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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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:	202270
Supporting Document/s:	SDN 1
Applicant's Letter Date	23 Sept 2010
CDER Stamp Date:	23 Sept 2010
Product:	Sitagliptin/Metformin XR FDC (MK-0431A XR)
Indication:	Type 2 Diabetes Mellitus
Applicant:	Merck
Review Division:	Division of Metabolism and Endocrinology Products (HFD-510)
Reviewer:	Patricia Brundage, Ph.D.
Supervisor/Team Leader:	Todd Bourcier, Ph.D.
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1 Executive Summary

1.1 Introduction

This is a 505(b)(2) application for the fixed dose combination (FDC) drug product of sitagliptin phosphate and extended release (XR) formulation of metformin hydrochloride (MK-0431A XR) for the treatment of patients with type 2 diabetes mellitus (T2DM). Both sitagliptin and metformin are approved oral antihyperglycemic agents. This 505(b)(2) application relies in part on the Agency's findings of the safety and efficacy as reflected in the approved product labels for Janumet® (sitagliptin/metformin IR FDC; Merck; NDA 22-044) and Glumetza® (metformin XR; Depomed Inc; NDA 21-748). Because the sponsor is the primary NDA holder for sitagliptin, all nonclinical information for this component of the FDC was available for review. Chemical characterization of metformin did not identify differences from the referenced product that required additional toxicological evaluation. No nonclinical studies with the FDC of sitagliptin and metformin XR (MK-0431A XR) were conducted in support of this 505(b)(2) application.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical studies with the FDC drug product of sitagliptin and metformin XR (MK-0431A XR) were performed. The potential toxicity of sitagliptin co-administered with metformin was previously evaluated in 3-month toxicology studies in the dog under NDA 22-044.

Information on the genotoxicity, carcinogenicity, and reproductive toxicity described in the reference listed drug labels of Janumet® (sitagliptin/metformin IR FDC) and Glumetza® (metformin XR) support the chronic administration of MK-0431A XR. Pregnancy Category 'B' is recommended for the FDC drug product given that both sitagliptin and metformin are labeled as Pregnancy Category 'B'.

To qualify an (b) (4) degradate of sitagliptin identified in MK-0431A XR at the proposed limit of (b) (4) which exceeds the qualification threshold (ICH Q3B(R2)), the sponsor conducted a 3-month toxicity study in rats and two *in vitro* genotoxicity studies (microbial mutagenesis assay and chromosomal aberration assay). Microbial mutagenesis and *in vitro* chromosomal aberration assays using (b) (4) batch of sitagliptin containing (b) (4) degradation products were negative supporting a (b) (4) limit for the (b) (4) degradation product. A 3-month rat toxicity study, in which rats were administered a 60 mg/kg (360 mg/m^2) dose of sitagliptin with and without the two (b) (4) degradation products (b) (4) (b) (4) showed that the hydrolysis degradates had no toxicological effect. Given that the expected level of degrade at (b) (4) (0.19 mg/m^2) associated with the MHRD of sitagliptin (100 mg; 62 mg/m^2) is approximately 6-fold less than the level assessed in the 3-month toxicity study in rats, the (b) (4) degradate is not expected to cause a toxicological effect in humans. Collectively, the findings of the 3-month toxicity study in rats and two negative *in vitro* genotoxicity studies (microbial mutagenesis assay and chromosomal aberration assay) support the (b) (4) limit for (b) (4) degradation product of sitagliptin.

1.3 Recommendations

1.3.1 Approvability

Pharmacology and Toxicology recommends the approval of MK-0431A XR for the proposed indication in adults.

1.3.2 Additional Non Clinical Recommendations

No additional nonclinical studies are required.

1.3.3 Labeling

For this 505(b)(2) application for which the sponsor did not conduct a nonclinical development/animal toxicology program with FDC, the language used in the label should be identical to the referenced drug labels of Janumet® (sitagliptin/metformin IR FDC) for sitagliptin and Glumetza® (metformin XR) for metformin XR. In the proposed labeling, the sections relative to the pharmacology/toxicology of sitagliptin and metformin are identical to the current Janumet® label. The sections of the proposed label discussing the pharmacology/toxicology of metformin were replaced with the information in the Glumetza® (metformin XR) label. Changes/additions to the proposed label are underlined.

8.1 Pregnancy

Metformin hydrochloride

(b) (4)

[redacted]

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, which represent 3 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparison for rats and rabbits, respectively. However, because animal reproduction studies are not always predictive of human response, Metformin HCl should not be used during pregnancy unless clearly needed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Metformin hydrochloride

(b) (4)

[redacted]

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