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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

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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.
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TABLE OF CONTENTS

1	EXECUTIVE SUMMARY	3
1.1	INTRODUCTION.....	3
1.2	BRIEF DISCUSSION OF NONCLINICAL FINDINGS	3
1.3	RECOMMENDATIONS	4
2	DRUG INFORMATION	5
3	STUDIES SUBMITTED.....	10
4	PHARMACOLOGY.....	10
5	PHARMACOKINETICS/ADME/TOXICOKINETICS	11
6	GENERAL TOXICOLOGY.....	12
7	GENETIC TOXICOLOGY	12
7.1	IN VITRO REVERSE MUTATION ASSAY IN BACTERIAL CELLS (AMES).....	13
7.2	IN VITRO CHROMOSOMAL ABERRATION ASSAYS IN MAMMALIAN CELLS	16
8	CARCINOGENICITY	20
9	REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY.....	21
10	SPECIAL TOXICOLOGY STUDIES	22
11	INTEGRATED SUMMARY AND SAFETY EVALUATION	26
12	REFERENCES.....	27

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/m²) dose of sitagliptin with and without the two (b) (4) degradation products (b) (4) showed that the hydrolysis degradates had no toxicological effect. Given that the expected level of degrade at (b) (4) (0.19 mg/m²) associated with the MHRD of sitagliptin (100 mg; 62 mg/m²) 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

[REDACTED] (b) (4)

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

[REDACTED] (b) (4)

Long-term carcinogenicity studies have been performed in Sprague Dawley rats at doses of 150, 300, and 450 mg/kg/day in males and 150, 450, 900, and 1200 mg/kg/day in females. These doses are approximately 2, 4, and 8 times in males, and 3, 7, 12, and 16 times in females of the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female rats. A carcinogenicity study was also performed in Tg.AC transgenic mice at doses up to 2000 mg applied dermally. No evidence of carcinogenicity was observed in male or female mice.

Genotoxicity assessments in the Ames test, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes) and *in vivo* mouse micronucleus tests were negative. Fertility of male or female rats was not affected by metformin when administered at dose up to 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body surface area comparisons.

2 Drug Information

2.1 Drug

CAS Registry Number

Sitagliptin Phosphate: 654671-77-9

Metformin HCl: 1115-70-4

Code Name

Sitagliptin Phosphate: MK-0431, L-000224715

Metformin HCl: MK-9378, L-000282095

Chemical Name

Sitagliptin Phosphate:

- 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-[3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine phosphate (1:1) monohydrate

Metformin HCl:

- N,N-dimethylimidodicarbonimidic diamide hydrochloride
- 1,1-dimethylbiguanide hydrochloride
- N,N-dimethylbiguanide hydrochloride
- N'-dimethylguanylguanidine hydrochloride

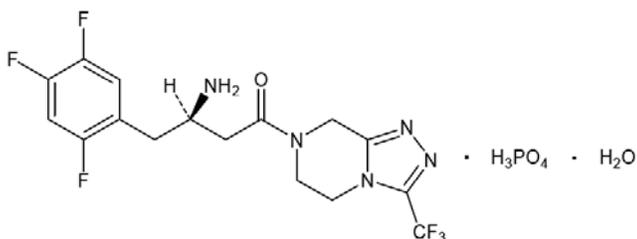
Molecular Formula/Molecular Weight

Sitagliptin Phosphate: C₁₆H₁₅F₆N₅O • H₃O₄P • H₂O/523.32

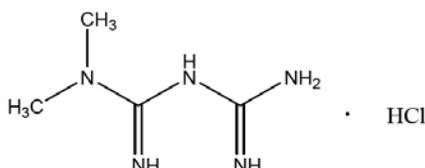
Metformin HCl: C₄H₁₁N₅ • HCl/165.63

Structure or Biochemical Description

Sitagliptin Phosphate:



Metformin:

**Pharmacologic Class**

Sitagliptin is dipeptidyl peptidase 4 inhibitor (DPP4 inhibitor); an antihyperglycemic agent.

Metformin is an antihyperglycemic agent.

2.2 Relevant NDAs and DMFs

NDA 21-995 (Januvia[®], sitagliptin phosphate)

NDA 22-044 (Janumet[™]; sitagliptin phosphate and metformin HCl IR)

NDA 21-748 (Glumetza[™]; metformin HCl XR)

DMF (b) (4) (Type II; (b) (4) metformin)

2.3 Drug Formulation

MK-0431A XR tablets contains 64.25 mg or 128.5 mg of sitagliptin phosphate (50 mg or 100 mg free base equivalent) and 500 mg or 1000 mg of extended-release metformin HCl (metformin XR). Three tablet strengths of the FDC drug product have been developed for registration:

- Sitagliptin/metformin XR 50 mg/500 mg (to be given as 2 tablets once daily)
- Sitagliptin/metformin XR 50 mg/1000 mg (to be given as 2 tablets once daily)
- Sitagliptin/metformin XR 100 mg/1000 mg (to be given as 1 tablet once daily)

MK-0431A XR tablets can be separated into three main components:

- A (b) (4) core that provides an extended release profile of metformin HCl
- A sitagliptin active coating over the (b) (4) core designed to provide immediate release of sitagliptin
- A polymeric film coating over the active (b) (4)

Sitagliptin is formulated as the monohydrate phosphate ^{(b) (4)}, which was extensively characterized during the Januvia[®] development program. ^{(b) (4)}

Metformin HCl will be purchased as a compendial grade material (conforming to the USP and/or Ph. Eur.) from ^{(b) (4)} under Type II DMF. No modifications to the chemical or physical properties of the drug substance are required for the formulation and the material is used as supplied.

Drug Product Unit Composition (Sponsor's Table)

Components	Compendial Testing	Function	Unit Strength (mg/tablet)			
			mg Sitagliptin Phosphate/mg	Metformin Hydrochloride		
			50/500	50/1000	100/1000	
Core Tablet			^{(b) (4)}			
Metformin Hydrochloride	USP-NF, Ph. Eur.					
Povidone ^{(b) (4)}	USP-NF, Ph. Eur.					
^{(b) (4)}	USP-NF, Ph. Eur.					
Hypromellose ^{(b) (4)}	USP-NF, Ph. Eur.					
^{(b) (4)}						
Microcrystalline Cellulose ^{(b) (4)}	USP-NF, Ph. Eur.					
Silicon Dioxide, Colloidal	USP-NF, Ph. Eur.					
Sodium Stearyl Fumarate	USP-NF, Ph. Eur.					
Core Tablet Weight						
API Film Coating						
Sitagliptin Phosphate [†]	-----					
Propyl Gallate	USP-NF, Ph. Eur.					
Hypromellose ^{(b) (4)}	USP-NF, Ph. Eur.					
Polyethylene Glycol ^{(b) (4)}	USP-NF, Ph. Eur.					
Kaolin ^{(b) (4)}	USP-NF					
^{(b) (4)}	USP-NF, Ph. Eur.					
^{(b) (4)} Film Coating						
^{(b) (4)}	USP-NF, Ph. Eur.					
^{(b) (4)}	-----					
Caruba Wax	USP-NF, Ph. Eur.					
Total Tablet Weight			11.56	15.89	17.21	
^{(b) (4)}						

2.4 Comments on Novel Excipients

All excipients are compendial grade with the exception of the ^{(b) (4)}. The ^{(b) (4)} formulations are mixtures of excipients ^{(b) (4)} (hydroxypropyl cellulose, and titanium dioxide) covered by USP-NF, Ph. Eur. and/or 21 CFR. Acceptance of the coating mixtures will be based on the supplier's certificates of analysis and in-house testing of characteristics and a suitable identification test.

