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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)

[redacted]

2 Drug Information

2.1 Drug

CAS Registry Number

Sitagliptin Phosphate: 16676-29-2

Simvastatin: 79902-63-9

Code Name

Sitagliptin Phosphate: MK-0431, L-000224715

Simvastatin: MK-0733

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

Simvastatin:

- [1S-[1a,3a,7β,8β(2S*,4S*),8aβ]]-1,2,3,7,8,8a-Hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl-2,2-dimethylbutanoate
- Butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a,hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester,[1S-[1a,3a,7β,8β(2S*,4S*), -8aβ]] (USP)
- 2,2-dimethylbutyric acid, 8-ester with (4R,6R)-6-[2-[(1S,2S,6R,8S,8aR)-1,2,6,7,8,8a-hexahydro-8-hydroxy-2,6-dimethyl-1-napthyl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one
- (1S,3R,7S,8S,8aR)-8-[2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8ahexahydronaphthalen-1-yl 2,2,-dimethylbutanoate (Ph. Eur.)

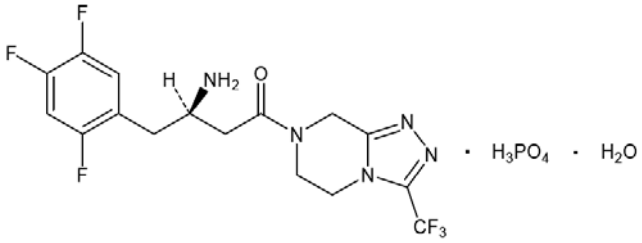
Molecular Formula/Molecular Weight

Sitagliptin Phosphate: $C_{16}H_{15}F_6N_5O \cdot H_3O_4P \cdot H_2O$/523.32

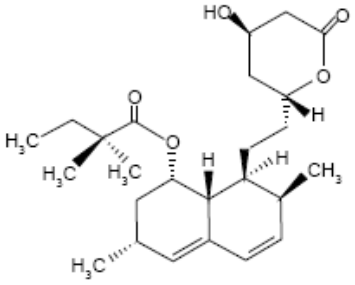
Simvastatin: $C_{25}H_{38}O_5$/418.57

Structure or Biochemical Description

Sitagliptin Phosphate:



Simvastatin:



Pharmacologic Class

Sitagliptin is dipeptidyl peptidase 4 inhibitor (DPP4 inhibitor); an anti-hyperglycemic agent.

Simvastatin is a competitive inhibitor of hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase.

2.2 Relevant NDAs and DMFs

NDA 21-995 (Januvia®; sitagliptin phosphate; Merck)
NDA 19-766 (Zocor®; simvastatin; Merck)

2.3 Drug Formulation

The FDC tablets consist of a bilayer configuration in which each layer is an immediate-release (IR) formulation of each drug. For initial registration, three tablet strengths of the FDC drug product have been developed:

- Sitagliptin/simvastatin 100 mg/10 mg
- Sitagliptin/simvastatin 100 mg/20 mg
- Sitagliptin/simvastatin 100 mg/40 mg

Each drug substance is an active ingredient of an approved drug product and is manufactured using the same chemistry, manufacturing, and controls as for its respective approved single-entity drug. The bilayer tablet is coated with an (b) (4) film coat.

Drug Product Unit Composition (Sponsor's Table)

Components	Compendial Testing	Function	Unit Strength (mg) Sitagliptin/Simvastatin 100 mg/10 mg	100 mg/20 mg	100 mg/40 mg	100 mg/80mg[1]
Sitagliptin Layer						
MK-0431	-	Active	128.5	128.5	128.5	(b) (4)
Dibasic calcium phosphate	USP / Ph. Eur.				(b) (4)	
Microcrystalline cellulose	NF / Ph. Eur.					
Croscarmellose sodium	NF / Ph. Eur.					
Sodium stearyl fumarate	NF / Ph. Eur.					
Magnesium stearate	NF / Ph. Eur.					
Simvastatin Layer						
(b) (4)		Active	10.00	20.00	40.00	
Butylated hydroxyanisole (BHA)	NF / Ph. Eur.				(b) (4)	
Ascorbic acid	USP / Ph. Eur.					
Citric acid monohydrate	USP / Ph. Eur.					
Lactose monohydrate	NF / Ph. Eur.					
(b) (4) starch	NF / Ph. Eur.					
(b) (4)	NF / Ph. Eur.					
	NF / Ph. Eur.					
	-					
	USP / Ph. Eur.					
Total Tablet Weight			518.3	622.4	827.6	
						(b) (4)

[1] Will not be marketed.

