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APPLICATION NUMBER:

22-350

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 28, 2009
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Cross-Discipline Team Leader Review
NDA #	22-350
Applicant	Bristol-Myers Squibb
Date of Submission	June 30, 2008
PDUFA Goal Date	July 30, 2009
Proprietary Name / Established (USAN) names	Onglyza (saxagliptin)
Dosage forms / Strength	2.5 mg and 5 mg tablets
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommended:	*Approval, pending agreement on labeling*

Cross Discipline Team Leader Review

1. Introduction

Incretin hormones, such as glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP), are released from the gastrointestinal tract during meals and stimulate insulin release from the pancreatic beta-cell in a glucose-dependent manner. GLP-1 and GIP have short half-lives (<2 minutes) due to rapid degradation by dipeptidyl peptidase (DPP)-4. Saxagliptin (proposed tradename Onglyza) is an oral DPP-4 inhibitor that has been developed by Bristol-Myers Squibb as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. The original user fee goal date for this application was April 30, 2009. An unexpected teratogenicity finding in a rat embryofetal development study designed to support the saxagliptin/metformin fixed-dose combination tablet (see below) prompted submission of the non-clinical study report to FDA within 3 months of the user fee goal date. The Division classified this submission as a major amendment and extended the user fee goal date by 3 months to July 30, 2009.

This memorandum discusses the saxagliptin new drug application (NDA) with a focus on key findings from the various review disciplines and the phase 2/3 development program.

2. Background

DPP-4 inhibitors tend to have modest efficacy but these medications appear to be generally well-tolerated with neutral effects on body weight and a low risk for hypoglycemia. Currently, Januvia (sitagliptin phosphate) is the only FDA-approved DPP-4 inhibitor. Labeled safety concerns with Januvia include postmarketing reports of hypersensitivity reactions, including Stevens-Johnson Syndrome, and minor increases in serum creatinine in patients with moderate or severe renal impairment. Postmarketing reports of pancreatitis in association with Byetta and Januvia are under FDA review. Other toxicities associated with at least one DPP-4 inhibitor include necrotic skin lesions in monkeys, sometimes near clinical exposures (e.g. vildagliptin, dutogliptin) and possible hepatotoxicity (vildagliptin).

In July 2008, the Division convened a public, 2-day advisory committee meeting to discuss cardiovascular assessment for drugs and biologics developed for the treatment of type 2 diabetes. After considering the recommendations of the advisory committee panel and other data, the Division published a December 2008 Guidance for Industry entitled *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. This guidance document requests that sponsors of new pharmacologic therapies for type 2 diabetes show that these treatments do not result in an unacceptable increase in cardiovascular risk. Of note, the saxagliptin NDA and two other NDAs for the treatment of type 2 diabetes were submitted to FDA prior to the July 2008 advisory committee meeting and prior to the December 2008 guidance. Nonetheless, FDA has requested that the sponsors for these three products provide adequate evidence of cardiovascular safety in accordance with the

guidance to support approvability. Therefore, cardiovascular safety was a major focus of the clinical and statistical reviews for saxagliptin.

3. CMC

The chemistry/manufacturing/controls (CMC) portion of the NDA was submitted as part of the Office of New Drug Quality Assessment (ONDQA) Quality-by-Design Pilot Program to explore science and risk-based approaches to assuring product quality. The drug substance for Onglyza is saxagliptin ( )available in dosage strengths of 2.5 mg and 5 mg. The saxagliptin molecule contains chiral centers but there is no chiral conversion *in vivo*. The drug product does not contain novel excipients and is manufactured using a

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(Based on stability data, the CMC reviewers are granting the two dosage strength presentations a 36-month stability period with labeling that states "Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]."

CMC has determined that the application qualifies for a categorical exclusion from an environmental assessment report because the expected introduction concentration of the active moiety at the point of entry into the aquatic environment is less than 1 part per billion.

The Office of Compliance issued an acceptable recommendation on the manufacturing facilities of the drug product.