(b) (4)
Sponsor's Table)

Film-Coating Ingredients	Reference
Hypromellose (b) (4)	USP-NF, Ph. Eur.
Hydroxypropyl Cellulose	USP-NF, Ph. Eur.
Titanium Dioxide	USP-NF, Ph. Eur.
FD&C Blue #2/Indigo Carmine Aluminum Lake	21 CFR 82.51, 21 CFR 82.102 and E132

(b) (4)
Sponsor's Table)

Film-Coating Ingredients	Reference
Hypromellose (b) (4)	USP-NF, Ph. Eur.
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(b) (4)
Sponsor's Table)

Film-Coating Ingredients	Reference
Hypromellose (b) (4)	USP-NF, Ph. Eur.
Hydroxypropyl Cellulose	USP-NF, Ph. Eur.
Titanium Dioxide	USP-NF, Ph. Eur.
FD&C Blue #2/Indigo Carmine Aluminum Lake	21 CFR 82.51, 21 CFR 82.102, and E132
Iron Oxide Yellow	USP-NF

The maximum daily intake of the compendial excipient hypromellose (b) (4) (b) (4) in the sitagliptin coating, would be up to (b) (4) which is greater than the level of hypromellose (b) (4) in approved drug products (b) (4). However, there is no toxicological concern regarding this excipient that would necessitate reducing the level.

2.5 Comments on Impurities/Degradants of Concern

Impurities

All metformin-related impurities (DMF (b) (4)) and sitagliptin-related impurities are within the ICH Q3A identification and qualification thresholds.

Sitagliptin Impurities (Sponsor's Table)

(b) (4)

(b) (4)

Degradants

Acceptance criteria were established for individual and total degradates in MK-0431A XR tablets in accordance with the ICH Q3B(R2) and are based on potential contributions from the drug substances, manufacture of drug product, and any increase during formal stability studies (FSS) or product characterization studies (PCS) of the drug product. All the release and shelf-life criteria are supported by release and stability data for 9 FSS batches (up to 52 weeks).

The limit of (b) (4) (release and shelf-life) for single unspecified metformin degradates in MK-0431A XR tablets meets the ICH Q3B(R2) reporting threshold based on the maximum daily clinical dose of metformin (2000 mg/day).

The proposed release and shelf-life limit for single unspecified sitagliptin degradates is (b) (4) which meets the ICH Q3B(R2) identification threshold based on the maximum daily clinical dose of sitagliptin (100 mg/day). (b) (4) studies identified a sitagliptin (b) (4) degradation

path. The proposed shelf-life limit for the identified (b) (4) degradant is (b) (4) (anticipated level at the proposed the two-year product expiry); the rate of degradate formation is dependent on relative humidity at 25°C. At (b) (4) the (b) (4) degradant (b) (4) exceeds the qualification limit. The lack of toxicity in a 3-month toxicity study in rats and two negative *in vitro* genotoxicity studies (microbial mutagenesis assay and chromosomal aberration assay) using a sitagliptin batch containing (b) (4) degradation products supports the (b) (4) limit for the (b) (4) degradation products.

No significant increase in the level of any degradates has been observed in FSS out to 52 weeks at the proposed storage condition of 25°C.

Sitagliptin (b) (4) Degradation Product (Sponsor's Figure)



Specifications for Degradates of MK-0431A XR (Sponsor's Table)

Tests	Acceptance Criteria	Test Methods
Metformin Degradates (release and shelf-life)	Any Unspecified: Max. (b) (4) Total Degradates: Max. (b) (4)	Assay, Degradate & Identity by HPLC Sec. 3.2.P.5.2.2-0431a-xrtablett
Sitagliptin Degradates (release and shelf-life)	Release: Any Unspecified: Max. (b) (4) Total Degradates: Max. (b) (4) Shelf-life: (b) (4) Degradate: Max. (b) (4) Any Unspecified: Max. (b) (4) Total Degradates: Max. (b) (4)	Assay, Degradate & Identity by HPLC Sec. 3.2.P.5.2.1-0431a-xrtablett

Degradates in FSS up to 52 Weeks (Sponsor's Table)

	TIME (Weeks)
ATTRIBUTES	(b) (4)
Degradates (%) - Sitagliptin (b) (4) Degradate	(b) (4)
Single Unspecified Degradate	(b) (4)
Total Degradates	(b) (4)
Degradates (%) - Metformin	(b) (4)
Single Unspecified Degradate	(b) (4)
Total Degradates	(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

The proposed dosing regimen is sitagliptin/metformin XR 50 mg/500 mg and 50 mg/1000 mg administered as two tablets once daily and sitagliptin/metformin XR 100 mg/1000 mg administered as one tablet once daily.

2.7 Regulatory Background

Sitagliptin (25, 50, and 100 mg tablets) was approved in 2006 as an oral antihyperglycemic in patients with T2DM (Januvia[®]; NDA 21-955) with a recommended dose of 100 mg/daily. In 2007, a FDC of sitagliptin and metformin IR (50 mg sitagliptin/500 mg metformin and 50 mg sitagliptin/1000 mg metformin tablets) was approved (Janumet[®]; NDA 22-044) for glycemic control in T2DM patients. Janumet[®] is administered twice daily with a maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin.

Metformin (IR formulation) was first approved in the United States in 1994 (Glucophage[®]; NDA 20-357) as an oral antihyperglycemic in patients with type 2 diabetes mellitus. The maximum recommended daily dose is 2550 mg in adults. Several extended release formulations were also approved:

- 2000/2002: extended release tablet containing 500 mg or 750 mg metformin (Glucophage XR[®], NDA 21-202).
- 2004: extended release tablet containing 500 mg or 1000 mg metformin (Fortamet[®], NDA 21-574)
- 2005: extended release tablet containing 500 mg or 1000 mg metformin (Glumetza[®]; NDA 21-748)

3 Studies Submitted

3.1 Studies Reviewed

This is a 505(b)(2) submission. The sponsor is referencing the Agency's previous findings of safety and efficacy for the reference listed drugs of Janumet[®] (sitagliptin/metformin IR) and Glumetza[®] (metformin XR; NDA 21-748) to support the nonclinical safety of MK-0431A XR (sitagliptin/metformin XR FDC). The sponsor conducted the following studies to qualify two (b) (4) degradates of sitagliptin:

- Microbial Mutagenesis Assay (TT #09-8168)
- Assay for Chromosomal Aberrations In Vitro, in Chinese Hamster Ovary Cells (TT #09-8623)
- Three-Month Oral Toxicity Study in Rats (TT #09-1239)

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

Nonclinical data supporting the safety the co-administration of are reviewed under NDA 22-044 by Dr. Todd Bourcier.