2.4 Comments on Novel Excipients

All excipients are compendial grade with the exception of the (b) (4)

(b) (4)

MK-0431D Excipients (Sponsor's Table)

Excipient	Reference‡
Dibasic calcium phosphate	USP-NF, Ph. Eur.
Microcrystalline cellulose	USP-NF, Ph. Eur.
Croscarmellose sodium	USP-NF, Ph. Eur.
Sodium stearyl fumarate	USP-NF, Ph. Eur.
Magnesium stearate (b) (4)	USP-NF, Ph. Eur.
(b) (4)	USP-NF, Ph. Eur.
Butylated hydroxyanisole (BHA)	USP-NF, Ph. Eur.
Ascorbic acid	USP-NF, Ph. Eur.
Citric acid monohydrate	USP-NF, Ph. Eur.
Lactose monohydrate	USP-NF, Ph. Eur.
Pre-gelatinized corn starch (b) (4)	USP-NF, Ph. Eur.

‡ Compendial testing will be performed according to at least one of the compendia listed as applicable for the target market.

Film-Coating Excipients for (b) (4) (Sponsor's Table)

Film-Coating Ingredients	Reference
polyvinyl alcohol – (b) (4)	USP-NF, Ph. Eur.
polyethylene glycol (b) (4)	USP-NF, Ph. Eur.
talc	USP-NF, Ph. Eur.
titanium dioxide	USP-NF, Ph. Eur.
iron oxide yellow	USP-NF, CFR 73.1200, E172
iron oxide red	USP-NF, CFR 73.1200, E172
iron oxide black	CFR 73.1200, E172

2.5 Comments on Impurities/Degradants of Concern

Impurities
Information on the characterization of impurities for sitagliptin and simvastatin are provided in NDA 21-995 and NDA 29-766, respectively.

Degradants
Acceptance criteria were established for individual and total degradates of sitagliptin and simvastatin in MK-0431D FDC tablets based on potential contributions from the drug substance, manufacture of drug product, and predicted increase given the 12-month formal stability studies (FSS) results of the drug product.

Sitagliptin
A limit of NMT (b) (4) was established for individual unspecified degradates of sitagliptin in MK-0431D FDC tablets, which meets the ICH Q3B(R2) identification threshold based on the maximum daily clinical dose of sitagliptin (100 mg sitagliptin). Although not observed in the FSS (through 52 weeks at the long term storage condition of 25°C/60% RH and through 26 weeks at the accelerated storage condition of 40°C/75% RH), a (b) (4) was identified as a potential degradant. While no limit for this (b) (4) is proposed, there is no notable toxicological concern regarding this potential degradant.

(b) (4)

Simvastatin
Release and shelf life criteria were established for the simvastatin degradation products. The main mode of degradation for simvastatin is oxidation and hydrolysis. The identified degradates include (b) (4) Single unspecified degradation products are specified at NMT (b) (4) (release and end of shelf life criteria), which is in accordance with the ICH Q3B(R2).

Simvastatin Degradation Products: Proposed Release and Shelf Specifications (Sponsor's Table)

(b) (4)

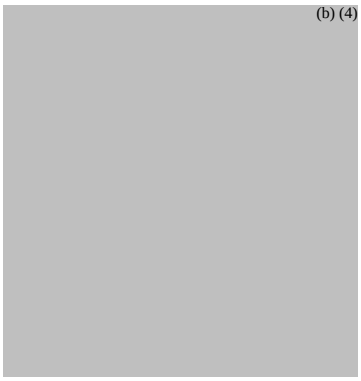
(b) (4)

The proposed release and shelf life limits for the degradants (b) (4) and (b) (4) meet the ICH Q3B(R2) qualification threshold based on the maximum daily clinical dose of simvastatin (40 mg simvastatin).

