CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-350

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	July 27, 2009
From	Mary H. Parks, M.D.
Subject	Division Director Summary Review
NDA/BLA # Supplement #	22-350
Applicant Name	Bristol Myer Squibb
Date of Submission	June 30, 2008
PDUFA Goal Date	July 31, 2009 (including 3-month extension for major amendment)
Proprietary Name / Established (USAN) Name	Onglyza® (saxagliptin)
Dosage Forms / Strength	2.5 and 5.0 tablets
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Naomi Lowy, M.D.
Statistical Review	Roswitha Kelly, M.S. (CMC Stats Review) Karl Lin, Ph.D. (Carci Stats Review) Joy Mele, M.S. Todd Sahlroot, Ph.D. Atair Rahman, Ph.D. (carci Stats Review) Thomas Permutt, Ph.D. Yi Tsong, Ph.D. (CMC Stats Review)
Pharmacology Toxicology Review	Fred Alavi, Ph.D. Todd Bourcier, Ph.D. Paul Brown, Ph.D.
CMC Review/OBP Review	Ali Al-Hakim, Ph.D. Shamista Chatterjee, Ph.D. Blair Fraser, Ph.D. John Hill, Ph.D. Christine Moore, Ph.D. Prafull Shiromani, Ph.D. Su Tran, Ph.D.
Microbiology Review	NA
Clinical Pharmacology Review	Sally Choe, Ph.D. Justin C. Earp, Ph.D. Wei Qiu, Ph.D.

	Christoffer Tornoe, Ph.D. Jaya Vaidyanathan, Ph.D. Immo Zdrojewski, Ph.D.
DDMAC	Robert Dean, M.B.A Kendra Jones, B.S. Sam Skariah, Pharm.D. Sangeeta Vaswani, Pharm D.
DSI	Susan Leibenhaut, M.D. Constance Lewin, M.D., M.P.H.
CDTL Review	Hylton Joffe, M.D., M.M.Sc.
OSE/DMETS	Kristina Arnwine, Pharm.D. Anne Crandall, Pharm.D. Melina Griffis, R.Ph. Carol Holquist, R.Ph. Denise Toyer, Pharm. D.
OSE/DSRCS	Jessica Diaz, RN, BSN Jodi Duckhorn, M.A.
Other	Lina Aljuburi, Pharm. D. Laurie Burke, (SEALD) Jeanne Delasko, RN, MS (SEALD) Abby Jacobs, Ph.D. (Executive CAC) David Jacobson-Kram, Ph.D. (Executive CAC) Barry Rosloff, Ph.D. (Executive CAC)

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Division Director Review

1. Introduction

Saxagliptin is a dipeptidyl peptidase-4 enzyme inhibitor (DPP4-inhibitor) developed for the management of hyperglycemia in patients with type 2 diabetes mellitus (T2DM). This is a relatively new class of anti-diabetic therapy whose mechanism of action targets the impaired release and availability of the incretin hormone, glucagon-like peptide-1 (GLP-1) in patients with type 2 diabetes. GLP-1 and another incretin hormone, glucose-dependent insulinotropic polypeptide (GIP), are released from the gastrointestinal tract in response to meals to further stimulate insulin release. Because GLP-1 is rapidly degraded by the serine protease, dipeptidyl peptidase 4, an inhibitor of this enzyme will prolong the half-life of this incretin hormone allowing for a more sustained effect on glucose control.

Unlike other anti-diabetic therapies, which control hyperglycemia through stimulation of insulin release from the pancreas (e.g. sulfonylureas or glinides), incretin-based therapies control hyperglycemia through a glucose-dependent manner thereby mitigating the risk of hypoglycemia. GLP-1 receptor agonists are another class of incretin-based therapies. These agents are manufactured to avoid susceptibility to enzyme degradation while maintaining sufficient cross-reactivity with the GLP-1 receptor to impart similar effects on glucose control as the native hormone.

Currently, Januvia (sitagliptin) is the only marketed DPP4-inhibitor in the United States.

b(4)

2. Background

Over the past two to three years, concerns regarding the cardiovascular safety profile of certain anti-diabetics have resulted in much debate within the scientific and regulatory community on the adequacy of the development programs for anti-diabetic therapies to ensure that these drugs do not contribute to excess cardiovascular mortality and morbidity in a patient population that is already at 2- to 4-fold risk of dying from heart disease.

On July 1 and 2, 2008, the FDA convened a public advisory committee meeting to discuss the role of CV assessment in the pre- and postmarket settings. The pivotal question raised to the panel members was:

It should be assumed that an anti-diabetic therapy with a concerning CV safety signal during Phase 2/3 development will be required to conduct a long-term cardiovascular trial. For those drugs or biologics without such a signal, should there be a requirement to conduct a long-term cardiovascular trial or to provide other equivalent evidence to rule out an unacceptable cardiovascular risk. (vote yes/no requested).

The outcome was 14 "yes" and 2 "no" votes.

Following this advisory committee meeting, the FDA issued a Final Guidance to Industry in December 2008 titled, *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.* With its release, the FDA also publicly announced that the recommendations in this guidance will be applied to all ongoing diabetes development programs and marketing applications pending before the agency. In order to gain approval, applicants must compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8.

At the time of its issuance, the FDA had three NDAs under review: ( ) saxagliptin (Onglyza), and liraglutide (Victoza). Saxagliptin and liraglutide were each presented at a public advisory committee meeting on April 1 and 2, 2009, respectively. b(4)

( ) Because none of these NDAs were conducted with knowledge of these new recommendations, the review division applied a uniform approach to assessing risk for these NDAs. This approach is clearly described by the clinical and statistical reviewers in their finalized review of this NDA and also in the advisory committee briefing materials. This memo will summarize how this applicant has met the new regulatory requirements for establishing sufficient cardiovascular safety for approval under Section 8.0.

The advisory committee meeting for saxagliptin focused only on the cardiovascular risk assessment. An in-depth review of efficacy was not presented by FDA at that time; however, the applicant did provide data supporting a conclusion that therapy with saxagliptin results in significant reductions in HbA1c, as both monotherapy and in combination with several other anti-diabetic agents. The finalized statistical review by Ms. Mele provides greater detail of the efficacy findings, including variables which may have influenced efficacy and flaws in the study designs which must be considered in the interpretation of efficacy. Section 7.0 of my memo will present the highlights of her findings.

In addition to cardiovascular safety, signals identified in the nonclinical program that have also directed the clinical safety review are summarized in this memo. Some of these safety signals appear to be a class effect observed in several clinical development programs (e.g., hypersensitivity reactions) or in the nonclinical toxicology programs (e.g., cutaneous lesions). Spontaneous postmarketing adverse event reports of pancreatitis for other incretin-based therapies have also necessitated a careful evaluation in this NDA.

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