4 Pharmacology

No nonclinical pharmacology studies were conducted for this 505(b)(2) submission for MK-0431A XR. The nonclinical pharmacology of sitagliptin and metformin (IR and XR), individually, were previously established. Information pertaining to sitagliptin and metformin is derived from the approved Janumet[®] (sitagliptin/metformin IR FDC) and Glumetza[®] (metformin XR) labels.

Sitagliptin

According to the approved label for Janumet[®] (sitagliptin/metformin IR):

Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity *in vitro* at concentrations approximating those from therapeutic doses.

Sitagliptin inhibits plasma DPP-4 activity in a dose- and concentration-dependent manner. *In vitro* measurement of DPP-4 inhibition indicates that near-maximal glucose lowering activity is associated with inhibition of plasma DPP-4 activity of approximately $\geq 80\%$ and enhancement of post-glucose challenge active GLP-1 concentrations of ≥ 2 -fold.

Metformin

According to the approved label for Glumetza[®] (metformin XR):

Metformin is an antihyperglycemic agent, which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Metformin has also been reported to increase GLP-1 concentrations (Drucker et al., 2006; Godarzi et al., 2005; Holst et al., 2008; Migoya et al., 2010).

5 Pharmacokinetics/ADME/Toxicokinetics

No nonclinical pharmacokinetic/ADME/toxicokinetic studies were conducted with MK-0431A XR. The nonclinical ADME properties and pharmacokinetics (PK) of sitagliptin and metformin XR, individually, were previously established. Doses of each component of the FDC are consistent with the doses approved for each drug separately; therefore, exposure margins achieved in the nonclinical toxicology program for each component are applicable to the proposed FDC product.

In lieu of nonclinical PK studies, the sponsor conducted clinical pharmacology studies including four biopharmaceutics studies (P112, P163, P164 and P147) and two PK studies (P012 and P165) in support of this 505(b)(2) submission for MK-0431A XR. Results of these clinical studies were evaluated by FDA's clinical pharmacology review team.

6 General Toxicology

No nonclinical toxicology studies were conducted with MK-0431A XR.

Nonclinical studies with sitagliptin were conducted in mice (3 months), rats (up to 6 months), dogs (up to 1 year), rhesus and cynomolgus monkeys (up to 3 months) under NDA 21-955 (Januvia[®]; sitagliptin), which is held by the sponsor of the proposed FDC product. The kidney (renal tubule degeneration and necrosis at ≥ 1500 mg/kg), liver (hepatocellular hypertrophy with \uparrow liver weight at ≥ 500 mg/kg; hepatocellular degeneration and necrosis at 2000 mg/kg), heart (myocardial degeneration and necrosis at ≥ 1500 mg/kg), teeth (1000 mg/kg), bone marrow (necrosis at 2000 mg/kg), and lymph nodes (2000 mg/kg) were identified as the target organs of toxicity in the rat. Some consistent neurological clinical signs (reduced activity, hunched posture, ataxia, tremor, and sporadic emesis) were present in all the dog studies at 50 mg/kg. Sitagliptin did not produce vascular/skin lesions in rhesus monkeys, as seen with some DPP4 inhibitors, when administered at doses up to 100 mg/kg (~25X MRHD of 100 mg; based on AUC) for 3 months.

The Glumetza[®] (metformin XR) label does not provide information regarding the nonclinical target organs of toxicity of metformin.

A series of studies conducted by the sponsor in support of NDA 22-044 for the sitagliptin/metformin IR FDC (Janumet[®]) evaluated the potential toxicity of sitagliptin co-administered with metformin IR to dogs. The combination of sitagliptin (2-50 mg/kg) and metformin (50 mg/kg) in dogs resulted in more numerous and earlier deaths than observed with metformin alone. However, the combination of sitagliptin and a lower dose of metformin (20 mg/kg), which better approximates human exposure, resulted in no deaths and yielded no evidence of exacerbated toxicity. Although it was determined that the deaths at 50 mg/kg of metformin were due to metformin toxicity and not to the combination, the possibility of slight exacerbated toxicity with clinical high exposure to metformin (≥ 400 $\mu\text{M}\cdot\text{h}$ [AUC]) and clinical exposure to sitagliptin (≥ 10 $\mu\text{M}\cdot\text{h}$ [AUC]) could not be ruled out.

7 Genetic Toxicology

No genetic toxicology studies were conducted with MK-0431A XR. The genotoxicity of sitagliptin and metformin, individually, were previously established in *in vitro* and *in vivo* genotoxicity studies. As summarized in the Janumet[®] (sitagliptin/metformin IR FDC) and Glumetza[®] (metformin XR) labels, neither drug product is genotoxic.

According to the approved label for Janumet[®] (sitagliptin/metformin IR):

Sitagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a Chinese hamster ovary (CHO) chromosome aberration assay, an *in vitro* cytogenetics assay in CHO, an *in vitro* rat hepatocyte DNA alkaline elution assay, and an *in vivo* micronucleus assay.

According to the approved label for Glumetza® (metformin XR):

Genotoxicity assessments in the Ames test, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes) and *in vivo* mouse micronucleus tests were negative.

In support of this 505(b)(2) submission for MK-0431A XR, *in vitro* microbial mutagenesis and chromosomal aberration assays were conducted using a (b) (4) sitagliptin batch containing (b) (4) degradation products to qualify a (b) (4) degradation product of sitagliptin at the proposed limit of (b) (4) in the drug product.

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Microbial Mutagenesis Assay (TT #09-8168) - GLP

Study No.: 09-8168
Study Report Location: EDR
Conducting Laboratory and Location: Merck Research Laboratories, West Point, PA
Date of Study Initiation: 9 December 2009
GLP Compliance: Yes
QA Statement: Yes
Drug, Lot #, and % Purity: MK-0431/sitagliptin (contains (b) (4) [degradates; artificially degraded] (b) (4), purity not applicable as material is artificially degraded)

Key Study Findings

- A (b) (4) batch of sitagliptin (b) (4) products was not mutagenic in the Ames test at concentrations up to 5000 µg/plate.

Methods

Strains:	TA100, TA1535, TA98, TA97a, and WP2 _{uvrA} pKM101
Concentrations in Definitive Study:	100, 300, 1000, 3000, and 5000 µg/plate (with and without S9)
Basis of Concentration Selection:	Used doses up 5000 µg/plate (limit dose)
Negative Control:	Water, acidified with 1 mM HCl, pH ~4.0
Positive Control:	<i>Salmonella</i> strains and <i>E. coli</i> strain WP2 _{uvrA} pKM101 (with and without S9): 2-aminoanthracene (2AA), 1 and 2 µg/plate with S9 and 2 and 5 µg/plate without S9 Diagnostic mutagens (without S9): Sodium azide (0.75 µg/plate), 4-Nitroquinoline-N-oxide (4NQO; 1 µg/plate); 2-Nitrofluorene (2NF; 1 µg/plate), and ICR-191, (1.5 µg/plate)
S9 Mix:	Liver from rats treated with phenobarbital and beta-naphthoflavone (MOLTOX, Inc.); 50 µL/plate, when appropriate
Formulation/Vehicle:	Acidified water
Incubation & Sampling Time:	Plates were incubated at 37°C for 48 hrs. Revertant colonies on the histidine or tryptophan deficient plates were counted and the supplemental plates examined for evidence of inhibition or contamination. Revertant colony counts on the test plates were averaged and compared with the appropriate control plate average.

