia at approved doses), and liver safety (at least one DPP-4 inhibitor – vildagliptin - has a signal for hepatotoxicity in the premarketing program).

Metformin, a biguanide, is recommended by the American Diabetes Association as first-line therapy for the treatment of type 2 diabetes. Metformin is generally well tolerated but can cause gastrointestinal symptoms such as nausea and diarrhea. These side effects are minimized by taking metformin with meals and by slowly uptitrating the dose. Gastrointestinal side effects may also be reduced by using metformin XR, which has a 20% lower Cmax but comparable overall exposure (area under the time-concentration curve or AUC) to metformin IR. Metformin XR is usually dosed once daily with the evening meal whereas metformin IR is usually dosed twice daily with breakfast and dinner. Glucophage XR, which is the metformin XR produced by BMS, is available as 500 mg and 750 mg tablets. The usual starting dose is 500 mg once daily with the evening meal with weekly uptitration by 500 mg to a maximum of 2000 mg once daily or a maximum of 1000 mg twice daily. The most serious adverse reaction of metformin therapy is lactic acidosis, which is rare, but is the basis for a contraindication in patients with renal impairment (metformin is substantially renally cleared).

The sponsor has proposed 3 dosage strengths for the FDC:

- Saxagliptin 5 mg / metformin XR 500 mg
- Saxagliptin 5 mg / metformin XR 1000 mg
- Saxagliptin 2.5 mg / metformin XR 1000 mg

(b) (4)

3. CMC

The Chemistry reviewers recommend approval without the need for postmarketing commitments. Please see Dr. Elsbeth Chikhale's review for details.

The drug product consists of a (b) (4) The commercial drug product will be manufactured at the BMS Mount Vernon facility. A Quality by Design approach was used for (b) (4)

The saxagliptin drug substance and manufacturing site is identical to that used for the saxagliptin NDA. The metformin drug substance information is provided in Drug Master Files (b) (4) and found by the CMC reviewers to be acceptable for use in this FDC NDA. The metformin XR (b) (4) is manufactured as per the current commercial process for Glucophage XR 500 mg. There is no currently marketed Glucophage XR 1000 mg tablet but there is a marketed Glucophage XR 750 mg tablet. The metformin XR 1000 mg (b) (4) for the FDC product is manufactured (b) (4) .

CMC found all excipients to be acceptable.

Based on the stability data, Dr. Chikhale recommends a shelf-life of 15 months for the blisters and 21 months for the bottles when stored at 20-25 degrees Celsius, (b) (4) .

Dr. Chikhale agrees with the sponsor's claim that the application qualifies for a categorical exclusion from an environmental assessment report.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology reviewers recommend approval of the NDA. Please see the reviews by Drs. Lauren Murphree Mihalcik and Todd Bourcier reviews for details.

Most of the nonclinical pharmacology and toxicology data for the FDC are derived from data established for saxagliptin and metformin XR as individual components. The sponsor conducted a bridging 3-month general toxicology study in dogs assessing saxagliptin and metformin separately and in combination. The doses used in this study achieved saxagliptin, BMS-510849 (the major saxagliptin metabolite) and metformin exposures (AUC) that were 70

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