CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200678Orig1s000

PHARMACOLOGY REVIEW(S)

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Memorandum

Pharmacology/Toxicology
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Products

NDA SECONDARY REVIEW MEMO

Date:	30 September 2010
NDA #	200678
Sponsor:	Bristol Myers Squibb
Drug:	Saxagliptin + metformin XR FDC
Primary Reviewer:	Lauren Murphree Mihalcik, Ph.D.
Secondary Reviewer:	Todd Bourcier, Ph.D.

BMS is seeking marketing approval for a fixed-dose combination product of saxagliptin and metformin extended release as a treatment for type 2 diabetes. Both pharmaceutical components are currently approved for the chronic treatment of type 2 diabetes. Saxagliptin is a dipeptidylpeptidase-4 inhibitor approved in 2009 (Onglyza, NDA 22350), and metformin XR is an extended release biguanide (Glucophage XR, NDA 21202). BMS owns all data relevant to saxagliptin but is in part relying the FDA's previous finding of safety and efficacy for metformin.

Dr. Lauren Murphree Mihalcik, the primary pharm/tox reviewer, recommends approval of NDA 200678. *I concur with Dr. Mihalcik's recommendation that the submitted nonclinical information supports approval of the saxa/met XR application.* Our recommendation is based on the available information for saxagliptin and metformin as monotherapies, and on toxicology studies conducted with the drugs in combination to assess general toxicity and embryofetal development.

The toxicology of saxagliptin and metformin in combination was evaluated in a 3-month study in dogs. Experimental groups assessed each drug separately and in combination for comparison. No toxicity unique to the drugs in combination was observed, and the toxicity of each drug separately was reasonably similar to the toxicology profile that supported approval of each drug component.

The applicant also submitted embryofetal development studies in rats and rabbits in support of the saxa/met XR combination and in response to a post-marketing requirement for the saxagliptin monotherapy NDA 22350. During the review cycle for NDA 22350, an embryofetal study conducted in rats with the saxa/met combination yielded a weak signal for neural tube defects (NTD). A relationship specific to the combination could not be excluded due to a study design that lacked separate arms for saxagliptin and metformin. Therefore, the Division imposed a PMR for the saxagliptin monotherapy NDA to conduct embryofetal studies in rats and rabbits

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with the drugs alone and in combination. BMS conducted these studies, and as reviewed by Dr. Murphree Mihalcik, these studies did not identify a drug-related neural tube defect as was seen in the original rat study, despite using higher doses of metformin alone or in combination with saxagliptin. Moreover, the 4.5% incidence of NTD observed in the original rat study was shown to be consistent with updated historical control data from the study site for this finding. Therefore, I concur with Dr. Murphree Mihalcik's conclusion that the saxa/met combination is not teratogenic in animals and that the original finding of NTD in rats was incidental to drug treatment. Pregnancy labeling for the saxa/met XR product and the saxagliptin monotherapy will be revised to reflect the most current embryofetal animal data.

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/s/

TODD M BOURCIER
10/01/2010
Pharm/tox recommends AP

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	200678
Supporting document/s:	1
Applicant's letter date:	29 December 2009
CDER stamp date:	29 December 2009
Product:	saxagliptin + metformin extended release (FDC)
Indication:	Type 2 Diabetes Mellitus
Applicant:	Bristol-Myers Squibb
Review Division:	Division of Metabolism and Endocrinology Products
Reviewer:	Lauren Murphree Mihalcik, Ph.D.
Supervisor/Team Leader:	Todd Bourcier, Ph.D.
Division Director:	Mary Parks, M.D.
Project Manager:	Mehreen Hai, Ph.D.

Template Version: December 7, 2009

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