Judgment

- Positive: (1) a 2-fold or greater increase in number of revertant colonies, and (2) a dose-related increase in number of revertant colonies.

Study Validity

Dose selection for the plate incorporation assay was adequate based on the limit dose (i.e., 5000 µg/plate). All test article concentrations and concurrent negative and positive controls were carried out in triplicate plates. Four or more doses had no inhibition of bacterial lawn or revertant growth and there were at least 5 analyzable doses with and without S9. The dose formulations were within nominal concentrations. The negative and positive controls were within acceptable ranges, and the positive controls produced the expected responses. 2-Aminoanthracene was the sole S9 positive control. The sponsor did not indicate that preliminary studies characterized the S9 with benzo[a]pyrene and 2-aminoanthracene were conducted.

Results

No precipitate was seen on the plates at any concentration tested. No inhibition of bacterial lawn or revertant growth was noted at any concentration tested. Artificially degraded MK-0431 and its (b) (4) degradation products did not produce 2-fold or greater increases in revertants relative to control. The positive control and diagnostic mutagens showed appropriate S9- and strain-dependent increases in revertants.

Microbial Mutagenesis Assay: Results with Artificially Degraded MK-0431 (Sponsor's Table)

Conc./Plate	TA100 14-DEC-2009				TA1535 14-DEC-2009				TA97a 14-DEC-2009			
	Without S-9		With S-9		Without S-9		With S-9		Without S-9		With S-9	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0 µg	201.0	17.0	222.0	7.8	25.9	9.5	23.4	4.7	236.8	22.9	289.2	17.2
100 µg	188.3	3.1	199.0	14.7	18.0	1.7	25.3	5.7	239.7	11.1	289.3	21.4
300 µg	193.0	10.1	203.3	4.0	25.7	2.3	32.7	2.1	242.7	33.5	292.0	32.0
1000 µg	192.3	30.9	220.7	13.6	20.0	1.7	24.3	7.4	232.0	21.1	287.7	29.0
3000 µg	187.7	20.0	212.3	23.1	23.7	6.5	28.3	2.5	220.7	10.7	298.0	29.8
5000 µg	172.7	14.0	215.7	11.8	23.0	3.6	24.7	1.2	219.3	13.3	284.0	14.0

Microbial Mutagenesis Assay: Results with Artificially Degraded MK-0431 (Sponsor's Table)

Conc./Plate	TA98 14-DEC-2009				WP2 uvrA pKM101 14-DEC-2009			
	Without S-9		With S-9		Without S-9		With S-9	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0 µg	48.3	7.6	57.3	7.6	169.6	21.6	182.9	14.3
100 µg	48.3	16.2	58.7	3.1	180.0	21.2	178.0	6.2
300 µg	44.3	5.1	56.3	12.1	167.7	11.2	160.0	4.6
1000 µg	47.7	13.6	56.0	9.0	165.0	16.4	176.7	17.6
3000 µg	45.3	4.0	57.0	11.1	159.3	6.7	188.7	12.5
5000 µg	50.7	4.6	65.0	7.2	153.3	9.1	173.7	2.1

Salmonella typhimurium/E. coli genotypes:
 TA100 his G46 (base substitution) ΔuvrB rfa pKM101 (R factor).
 TA1535 his G46 (base substitution) ΔuvrB rfa.
 TA97a his D6610 (frameshift) ΔuvrB rfa pKM101 (R factor).
 TA98 his D3052 (frameshift) ΔuvrB rfa pKM101 (R factor).
 WP2 uvrA pKM101 (trp-) ΔuvrA pKM101 (R factor).

S-9 = Metabolic activation.
 SD = Standard deviation.

Microbial Mutagenesis Assay: Results with Positive Control Mutagens (Sponsor's Table)

Mutagen [†]	S-9 +/-	Conc./ Plate	<i>Salmonella typhimurium</i> strains							
			TA1535		TA97a		TA98		TA100	
			Fold Inc	Fold Inc	Fold Inc	Fold Inc	Fold Inc	Fold Inc		
Sodium azide	-	0.75 µg	16.4	0.9	0.9	3.3				
ICR-191	-	1.5 µg	1.2	6.2	3.5	1.8				
2-Nitrofluorene	-	1.0 µg	1.0	1.5	9.5	3.7				
4NQO	-	1.0 µg	4.0	4.0	11.9	12.0				
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
DMSO	-	100 µL	22.8	6.6	219.8	17.2	48.7	9.2	175.3	17.0
2AA	-	1.0 µg	26.7	4.0	232.7	19.4	50.7	12.5	191.7	10.3
2AA	-	2.0 µg	22.3	6.8	234.7	7.0	52.7	4.2	210.3	12.0
DMSO	+	100 µL	29.7	8.3	291.3	31.8	58.0	17.3	207.2	14.6
2AA	+	1.0 µg	96.0	14.8	555.3	18.0	363.3	35.6	607.3	34.4
2AA	+	2.0 µg	202.0	6.6	872.3	56.6	742.7	55.4	1194.7	60.5
Distilled Water	-	100 µL	28.0	7.9	236.0	13.5	48.0	4.4	206.0	31.8

Microbial Mutagenesis Assay: Results with Positive Control Mutagens (Sponsor's Table)

Mutagen [†]	S-9 +/-	Conc./ Plate	<i>Escherichia coli</i> strains	
			WP2 uvrA pKM101	Fold Inc
Sodium azide	-	0.75 µg		1.0
ICR-191	-	1.5 µg		1.4
2-Nitrofluorene	-	1.0 µg		1.1
4NQO	-	1.0 µg		6.0
			Mean	SD
DMSO	-	100 µL	152.2	13.8
2AA	-	2.0 µg	171.3	19.6
2AA	-	5.0 µg	147.3	18.1
DMSO	+	100 µL	164.5	18.9
2AA	+	2.0 µg	358.3	41.2
2AA	+	5.0 µg	887.7	8.5
Distilled Water	-	100 µL	159.0	5.6
[†] = Sodium azide was dissolved in water; all other compounds, in DMSO. SD = Standard Deviation. S-9 = Metabolic activation.				
2AA = 2-Aminoanthracene DMSO = Dimethyl sulfoxide 4NQO = 4-Nitroquinoline-N-oxide				

7.2 In Vitro Chromosomal Aberration Assays in Mammalian Cells**Assay for Chromosomal Aberrations In Vitro, in Chinese Hamster Ovary Cells (TT #09-8623) - GLP**

Study No.: 09-8623
Study Report Location: EDR
Conducting Laboratory and Location: Merck Research Laboratories, West Point, PA
Date of Study Initiation: 9 December 2009
GLP Compliance: Yes
QA Statement: Yes
Drug, Lot #, and % Purity: MK-0431/sitagliptin (contains (b) (4) degradates; artificially degraded), L-000224715-013D00, purity not applicable as material is artificially degraded

Key Study Findings

- A (b) (4) batch of sitagliptin with (b) (4) degradation products did not induce chromosomal aberrations in the absence or presence of S9 in CHO cells.
- In the cultures treated for 20 hours without S9, sitagliptin and its (b) (4) degradation products caused an increase in polyploidy metaphases at 0.9 and 1 mg/mL (12-14%), which exceeded the historical control range for polyploidy (0-7%).