(b) (4) Probe stability studies performed during formulation development revealed the formation of the (b) (4) when the drug product was stored at accelerated temperature and humidity conditions. The proposed release specification is NMT (b) (4). According to the sponsor, a (b) (4) level for the highest sitagliptin/simvastatin tablet strength of 100 mg/40 mg, when reported against a simvastatin reference standard, corresponds to (b) (4). Relative to the combined amount of sitagliptin and simvastatin, a (b) (4) level in these tablets corresponds to an actual degradate level of (b) (4); see sponsor's calculation adjustment for the (b) (4) level below. The proposed shelf-life specification for the (b) (4) which is the growth anticipated over the proposed (b) (4) shelf life and allows for method variability. At the proposed shelf life specification of NMT (b) (4) the sponsor calculated the actual (b) (4) level for the highest sitagliptin/simvastatin tablet strength of 100 mg/40 mg to be (b) (4) based on the sum of both activities (sitagliptin and simvastatin). Thus, the actual degradate levels of the (b) (4), which are less than (b) (4) do not exceed the ICH Q3B(R2) qualification threshold of NMT 0.2%.

Sponsor's Calculation Adjustment for (b) (4) Level at NMT (b) (4) (Release Specification)

- Mass of (b) (4) based on simvastatin working standard (100% label claim = 40 mg) = (b) (4) * 40 mg = (b) (4)
- Actual level of (b) (4) based on sum of both actives (sitagliptin + simvastatin) = (b) (4)/(100+40) mg = (b) (4)



2.6 Proposed Clinical Population and Dosing Regimen

The MK-0431D is intended for the treatment of patients with T2DM and hypercholesterolemia. Doses of 100 mg/10 mg, 100 mg/20 mg, and 100 mg/40 mg (sitagliptin/simvastatin) should be taken as a single daily dose in the evening, with or without food.

2.7 Regulatory Background

Sitagliptin was approved in 2006 as an oral anti-hyperglycemic agent to improve glycemic control in adults with T2DM. The recommended dose is 100 mg once daily.

Simvastatin was approved in 1991 as oral hypocholesterolemic agent. It is currently indicated to reduce cardiovascular (CV) events/deaths in patients at high risk of CV events (e.g., diabetes, CHD, etc) and to reduce high cholesterol associated with a variety of conditions. Simvastatin is available at doses of 5 mg (starting dose for patients with severe renal impairment and patients on cyclosporine or danazol), 10 mg, 20 mg, 40 mg, and 80 mg. For adults, the recommended starting dose is 20-40 mg/day. In adolescents (10-17 years of age) with heterozygous familial hypercholesterolemia, the recommended dosing range is 10-40 mg/day.

Extensive clinical experience exists for both drugs.

3 Studies Submitted

3.1 Studies Reviewed

The nonclinical safety and efficacy of sitagliptin and simvastatin, individually, has been fully evaluated for chronic administration under NDA 21-995 (Januvia®; sitagliptin; Merck) and NDA 19-766 (Zocor®; simvastatin; Merck). The sponsor conducted a 3-month oral toxicity study in the rat with co-administration of sitagliptin and simvastatin to determine (1) the potential toxicity and toxicologic interaction and toxicokinetic profile of co-administration of sitagliptin and simvastatin, and (2) the toxicokinetic profile of L-654969 (an active metabolite of simvastatin [simvastatin acid]).

No *a priori* safety concern stemming from the combined mechanisms of action for sitagliptin and simvastatin.

Possible drug-drug interactions addressed in clinical studies.

No preclinical reproductive studies with the FDC were required as simvastatin carries pregnancy category X labeling, which will be applied to the FDC product.

Sponsor conducted a 3-month oral toxicity study in the rat with the co-administration of sitagliptin and simvastatin to determine (1) the potential toxicity and toxicologic interaction and toxicokinetic profile of co-administration of sitagliptin and simvastatin, and (2) the toxicokinetic profile of L-654969 (an active metabolite of simvastatin [simvastatin acid]).

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

None.

4 Pharmacology

4.1 Primary Pharmacology

No pharmacology studies were conducted for this submission for MK-0431D. The pharmacology of sitagliptin and simvastatin were previously established individually under NDA 21-995 (sitagliptin) and NDA 19-766 (simvastatin). For the FDC product MK-0431D, there were no *a priori* safety concerns stemming from the combined mechanisms of action for sitagliptin and simvastatin.

Mechanism of Action

Sitagliptin
According to the approved label for Januvia™ (sitagliptin):

> 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 insulinotropic 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.

Simvastatin
Simvastatin is a competitive inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA). This enzyme is the rate limiting step in cholesterol synthesis which catalyzes the conversion of HMG-CoA to mevalonic acid. Simvastatin treatment significantly reduces plasma levels of low-density lipoprotein cholesterol (LDL-C), and has beneficial effects on a variety of other lipid parameters, including triglycerides, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, and apolipoproteins B and A-I.

