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APPLICATION NUMBER:

22-350

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	22,350
Submission Code	N000
Letter Date	June 30, 2009
Stamp Date	June 30, 2009
PDUFA Goal Date	July 30, 2009
Reviewer Name	Naomi Lowy, MD
Review Completion Date	May 14, 2009
Established Name	Saxagliptin
(Proposed) Trade Name	Onglyza
Therapeutic Class	Dipeptidyl-peptidase IV inhibitor
Applicant	Bristol-Myers Squibb Company
Priority Designation	S
Formulation	Oral tablet
Dosing Regimen	5 mg daily 2.5 mg daily (moderate, severe, or end-stage renal impairment)
Indication	Treatment of type 2 diabetes
Intended Population	Adults

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1 Recommendations/Risk Benefit Assessment

Saxagliptin (ONGLYZA™) is an orally-active, reversible dipeptidyl peptidase 4 (DPP4) inhibitor that has been developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. The Sponsor is seeking three indications: as monotherapy, in combination therapy with metformin, a sulfonyurea (SU), or a thiazolidinedione (TZD), when the single agent alone does not provide adequate glycemic control, and as initial combination with metformin, when treatment with dual saxagliptin and metformin is appropriate. The proposed usual clinical dose is 5 mg once daily, with a recommended dose of 2.5 mg once daily in subjects with moderate or severe renal impairment, and end-stage renal disease requiring hemodialysis.

1.1 Recommendation on Regulatory Action

According to my review of the clinical data, I recommend approval of saxagliptin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (although the Sponsor requested individual indications for various treatment settings, the Division has streamlined the indications for anti-diabetic drugs). The Sponsor has demonstrated modest efficacy along with an acceptable safety profile. However, the following recommendations also apply:

- A dose reduction to 2.5 mg when saxagliptin is used with CYP3A4/5 inhibitors, such as ketoconazole.
- As of the completion of this Review, recommendations regarding the use of saxagliptin in women of childbearing potential have not been finalized. This issue arose out of a pre-clinical study done to support the fixed dose combination of saxagliptin and metformin in which certain fetal abnormalities were seen (discussed in Section 4.3). Final decisions regarding this issue will be addressed in a pharmacology/toxicology memorandum and the Cross Discipline Team Leader (CDTL) memorandum.

1.2 Risk Benefit Assessment

Although there are a number of available medical therapies available for type 2 diabetes mellitus (Section 2.2), the progressive nature of the disease demands new therapies that can safely and effectively be used either alone or added on to the current armamentarium of drugs. Given that the Sponsor has demonstrated efficacy in monotherapy and combination therapy settings, saxagliptin can play a useful role in type 2 diabetes treatment.

The Sponsor conducted six Phase 3 studies (referred to as "Core Phase 3 studies" in this Review) that were randomized, double-blind, and placebo-controlled (two monotherapy studies, three add-on combination studies to metformin, sulfonylurea, and a thiazolidinedione, and one initial combination with metformin study). In the Phase 3 program, the Sponsor chose to study 3 doses

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