Reviewer's Comments

The increase in polyploidy prompted the sponsor to re-evaluate the 20-hour treatment of the original chromosomal aberration assay conducted with an (b) (4) batch of sitagliptin in 2002 as there was no report of endoreduplication or polyploidy in the 20-hour cultures in the original *in vitro* chromosomal aberration assay report (NDA 21-995); the results of the re-evaluation were submitted under IND 103183 (SDN23). The re-evaluation of the 20-hour treatment cultures showed an increase in polyploidy metaphases (10%) at the highest sitagliptin concentration

evaluated (1 mg/mL), which exceeded historical control data. Given that an increase in polyploidy metaphases was observed with the (b) (4) batches, the increase was considered to be attributable to sitagliptin, not the (b) (4) degradates.

Based on the absence of mutagenesis and clastogenesis, the increase in polyploidy associated with sitagliptin is not due to a direct interaction with DNA but to an unidentified indirect mechanism. There is no particular cause for concern regarding the *in vivo* genotoxicity of the drug given the negative mouse bone marrow micronucleus study using up to 2000 mg/kg sitagliptin. Also, a drug concentration of 0.4 mg/mL did not produce polyploidy and is approximately 800-fold higher than the therapeutic drug concentration; indirect mechanisms of action are generally thought to have thresholds for effects on DNA, whereas agents that directly interact with DNA do not.

Methods

Cell Line:	Chinese hamster ovary, subclone WBL (b) (4) less than or equal to 15 passages since cloning
Concentrations in Definitive Study:	3-hr treatment with S9: 1, 1.2, 1.4, 1.6, 1.7, 1.8, 1.9, 2, 2.25, and 2.5 mg/mL 3-hr treatment without S9: 0.6, 0.8, 1, 1.2, 1.4, 1.6, 1.8, 2, 2.25, and 2.5 mg/mL 20-hr treatment without S9: 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, and 1.2 mg/mL
Basis of Concentration Selection:	Based on previous dose range finding assay using (b) (4) MK-0413 (TT #02-8620)
Negative Control:	0.1 mM HCl in Water, pH about 4.0 (Acidified Water)
Positive Control:	Mitomycin C (without metabolic activation) and cyclophosphamide (with metabolic activation)
S9 Mix	Liver from rats treated with beta-naphthoflavone and phenobarbital (MOLTOX, Inc.)
Formulation/Vehicle:	Acidified Water
Incubation & Sampling Time:	2 treatment durations: 3-hour treatment with or without S-9 and a continuous treatment without S-9 (about 20 hours). The cells are fixed for analysis of chromosome aberrations ~20 hours from the beginning of treatment (~1.5 normal cell cycle lengths). Polyploidy and endoreduplication are reported if frequencies in treated cultures exceed those for solvent controls for the assay overall.

Judgment

- Positive: if there are two positive points (positive point equals statistically significant increase in the percentage of cells with aberrations) within a series without greatly exceeding a 50% reduction in growth.

- Equivocal: if there is one positive point; considered equivocal until repeated in another assay
- Statistical analysis was not required for a given series when the percentages of cells with chromosomal aberrations at all concentrations of test article are within the historical control range for negative and/or solvent control cultures.

Study Validity

Appropriate positive controls (cyclophosphamide and mitomycin C) were used with and without metabolic (S9) activation. 200 cells/dose were scored under code from a minimum of three doses of test article and from negative and/or solvent controls. Although a separate growth inhibition dose-range finding study was not conducted, doses were selected based on the results of a previous dose range finding assay using (b) (4) MK-0413 (TT #02-8620). Cell growth reduction exceeding 50% of concurrent solvent control was reached. The incidence of structural/numerical aberrant cells in the negative and positive controls was within acceptable ranges. The dose formulation analysis demonstrated that the drug concentrations met the acceptance criteria. Consequently, the study is considered valid.

Results

Cytotoxicity

The top dose levels scored for chromosome aberrations were limited by cytotoxicity. No test article precipitate was evident in any cultures scored for aberrations. At the top doses scored (1.7 mg/mL with S9, 1.6 mg/mL [3-hour treatment] without S9, and 1 mg/mL [20-hour treatment] without S9), cell growth at 20 hours was reduced to 48, 62, and 45% of concurrent solvent controls. Doses only slightly higher were excessively toxic. The two lower doses scored were selected to span a range of cytotoxicities.

Chromosomal Aberrations

In cultures treated with sitagliptin and its (b) (4) degradation products, there were no increases in structural chromosome aberrations over concurrent solvent controls that are also outside the typical historical control range were negative. The maximum level of aberrations observed, 3% after the 3-hour treatments with and without S9 is within the typical historical control range of 0-5% and is similar to concurrent solvent controls.

Endoreduplication/Polyploidy

There were increases in polyploid metaphases in cultures treated for 20 hours. The increase polyploid cells at the mid dose (0.9 mg/mL; 12%) and highest dose (1 mg/mL; 14%) after the 20-hour treatment without S9 exceeds the historical control range for polyploidy (0-7%). Possible mechanisms include inhibition of normal DNA synthesis and/or temporary cell cycle block in the G2 phase, in addition to cytotoxicity.

**Chromosomal Aberration and Cytotoxicity at 3-Hr with and without S9
(Sponsor's Table)**

Treatment	Cell Growth (PD, % Control)	% Aberrant Cells	Frequency Abs per 100 Cells ^a	% Endos ^b	% Polys ^c
With S-9 (3-Hour Treatment)					
Water, acidified (5%)	100	2.50	2.50	0.2	1.4
Water, acidified (5%)	100	2.50	3.50	0.0	1.8
Cyclophosphamide (2.5 µM)	82	5.50	6.00	NS	NS
Cyclophosphamide (10 µM) ^e	58	64.00**	88.00	NS	NS
MK-0431					
1.0 mg/mL	86	3.00	3.00	0.6	0.6
1.2 mg/mL	80	NS			
1.4 mg/mL	77	NS			
1.6 mg/mL	59	2.50	2.50	0.4	1.8
1.7 mg/mL	48	2.50	3.00	0.2	1.4
1.8 mg/mL	31	NS			
1.9 mg/mL	0	NS			
2.0 mg/mL	Dead, discarded				
2.25 mg/mL	Dead, discarded				
2.50 mg/mL	Dead, discarded				
Without S-9 (3-Hour Treatment)					
Water, acidified (5%)	100	2.00	2.00	NS	NS
Water, acidified (5%)	100	1.50	2.00	NS	NS
Mitomycin C (0.5 µM)	82	6.50	7.00	NS	NS
Mitomycin C (1.5 µM) ^d	67	34.00**	52.00	NS	NS
MK-0431					
0.6 mg/mL	95	1.00	1.50	NS	NS
0.8 mg/mL	91	NS			
1.0 mg/mL	89	NS			
1.2 mg/mL	83	NS			
1.4 mg/mL	82	3.00	4.00	NS	NS
1.6 mg/mL	62	1.50	1.50	NS	NS
1.8 mg/mL	37	NS			
2.0 mg/mL	Dead, discarded				
2.25 mg/mL	Dead, discarded				
2.50 mg/mL	Dead, discarded				