4.2 Secondary Pharmacology

No nonclinical secondary pharmacology studies were conducted for this submission for MK-0431D.

4.3 Safety Pharmacology

No nonclinical safety pharmacology studies were conducted for this submission for MK-0431D. The safety pharmacology of sitagliptin and simvastatin were previously established individually under NDA 21-995 (sitagliptin) and NDA 19-766 (simvastatin).

Sitagliptin
Safety assessment of neurological, renal, pulmonary, and gastrointestinal effects of sitagliptin did not identify any significant liability. Although sitagliptin clearly inhibits hERG potassium current *in vitro* at concentrations that markedly exceed human exposure, it does represents a potential cardiac conduction liability. No treatment-related changes in QT or other ECG interval were identified in telemetered dogs at doses up to 50 mg/kg.

Simvastatin
Simvastatin and its metabolite simvastatin acid are well tolerated in the human cardiovascular, respiratory and gastrointestinal systems in humans.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The pharmacokinetics/ADME of sitagliptin and simvastatin were previously established individually under NDA 21-995 (sitagliptin) and NDA 19-766 (simvastatin).

Sitagliptin
An oral dose of sitagliptin is rapidly absorbed. Sitagliptin is widely distributed in tissues with tissue concentration of the drug generally exceeding that in plasma except in the brain, eyes,

and bone. Sitagliptin is predominantly eliminated by renal mechanisms, but is also excreted in the feces via biliary secretion. Metabolism is minimal with unchanged material accounting for the major compound-related component in the plasma, urine and bile. Oxidative conversion is mediated primarily by CYP3A4 and secondarily by CYP2C8. No active human metabolites of sitagliptin have been identified. Sitagliptin does not appear to inhibit CYP450 enzymes nor induce CYP3A4. Sitagliptin is a p-glycoprotein and hOAT3 substrate, but does not interfere in the shuttling of other substrates via these transporters *in vitro.* Plasma protein binding is moderate (30%) and does not differ between species.

Simvastatin

Simvastatin is rapidly absorbed in rats, dogs and humans. Simvastatin is administered as the inactive lactone prodrug and is hydrolyzed in the plasma and liver to the ß-hydroxy acid form (simvastatin acid) for pharmacological activity. Simvastatin has low systemic bioavailability due to the extensive first-pass hepatic extraction and extensive biliary excretion. In rats, dogs, and humans, biliary excretion is the major route of elimination. Tissue distribution studies in mice, rats, and dogs indicate that simvastatin achieves relatively high concentrations in the liver. Simvastatin is extensively metabolized. At least eight metabolites are identified in the dog, rat and human. The simvastatin metabolites 6'-hydroxy, 3"-hydroxy, 6'-hydroxymethyl and 6'-carboxylic acid were active, and contribute to the pharmacological activity of simvastatin. CYP3A is the major enzyme responsible for simvastatin metabolism. Simvastatin and its active acid form are highly bound to plasma proteins, primarily to albumin (~95%). Protein binding is comparable in dog and man.

Nonclinical Co-administration of Sitagliptin and Simvastatin

The nonclinical toxicokinetics (AUC, Cmax, and Tmax) of sitagliptin, simvastatin, and simvastatin acid (L-654969; active simvastatin metabolite) were assessed in rats co-administered sitagliptin (180 mg/kg) and simvastatin (30 and 60 mg/kg) for 3 months as part of a toxicology study. Toxicokinetic findings are discussed in the General Toxicology section under the study.

3-Month Rat TK at Week 13 (Sponsor's Table)