CMC deficiencies identified during the review have been adequately resolved. All Drug Master Files are acceptable or the pertinent information has been adequately provided. The CMC reviewers have determined that the drug product is acceptable and recommend approval of the NDA. Please see reviews by Drs. Sharmista Chatterjee, John Hill, Prafull Shiromani, and Christine Moore for further details.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewers have concluded that there are reasonable safety margins between animal toxicities and clinical exposures with the proposed maximum daily dose of 5 mg, and recommend approval pending agreement on labeling. As explained below, the reviewers are also recommending two required non-clinical postmarketing studies to further explore an unexpected teratogenicity finding in a rat embryofetal development study that co-administered saxagliptin and metformin. The sponsor has already initiated these studies but the pharmacology/toxicology reviewers have determined that the protocols are inadequate (e.g., too high a dose of metformin is being tested). The Division is in the process of communicating the protocol inadequacies to the sponsor and has informed the sponsor that new studies will be needed. Please see reviews by Drs. Fred Alavi, Todd Bourcier, and Paul Brown for further details.

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In this embryofetal study, two fetuses from one litter of rats that had been exposed to co-administered saxagliptin (at doses 114-fold above clinical exposures) and metformin (at doses 4-fold above clinical exposures with the 2,000 mg daily dose) developed malformations (one case of craniorachischisis, a rare neural tube defect involving incomplete closure of the skull and spinal cord, and one case of cleft palate). The sponsor attributed this finding to metformin alone (via potential alterations to vitamin B_{12} and folate) but the embryofetal study did not have a metformin alone treatment arm to support this assertion. Furthermore, Dr. Bourcier notes that this study had two combination dose groups that had equal exposures to metformin, yet teratogenicity occurred only in the group with the higher dose of saxagliptin. In addition, Dr. Bouricer notes that the original embryofetal studies conducted for metformin did not report craniorachischisis.

Based on this finding, the pharmacology/toxicology reviewers are recommending that the Division require two non-clinical postmarketing studies under the FDA Amendments Act (FDAAA), one in rats and another in rabbits, that further explores this signal using study designs that include separate treatments arms for metformin alone, saxagliptin alone, and the combination of saxagliptin+metformin.

Results from this study have relevance to the saxagliptin NDA because saxagliptin will be frequently co-administered with metformin, if approved. Therefore, the pharmacology/ toxicology reviewers are recommending a statement in the label describing this finding and will reassess the labeling once results from these two more definitive studies are available. Of note, the reviewers (with input from the Associate Director and Director of Pharmacology/Toxicology and the Reproductive Toxicology Subcommittee at FDA) are recommending Pregnancy Category B for saxagliptin, because saxagliptin alone was not teratogenic in rats and rabbits at very high exposure multiples.

Saxagliptin is metabolized by CYP3A4 to active metabolite BMS-510849 in all test species. This active metabolite is two-fold less potent than saxagliptin but more selective at inhibiting DPP-4 versus off-target DPP-8 and DPP-9. In patients with diabetes, exposures to this metabolite are 4-7-fold higher than exposures to saxagliptin whereas in animals, exposures to this metabolite are no greater than exposures to saxagliptin. Nonetheless, Dr. Alavi has determined that this metabolite and several minor metabolites formed in humans have been adequately assessed for toxicity in the non-clinical studies.

Brain lesions occurred in male rats administered very high doses (>350-fold safety margin) of saxagliptin. Per Dr. Bourcier, the sponsor has convincingly demonstrated that these lesions are caused by release of cyanide from saxagliptin via CYP2C11, an androgen-regulated metabolizing enzyme that is abundant in male rats but not present in humans. Per Dr. Alavi, saxagliptin administration to female rats and to both genders of other species used in non-clinical studies did not lead to measurable quantities of cyanide. In addition, whole blood cyanide concentrations were below the limit of quantification in all healthy volunteers receiving up to 40 mg of saxagliptin daily for 14 consecutive days in Study 181031. Dr. Alavi

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