Chromosomal Aberration and Cytotoxicity at 20-Hr (Short-Term) without S9 (Sponsor's Table)

Treatment	Cell Growth (PD, % Control)	% Aberrant Cells	Frequency Abs per 100 Cells ^a	% Endos ^b	% Polys ^c
Without S-9 (20-Hour Treatment)					
Water, acidified (5%)	100	1.00	1.00	0.0	1.4
Water, acidified (5%)	100	1.00	1.00	0.0	1.4
MK-0431					
0.4 mg/mL	91	2.00	2.00	0.0	1.2
0.5 mg/mL	87	NS			
0.6 mg/mL	82	NS			
0.7 mg/mL	78	NS			
0.8 mg/mL	72	NS			
0.9 mg/mL	60	2.00	2.50	0.0	11.8
1.0 mg/mL	45	1.00	1.00	0.4	13.8
1.1 mg/mL	30	NS			
1.2 mg/mL	25	NS			

PD = Population doubling.
NS = Not scored.
Water, Acidified = 0.1 mM HCl in Water, pH about 4.0.
Cyclophosphamide (CP) and Mitomycin C (MMC) are positive controls.
^a The total number of aberrations per 100 cells, since a cell may have more than one aberration.
^b The number of endoreduplicated metaphases based on 500 cells.
^c The number of polyploid metaphases based on 500 cells.
200 cells scored for aberrations per point except where noted.
^d 50 cells scored for aberrations.
^e 25 cells scored for aberrations.
*** A positive point that is statistically significant $p \leq 0.01$ compared to the relevant control group using a one-sided Fisher's exact test and is also outside the historical solvent control range.

CHO Cells Historical Controls: Frequency of Polyploidy in Negative and Solvent Controls (Studies from TT #03-8684 to TT #09-8623) (Sponsor's Table)

	With S-9	Without S-9
Combined mean percent \pm standard deviation:	2.85 \pm 1.89	2.23 \pm 1.43
Number of cultures scored ^a :	112	159
Range for individual cultures:	0.00 to 9.00	0.00 to 7.00
<u>With and Without S-9</u>		
Overall mean percent \pm standard deviation:	2.49 \pm 1.66	
Total cells scored:	135000	
Total polyploid metaphases:	3357	
Overall range for individual cultures:	0.00 to 9.00	

^a 500 cells are typically scored per culture.

8 Carcinogenicity

No carcinogenicity studies were conducted for this 505(b)(2) submission for MK-0431A XR. The carcinogenicity of sitagliptin and metformin, individually, were each previously established in two rodent species (mouse and rat) as discussed in the approved labels for Jamumet[®] (sitagliptin/metformin IR FDC) and Glumetza[®] (metformin XR). Only sitagliptin in the rat was associated with neoplastic findings (i.e., liver adenoma/carcinoma) for which a NOEL was established (20X MHRD of 100 mg/day; based on AUC).

Sitagliptin

According to the approved label for Jamumet[®] (sitagliptin/metformin IR FDC):

A two-year carcinogenicity study was conducted in male and female rats given oral doses of sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of combined liver adenoma/carcinoma in males and females and of liver carcinoma in females at 500 mg/kg. This dose results in exposures approximately 60 times the human exposure at the maximum recommended daily adult human dose (MRHD) of 100 mg/day based on AUC comparisons. Liver tumors were not observed at 150 mg/kg, approximately 20 times the human exposure at the MRHD. A two-year carcinogenicity study was conducted in male and female mice given oral doses of sitagliptin of 50, 125, 250, and 500 mg/kg/day. There was no increase in the incidence of tumors in any organ up to 500 mg/kg, approximately 70 times human exposure at the MRHD.

Metformin

According to the label for Glumetza[®] (metformin XR):

Long-term carcinogenicity studies have been performed in Sprague Dawley rats at doses of 150, 300, and 450 mg/kg/day in males and 150, 450, 900, and 1200 mg/kg/day in females. These doses are approximately 2, 4, and 8 times in males, and 3, 7, 12, and 16 times in females of the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female rats. A carcinogenicity study was also performed in Tg.AC transgenic mice at doses up to 2000 mg applied dermally. No evidence of carcinogenicity was observed in male or female mice.

9 Reproductive and Developmental Toxicology

No nonclinical reproductive toxicology studies were conducted for this 505(b)(2) submission for MK-0431A XR. The reproductive and developmental toxicity of sitagliptin and metformin, which were previously established separately, are discussed in the approved labels for Jamumet[®] (sitagliptin/metformin IR FDC) and Glumetza[®](metformin XR). The proposed Pregnancy Category B labeling for MK-0431A XR is based on the pregnancy category B classification of both sitagliptin and metformin.

Sitagliptin

Sitagliptin is classified in Pregnancy Category B based on a series of reproductive toxicity studies in rats and rabbits. According to the approved label for Janumet[®] (sitagliptin/metformin IR FDC):

Reproduction studies have been performed in rats and rabbits. Doses of sitagliptin up to 125 mg/kg (approximately 12 times the human exposure at the maximum recommended human dose) did not impair fertility or harm the fetus. There are, however, no adequate and well-controlled studies with sitagliptin in pregnant women.

Sitagliptin administered to pregnant female rats and rabbits from gestation day 6 to 20 (organogenesis) was not teratogenic at oral doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), or approximately 30 and 20 times human exposure at the maximum recommended human dose (MRHD) of 100 mg/day based on AUC comparisons. Higher doses increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100 times human exposure at the MRHD.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 decreased body weight in male and female offspring at 1000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats.

Placental transfer of sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours postdose. Placental transfer of sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.

Metformin

Metformin is classified in Pregnancy Category B based on a series of reproductive toxicity studies in rats and rabbits. According to the approved label for Glumetza[®] (metformin XR):

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.

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma.

10 Special Toxicology Studies

In support of this 505(b)(2) submission for MK-0431A XR, a 3-month oral toxicity study in rats was conducted with sitagliptin to qualify two sitagliptin (b) (4) degradation products.

Three-Month Oral Toxicity Study in Rats (TT #09-1239)

Study #	09-1239
Study Report Location	EDR
Conducting Laboratory and Location	Merck Research Laboratories West Point, PA
Date of Study Initiation	28 October 2009
GLP Compliance	Yes
QA Statement	Yes
Drug, Lot #, and % Purity	MK-0431, L-000224715-010X023, 100 w% MK-0431, L-000224715-010X048, 99.24 w%

Key Study Findings

- The (b) (4) degradates of sitagliptin did not produce toxicity or changes in the toxicokinetics of sitagliptin.

Reviewer's Comments

The 60 mg/kg dose of sitagliptin is well below the NOAEL for treatment-related toxicity in the rat. Therefore, no treatment-related toxicity was expected. Exposure at this dose is approximately 6-fold higher than therapeutic exposure, based on AUC.