	MK-0733/MK-0431 (mg/kg/day)											
	Control[c]		30/0		60/0		0/180		30/180		60/180	
	F	M	F	M	F	M	F	M	F	M	F	M
Number of Animals	10	10	10	10	10	10	10	10	10	10	10	10
Toxicokinetics – Drug Week 13, MK-0431[d]												
$AUC_{0\text{-}24\ hr}$ (µM•hr)	-	-	N/A	N/A	N/A	N/A	171	154	129	256	191	161
C_{max} (µM)	-	-	N/A	N/A	N/A	N/A	29.2	26.6	22.7	27.7	20.9	29.9
T_{max} (hr)	-	-	N/A	N/A	N/A	N/A	2.0	1.0	2.0	2.0	2.0	1.0
Toxicokinetics – Drug Week 13, MK-0733[e]												
$AUC_{0\text{-}24\ hr}$ (µM•hr)	-	-	0.851	0.237	1.60	0.609	N/A	N/A	0.347	0.254	1.68	0.686
C_{max} (µM)	-	-	0.550	0.121	0.583	0.154	N/A	N/A	0.0884	0.0629	0.192	0.278
T_{max} (hr)	-	-	0.50	0.50	2.0	1.0	N/A	N/A	2.0	0.50	0.50	0.50
Toxicokinetics – Drug Week 13, L-000654969[f]												
$AUC_{0\text{-}24\ hr}$ (µM•hr)	-	-	9.02	2.98	15.5	6.23	N/A	N/A	4.71	4.74	13.6	5.59
C_{max} (µM)	-	-	3.52	1.01	7.04	1.86	N/A	N/A	0.930	0.390	1.76	1.12
T_{max} (hr)	-	-	2.0	2.0	2.0	2.0	N/A	N/A	2.0	0.50	0.50	1.0

[a] MK-0431D = combination of MK-0733 (simvastatin)/MK-0431 (sitagliptin).
[c] Control animals were dosed with MK-0733 vehicle immediately followed by administration of MK-0431 vehicle.
[f] Drug concentrations in plasma from all control group animals for L-000654969 were below the LLQ of the bioanalytical method (LLQ = 0.011 µM).
- = No noteworthy findings.
N/A = Not Applicable.

The sponsor also conducted clinical studies to assess the pharmacokinetics and possible drug-drug interaction of the co-administration of sitagliptin and simvastatin.

6 General Toxicology

The nonclinical toxicology of sitagliptin and simvastatin were previously established individually under NDA 21-995 (sitagliptin) and NDA 19-766 (simvastatin). Sitagliptin-related toxicities in the mouse (kidney), rat (kidney, liver, heart, teeth, bone marrow, and lymph nodes), and dog occurred at very large multiples of clinical exposure; NOAELs with large safety factors were established for all toxicities. Simvastatin-related toxicities occurred in the liver (rat, rabbit and dog), skeletal muscle, nonglandular forestomach (rat only), CNS (dog only), and testes (dog only). Hepatotoxicity and skeletal muscle degeneration in nonclinical species occurred at doses similar to or moderately above clinical exposure. Simvastatin-related hepatotoxicity is characterized by morphologic changes in rats and rabbits, and transaminase elevations in dogs without a morphologic correlate. Simvastatin achieves relatively higher concentrations in liver, the target organ, relative to other tissues. The liver also is the site where interconversion between simvastatin (inactive lactone) and simvastatin acid occurs.

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 nonclinical study in rats co-administered sitagliptin and simvastatin to rule out possible interactions on the skeletal muscle or other potential interactions.

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

Study #	TT #09-1083
Study Report Location	EDR
Conducting Laboratory and Location	Merck Research Laboratories West Point, PA
Date of Study Initiation	25 March 2009
GLP Compliance	Yes
QA Statement	Yes
Drug, Lot #, and % Purity	MK-0733, L-000644128-000U222, 99.3% MK-0431, L-000224715-010X023, 100%

Key Study Findings

- Systemic exposure (AUC) for sitagliptin (180 mg/kg; 163-193 μM·h [AUC]) in this study provided ~20X safety margin over the AUC at the clinical dose of 100 mg/day (8.5 μM•hr [AUC]).
- The combined systemic exposure (AUC) simvastatin and simvastatin acid (active metabolite; L-654969) provided safety margins of ~20-66X (3-10 μM·h [AUC]) and ~47-114X (7-17 μM·h [AUC]) at doses of 30 mg/kg and 60 mg/kg simvastatin, respectively, based on a maximum clinical dose of 40 mg/day (0.15 μM•hr [AUC]).
- No adverse muscle or pancreas effects were observed in animals co-administered sitagliptin and simvastatin.
- Adverse liver effects (↑ ALT, ↑ liver weight [females], hepatocellular hypertrophy [females], and bile duct hyperplasia [males]) were associated with the high dose (HD) of simvastatin (60 mg/kg; 7-17 μM·h; ~47-113X MHRD). An increase in ALT levels and liver weight were also observed at both doses of simvastatin (≥30 mg/kg; 3-10 μM·h; ~33X MHRD) when co-administered with sitagliptin (180 mg/kg; 163-193 μM·h ~20X MHRD) suggesting a possible drug-drug interaction between sitagliptin and simvastatin with regards to liver toxicity.
- Treatment-related adverse nonglandular stomach effects (↑ wall thickness, acanthosis and/or hyperkeratosis of the mucosa, and inflammation) and thyroid effects (↑ thyroid

