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APPLICATION NUMBER:

202343Orig1s000

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:	202343
Supporting Document/s:	SDN
Applicant's Letter Date	7 Dec 2010
CDER Stamp Date:	7 Dec 2010
Product:	(MK-0431D)
Indication:	Type 2 diabetes mellitus (T2DM) and hyperlipedemia
Applicant:	Merck
Review Division:	Division of Metabolism and Endocrinology Products (HFD-510)
Reviewer:	Patricia Brundage, Ph.D.
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1 Executive Summary

1.1 Introduction

This is a 505(b)(1) application for the fixed dose combination (FDC) drug product of sitagliptin phosphate and simvastatin (MK-0431D) for the treatment of patients with Type 2 diabetes mellitus (T2DM) and hyperlipidemia. Sitagliptin (Januvia®; Merck; NDA 21-995) was approved by the FDA as an oral anti-hyperglycemic agent, and simvastatin (Zocor®; Merck; NDA 19-766) was approved as an oral anti-hypercholesterolemic agent. Both drug products are approved for chronic use.

This 505(b)(1) application relies primarily on the Agency's findings of safety and efficacy for Januvia® (sitagliptin) and Zocor® (simvastatin). As the sponsor is the primary NDA holder for sitagliptin and simvastatin, all nonclinical information for both components of the FDC were available for review.

The sponsor conducted clinical pharmacology studies to assess the pharmacokinetics of the drug combination as well as possible drug-drug interactions between sitagliptin and simvastatin.

1.2 Brief Discussion of Nonclinical Findings

The nonclinical pharmacology, pharmacokinetics/ADME properties, and toxicity of sitagliptin and simvastatin have been established individually under NDA 21-995 (sitagliptin) and NDA 19-766 (simvastatin).

Due to the concern of possible toxicologic interactions between sitagliptin and simvastatin, especially regarding adverse effects on the skeletal muscle, the sponsor conducted a 3-month co-administration toxicology study in rats to assess the potential toxicity due to co-administration of sitagliptin and simvastatin. There was no mortality or significant adverse clinical effects associated with the co-administration of sitagliptin and simvastatin at exposures greater than 20 times those at the maximum clinical dose of either drug in the FDC. Although there were no adverse muscle or pancreas effects associated with either drug administered alone or in combination, co-administration of sitagliptin and simvastatin did cause an increase in adverse liver effects.

Administration of the simvastatin high dose (60 mg/kg; ~47-114X MHRD; based on AUC) caused an increase in liver weight, hepatocellular hypertrophy, and an increase in ALT levels (~2-3X ↑ compared to controls). Although these effects were not observed in animals administered sitagliptin alone, the co-administration of sitagliptin (180 mg/kg; ~20X MHRD; based on AUC) and simvastatin caused a slightly greater dose-related increase in liver weight (females only) and ALT levels with both the low (30 mg/kg; ~20-66X MHRD; based on AUC) and high (60 mg/kg; ~47-114X MHRD; based on AUC) simvastatin doses suggesting a possible drug-drug interaction between sitagliptin and simvastatin with regards to liver toxicity. Although the sponsor did not establish a NOAEL for the additional increases in liver weight and ALT levels, these adverse liver effects are clinically monitorable. Co-administration of the simvastatin high dose (60 mg/kg; ~47X MHRD; based on AUC) and sitagliptin (180 mg/kg; ~20X MHRD; based on AUC) also caused bile duct hyperplasia. Given that there were no similar findings in animals administered the simvastatin high dose or sitagliptin alone and that bile duct proliferation/hyperplasia was previously observed in rats in studies conducted under NDA 21-995 (sitagliptin) and NDA 19-766 (simvastatin), this finding suggests a potential

drug-drug interaction. However, as a NOEL (30 mg simvastatin/180 mg sitagliptin) was established for this finding at approximately 20 times the human exposure at the MRHD, this is of minimal concern clinically.

Simvastatin treatment was associated with adverse effects in the nonglandular stomach and thyroid. These findings were not markedly affected by the co-administration of sitagliptin. Moreover, they are consistent with those observed in the rat in toxicology studies conducted in support of NDA 19-766 (simvastatin) and are not considered to be clinically relevant.

Information from the genotoxicity, carcinogenicity, and reproductive studies conducted under NDA 21-995 (sitagliptin) and NDA 19-766 (simvastatin) support the chronic administration of MK-0431A XR. Pregnancy category X is recommended for the FDC drug product given that simvastatin is classified in pregnancy category X because lipid lowering drugs offer no benefit during pregnancy when cholesterol and cholesterol derivatives are needed for normal fetal development.

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

The nonclinical labeling information for the FDC drug product of sitagliptin and simvastatin (MK-0431D) is similar to the language used in the labels for which the sponsor is the primary NDA holder for both drug products. The safety margin for simvastatin regarding the teratogenicity studies (under Section 8.1) will need to be corrected to account for the maximum simvastatin dose of 40 mg/day; change to the proposed label is underlined. Additionally, the paragraph discussing the results of the 3-month rat co-administration study should be deleted as it does not contain nonclinical data pertinent to the safe/effective use of the drug.

8.1 Pregnancy

Simvastatin

Simvastatin was not teratogenic in rats or rabbits at doses (25, 10 mg/kg/day, respectively) that resulted in 6 times the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related statin, skeletal malformations were observed in rats and mice.

13.2 Animal Toxicology and/or Pharmacology

(b) (4)

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