Methods

Doses	60 mg/kg
Frequency of Dosing	Daily
Route of Administration	Oral gavage
Dose Volume	5mL/kg
Formulation/Vehicle	0.5% (w/v) Methylcellulose with 5 mM hydrochloric Acid in deionized water
Species/Strain	Rat, Sprague-Dawley, CrI:CD(SD)
Number/Sex/Group	10/sex/group
Age	5 weeks
Weight	Females: 109.3-129.6 g Males: 130.1-156.0 g
Unique Study Design	MK-0431 (L-000224715-010X048) was spiked with [REDACTED] (b) (4) [REDACTED] degradates.
Deviation from Study Protocol	None

Observations Times and Results**Mortality**

Daily observations with less frequent examinations on weekends and holidays.

There were no unscheduled deaths.

Clinical Signs

Daily observations with less frequent examinations on weekends and holidays.

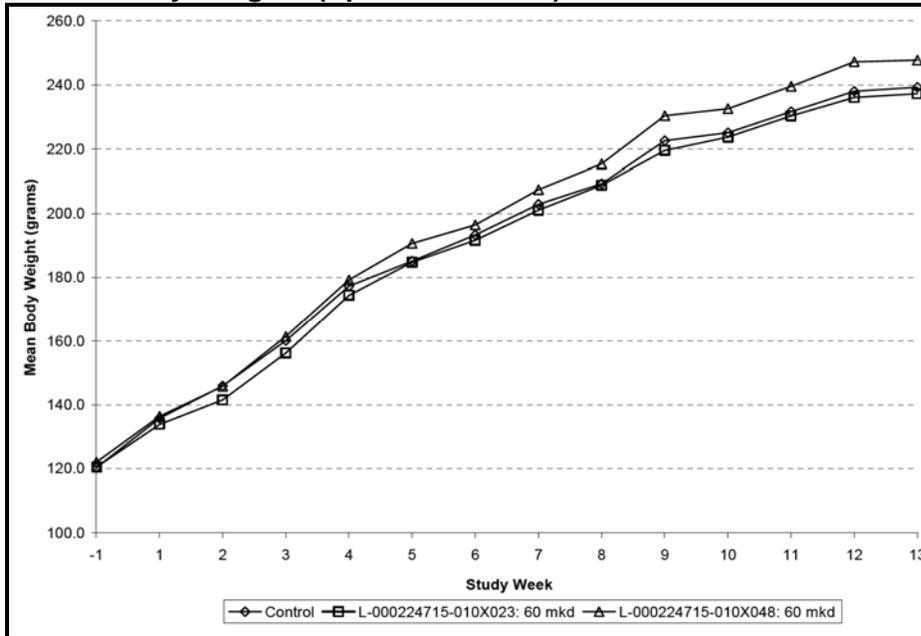
There were no test article-related physical sign findings.

Body Weights

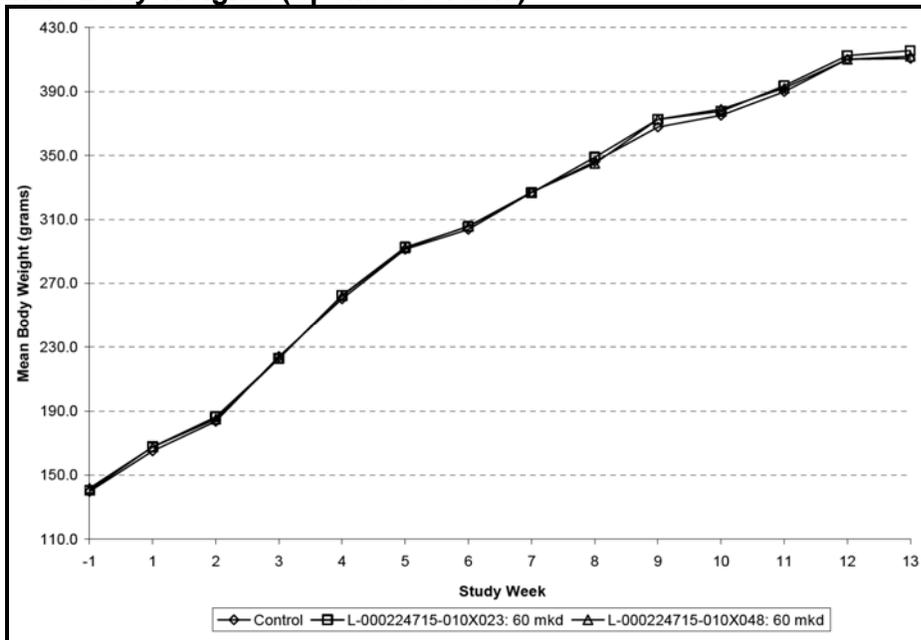
Pretest and once weekly during dosing (Weeks 1-13).

There were no test article-related body weight changes.

Female Body Weights (Sponsor's Table)



Male Body Weights (Sponsor's Table)



Food Consumption

Twice weekly.

There were no changes in food consumption considered test article-related.

Ophthalmoscopy

Weeks 4 and 12; indirect ophthalmoscopy and slit lamp biomicroscopy; control and Group 3 animals only.

There were no test-article related ophthalmic findings.

Hematology

Weeks 4 and 12; fasted overnight.

There were no test-article related hematologic changes.

Clinical Chemistry

Weeks 4 and 12; fasted overnight.

There were no test-article related clinical chemistry changes.

Urinalysis

Week 12; overnight urine collections.

There were no test article-related urinalysis findings.

Gross Pathology

All animals at scheduled necropsies.

There were no test article-related gross findings.

Organ Weights

All animals at scheduled necropsies; expressed as absolute weight, weight as a percent of body weight, and weight as a percent of brain weight.

There were no test article-related changes in organ weight.

Histopathology

Control and L-000224715-010X048 groups at scheduled necropsies.

There were no test article-related changes in histopathological changes.

Toxicokinetics

There was no difference in mean systemic exposure (AUC_{0-24h}) and mean C_{max} values between the lots L-000224715-010X023 and L-000224715-010X048 in Study Week 13.

MK-0431 (mg/kg/day) ^a	Sex	$AUC_{0-24\text{ hr}}$ ($\mu\text{M}\cdot\text{hr}$)	C_{max} (μM)	T_{max} (hr)
60*	Female	50.8 ± 2.79	14.1 ± 3.15	0.50 ± NC
	Male	67.8 ± 3.62	13.2 ± 0.0768	2.0 ± NC
	All	59.3 ± 3.06	13.4 ± 1.61	0.50 ± NC
60**	Female	51.0 ± 1.97	12.1 ± 1.77	0.50 ± NC
	Male	66.6 ± 4.32	17.3 ± 1.34	0.50 ± NC
	All	58.8 ± 2.93	14.7 ± 1.54	0.50 ± NC

11 Integrated Summary and Safety Evaluation

This is a 505(b)(2) application for the fixed dose combination (FDC) drug product of sitagliptin and extended release (XR) formulation of metformin hydrochloride (MK-0431A XR) for the treatment of patients with type 2 diabetes mellitus (T2DM). This 505(b)(2) application relies primarily on the Agency findings of the safety and efficacy as reflected in the approved product labels for Janumet[®] (sitagliptin/metformin IR FDC) and Glumetza[®] (metformin XR), which are both approved for chronic use. No nonclinical studies were conducted with MK-0431A XR in support of this application. The only nonclinical studies conducted in support of this application were a 3-month toxicity study in rats and two *in vitro* genotoxicity studies (microbial mutagenesis assay and chromosomal aberration assay) to qualify the sitagliptin (b) (4) degradate at the proposed limit of (b) (4) which exceeds the qualification threshold (ICH Q3B(R2)). No nonclinical pharmacology, ADME/PK, or toxicology studies were conducted with the FDC of sitagliptin and metformin XR (MK-0431A XR). The sponsor bridged the existing safety and efficacy data from studies with sitagliptin (Januvia[®]), metformin XR (Glumetza[®]) and the combination of sitagliptin and metformin IR (Januvia[®] and Janumet[®] programs) to MK-0431A XR by demonstrating the bioequivalence of MK-0431A XR and the co-administration of sitagliptin and metformin XR (Glumetza[®]) in clinical pharmacology studies.