weight and follicular epithelial hypertrophy) were associated with the simvastatin HD (60 mg/kg; 7-17 μM·h; ~47-113X MHRD) and were not markedly affected by the co-administration of sitagliptin.
- Transient salivation was attributable to sitagliptin treatment. Excess salivation, which was previously associated with sitagliptin treatment in rats, was attributed to poor palatability of the drug.
- Sitagliptin systemic exposure was not affected co-administration of simvastatin. Interestingly, simvastatin (~3-6X ↓) and L-654969 (~2-4X ↓) exposures were lower in the animals co-administered the simvastatin low dose (LD; 30 mg/kg) and sitagliptin compared to those administered only the simvastatin LD. A similar effect was not observed with the HD of simvastatin.

Reviewer's Comments
- Although a NOAEL was not established for the treatment-related liver effects (↑ ALT and liver weight) associated with the co-administration of simvastatin and sitagliptin, potential treatment-related adverse liver effects are clinically monitorable. Additionally, the sponsor administered doses of sitagliptin and simvastatin that provided exposures ≥20 times the maximum clinical exposure, so it is possible that adverse liver effects may not occur at clinical exposures.
- The bile duct hyperplasia in males co-administered sitagliptin (180 mg/kg) and the simvastatin HD (60 mg/kg) is possibly due to the co-administration of the drugs as bile duct hyperplasia was previously observed in rats in studies conducted under NDA 21-995 (sitagliptin; 2-year study) and NDA 19-766 (simvastatin; 14-week study). However, the sponsor has established a NOEAL for the bile duct hyperplasia (30/180 mg/kg) with an adequate margin of safety (~20-66X MHRD; based on AUC).
- The following was the rationale for dose selection by the sponsor: *The HD of simvastatin (60 mg/kg) was anticipated to produce very slight or no skeletal muscle degeneration in rats following 3-month oral administration. The sitagliptin dose of 180 mg/kg was a NOEL when orally administered to rats for up to 6 months and was expected to provide ~20-fold exposure margin based on exposure at the clinical dose (100 mg; 8.5 μM•hr).* While the study results suggest that exacerbation of simvastatin-related skeletal muscle toxicity by sitagliptin is unlikely, administration of a higher simvastatin dose closer to that previously found to produce skeletal muscle degeneration (e.g., 180 mg/kg in the 14-week rat study) would have been optimal to better examine possible interactions of the two drugs on with regard to myotoxicity.

Doses	0, 30/0, 60/0, 0/180, 30/180, and 60/180 mg/kg (simvastatin[MK-0733]/sitagliptin[MK-0431])
Frequency of Dosing	Daily
Route of Administration	Oral gavage
Dose Volume	2.5 mL/kg
Formulation/Vehicle	MK-0733 vehicle: 0.5% methylcellulose in deionized water MK-0431 vehicle: 0.5% methylcellulose with 5 mM HCl in deionized water
Species/Strain	Rat, Sprague-Dawley, Crl:CD(SD)
Number/Sex/Group	10/sex/group
Age	5 weeks
Weight	Females: 109-141 g Males: 129-163 g
Unique Study Design	MK-0733 (or MK-0733 vehicle) was dosed first, followed immediately by administration of MK-0431 (or MK-0431 vehicle); control animals were dosed with MK-0733 vehicle immediately followed by administration of MK-0431 vehicle.
Deviation from Study Protocol	None

Observations Times and Results
Mortality
Daily observations with less frequent examinations on weekends and holidays.

All animals survived to scheduled termination.

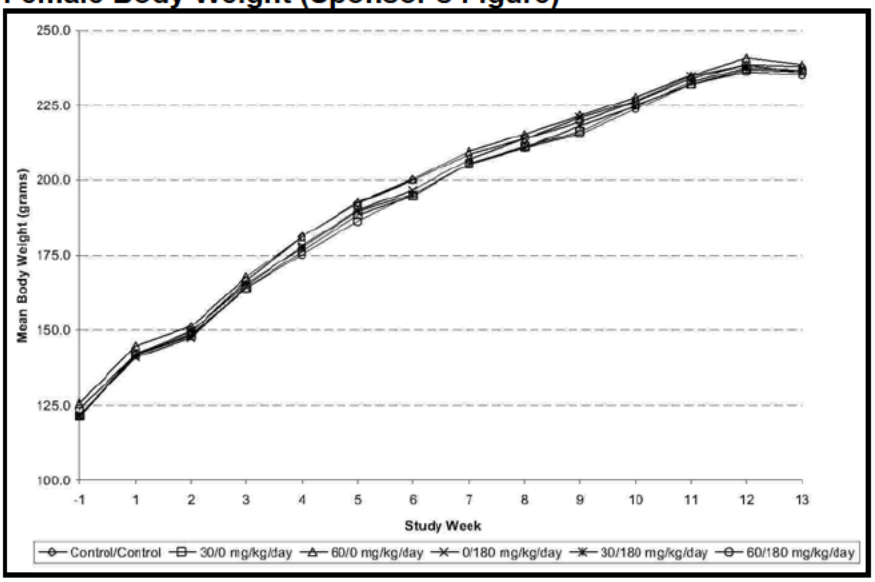
Clinical Signs
Daily observations with less frequent examinations on weekends and holidays.

There was treatment-related transient salivation (starting at Week 2 until termination) in all sitagliptin-treated groups (0/180, 30/180, and 60/180 mg/kg groups). This finding, which was noted in previous toxicology studies conducted NDA 21-995, was attributed to the poor palatability of the drug.

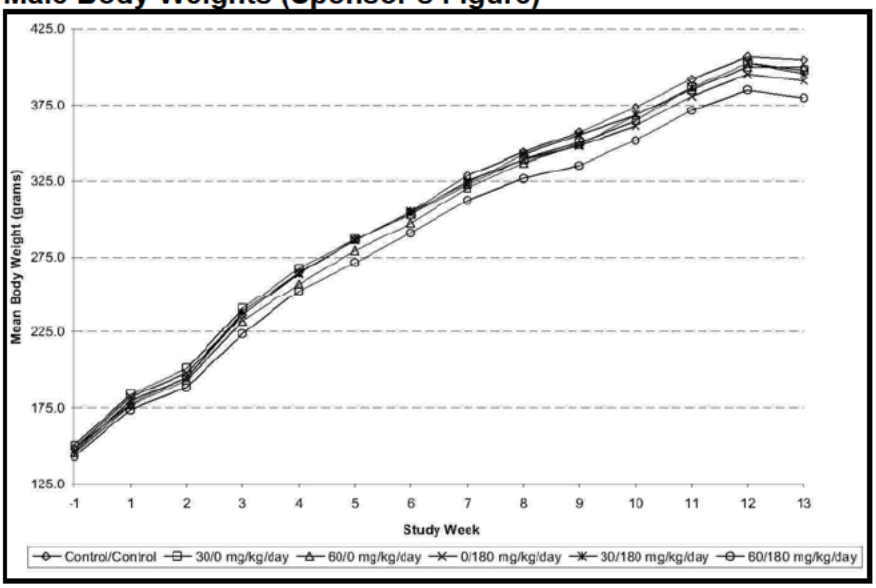
Body Weights
Pretest and once weekly during dosing (Weeks 1-13).

In males co-administered the HD of simvastatin and sitagliptin (60/180 mg/kg group), there was a slight decrease in body weight starting at Week 2 until termination. However, the overall decrease in weight gain was minimal in all groups.

Female Body Weight (Sponsor's Figure)



Male Body Weights (Sponsor's Figure)



Males		
Dose (mg/kg)	**BW Gain (g)**	**BW % Control/ % Decrement**
0	256.2	--
30/0	247.4	↓ 3%
60/0	254.8	↓ 1%
0/180	242.8	↓ 5%
30/180	249.4	↓ 3%
60/180	236.7	↓ 8%

Females		
Dose (mg/kg)	BW Gain (g)	BW % Control/ % Decrement
0	116.7	--
30/0	115	↓ 2%
60/0	112.9	↓ 3%
0/180	114.3	↓ 2%
30/180	115.5	↓ 1%
60/180	111	↓ 5%

Food Consumption
Twice weekly.

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

Ophthalmoscopy
Weeks 3 and 12; indirect ophthalmoscopy and slit lamp biomicroscopy. 30/0 group not examined

There were no test-article related ophthalmic findings.

Hematology
Weeks 4, 8, and 12; fasted overnight. Analysis of coagulation parameters at necropsy. Blood smears from animals in the control and HD groups were examined for cell morphology.