Pharmacology

Sitagliptin and meformin XR are approved oral antihyperglycemic agents. Sitagliptin is a selective dipeptidyl peptidase IV (DPP-4) inhibitor that protects the incretin peptides glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) from enzymatic degradation by DPP-4. This increases the circulating levels of active forms of GLP-1 and GIP, which increases insulin synthesis and release from pancreatic beta cells and lowers glucagon secretion from pancreatic alpha cells. Metformin suppresses hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin has also been reported to increase GLP-1 concentrations (Drucker et al., 2006; Godarzi et al., 2005; Holst et al., 2008; Migoya et al., 2010).

ADME/PK

The nonclinical ADME properties and pharmacokinetics (PK) of sitagliptin and metformin XR, individually, were previously established.

Toxicology

No toxicology studies were conducted with MK-0431A XR for this 505(b)(2) submission. The potential toxicity of sitagliptin co-administered with metformin was previously evaluated in dogs in a 3-month study under NDA 22-044. Co-administration of sitagliptin (2-50 mg/kg; ~10-300 $\mu\text{M}\cdot\text{h}$ [AUC]) and a 20 mg/kg dose of metformin (~200-300 $\mu\text{M}\cdot\text{h}$ [AUC]) resulted in no deaths and yielded no evidence of exacerbated toxicity. However, the co-administration of sitagliptin (2-50 mg/kg; ~10-300 $\mu\text{M}\cdot\text{h}$ [AUC]) and a higher dose of metformin (50 mg/kg; ≥ 400 $\mu\text{M}\cdot\text{h}$) did result in more numerous and earlier deaths than observed with metformin alone. As metformin exposure following repeat dosing (7 days) with MK-0431A XR (100 mg metformin XR/2000 mg sitagliptin) was ~122 $\mu\text{M}\cdot\text{h}$, there is no concern regarding exacerbated toxicity associated with MK-0431A XR.

The reproductive toxicity, genotoxicity, and carcinogenicity studies described in the approved labeling for Janumet[®] (sitagliptin/metformin IR FDC) and Glumetza[®] (metformin XR) support the chronic administration of MK-0431A XR.

Only sitagliptin in the rat was associated with neoplastic findings (i.e., liver adenoma/carcinoma) for which a NOEL was established (20X MHRD of 100 mg/day; based on AUC).

Both reference listed drug labels carry Pregnancy Category 'B' labeling warranting the recommendation of Pregnancy Category 'B' for MK-0431A XR.

The sponsor conducted a 3-month toxicity study in rats and two *in vitro* genotoxicity studies (microbial mutagenesis assay and chromosomal aberration assay) to qualify (b) (4) (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)). Microbial mutagenesis and *in vitro* chromosomal aberration assays using an (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/m²) dose of sitagliptin with and without the two (b) (4) degradation products (b) (4) (b) (4) showed that the (b) (4) degradates had no toxicologic effect. Given the proposed limit of (b) (4) for the (b) (4) degradate of sitagliptin (b) (4) degradate not identified in drug product), the maximum recommended clinical dose of 100 mg/day (1.67 mg/kg; 62 mg/m²) would be associated with not more than (NMT) (b) (4) of the (b) (4) degradate. As this is approximately (b) (4) less than the (b) (4) degradate level assessed in the 3-month toxicity study in rats, this level 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) using a sitagliptin batch containing (b) (4) degradation products support the (b) (4) limit for the (b) (4) degradation product of sitagliptin.

12 References

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Goodarzi MO, Bryer-Ash M. Metformin revisited: re-evaluation of its properties and role in the pharmacopoeia of modern antidiabetic agents. *Diabetes Obes Metab.* 2005;7(6):654-65.

Holst JJ, Deacon CF, Vilsbøll T, Krarup T, Madsbad S. Glucagon-like peptide-1, glucose homeostasis and diabetes. *Trends Mol Med.* 2008;14:161-8.

Migoya EM, Bergeron R, Miller JL, Snyder RN, Tanen M, Hilliard D, Weiss B, Larson P, Gutierrez M, Jiang G, Liu F, Pryor KA, Yao J, Zhu L, Holst JJ, Deacon C, Herman G, Thornberry N, Amatruda J, Williams-Herman D, Wagner JA, Sinharoy R. Dipeptidyl peptidase-4 inhibitors administered in combination with metformin result in an additive increase in the plasma concentration of active GLP-1. *Clin Pharmacol Ther.* 2010;88(6):801-8.

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/s/

PATRICIA M BRUNDAGE
05/23/2011

TODD M BOURCIER
05/23/2011
I concur. P/T recommends AP

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202270 **Applicant:** Merck

Stamp Date: 23 Sept 2010

Drug Name: MK-0431A XR **NDA/BLA Type:** NDA 505(b)(2)

Based on the ICH Guidance M3 (R2) and agreement from the FDA, the toxicology data previously submitted to support the NDAs for the FDC of sitagliptin and metformin immediate release (IR) formulation (JANUMET™; Merck; NDA 22-044) and metformin hydrochloride extended release (XR) tablets (GLUMETZA™; Depomed, Inc.; NDA 21-748) support the NDA for MK-0431A XR. A 3-month oral toxicity study in rats, a microbial mutagenesis assay, and an *in vitro* chromosomal aberration assay were conducted with sitagliptin (MK-0431) to support the qualification of two (b)(4) degradation products.

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		No nonclinical studies with the combination of sitagliptin and extended-release metformin were required to support registration (EOP2).
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		The proposed labeling sections relative to pharmacology/toxicology are identical to the current JANUMET™ label.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		To support the qualification of two (b) (4) degradation products (b) (4) of MK-0431, a 3-month oral toxicity study in rats, a microbial mutagenesis assay, and an <i>in vitro</i> chromosomal aberration assay were conducted. The studies appear to support a (b) (4) (w/w) specification for each degradation product.
11	Has the applicant addressed any abuse potential issues in the submission?	n/a		Abuse of either component is not expected.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	n/a		

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

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/s/

PATRICIA M BRUNDAGE
11/04/2010

TODD M BOURCIER
11/04/2010
NDA fileable for pharm/tox