There were no test article-related hematological changes.

Clinical Chemistry
Weeks 4, 8, and 12; fasted overnight.

In males and females at Week 12, there was an increase in ALT in animals dosed at 60/0 mg/kg (2X ↑), 30/180 mg/kg (2X ↑), and 60/180 mg/kg (3X ↑) compared to controls. Although there were no treatment-related changes in ALT caused by sitagliptin administered alone (0/180 mg/kg group), ALT levels in the animals co-administered sitagliptin and simvastatin (30/180 and 60/180 mg/kg groups) were notably higher (~2X ↑) than in those administered simvastatin alone (30/0 and 60/0 mg/kg groups) suggesting the co-administration of the two drugs synergistically increase ALT. Moreover, there was an increase in ALT levels from Week 8 to Week 12 indicating that it is progressive with treatment.

There was also a slight increase in the A/G ratio and albumin (~1X) in females administered the simvastatin HD with and without sitagliptin (60/0 and 60/180 mg/kg). However, there was no marked increase in the A/G ratio or albumin level in animals co-administered sitagliptin and simvastatin compared to those administered the HD of simvastatin alone indicating that sitagliptin did not potentiate these simvastatin-related increases.

Liver Markers (Females)						
Dose (mg/kg)	Albumin (g/dl)		A/G Ratio		ALT (u/l)	
	Wk 8	Wk 12	Wk 8	Wk 12	Wk 8	Wk 12
0	3.7	3.7	1.7	1.5	31	34
30/0	3.9	4	1.6	1.8	34	30
60/0	4	4.2	2	1.8	41	66
0/180	3.8	4	1.7	1.6	33	31
30/180	3.8	4	1.7	1.7	43	57
60/180	4.1	4.4	2	1.9	77	116

Shaded values indicate $p < 0.05$ compared to control

Liver Markers (Males)						
Dose (mg/kg)	Albumin (g/dl)		A/G Ratio		ALT (u/l)	
	Wk 8	Wk 12	Wk 8	Wk 12	Wk 8	Wk 12
0	3.3	3.4	1.5	1.5	38	35
30/0	3.5	3.4	1.6	1.5	39	37
60/0	3.4	3.4	1.6	1.5	47	64
0/180	3.4	3.4	1.5	1.4	35	35
30/180	3.4	3.4	1.6	1.4	48	54
60/180	3.5	3.5	1.6	1.5	69	109

Shaded values indicate $p < 0.05$ compared to control

Urinalysis
Week 12; overnight urine collections. Volume, pH, specific gravity, protein, bilirubin, glucose, occult blood, ketones, and urinary sediment.

There were no test article-related urinalysis changes.

Gross Pathology
All animals at scheduled necropsies.

Increased wall thickness of the nonglandular stomach occurred in all dose groups administered simvastatin. In the groups co-administration of sitagliptin and simvastatin (HD and LD), there was an increased incidence of a thickened nonglandular stomach wall compared to those administered simvastatin alone. Increased wall thickness of the nonglandular stomach was previously observed in the rat in toxicology studies conducted under NDA 19-766 (simvastatin). The increase in the wall thickness of the nonglandular stomach corresponds with the histopathological finding of mucosal acanthosis/hyperkeratosis in the stomach in the groups administered the simvastatin HD with and without sitagliptin. While there was an increase in the incidence of the finding of wall thickness, there was no notable increase in the incidence of histopathological findings in the stomach.

Males and females administered the simvastatin HD with and without sitagliptin (60/180 and 60/0 mg/kg) had enlarged thyroids. This corresponds to the treatment-related increases in thyroid weight and follicular cell hypertrophy associated with simvastatin.

One female dosed at co-administered the simvastatin HD and sitagliptin had an enlarged liver.

Gross Pathology (Sponsor's Table)

	MK-0733/MK-0431 (mg/kg/day)											
	Control[c]		30/0		60/0		0/180		30/180		60/180	
	F	M	F	M	F	M	F	M	F	M	F	M
Number of Animals	10	10	10	10	10	10	10	10	10	10	10	10
Gross Pathology (Incidence)												
Liver												
Increased size	0	0	0	0	0	0	0	0	0	0	1	0
Thyroid												
Increased size	0	0	0	0	0	1	0	0	0	0	**3**	1
Decreased size	0	0	0	0	0	0	0	0	0	**1**	0	0
Stomach												
Focus	1	0	0	0	0	0	0	0	0	**1**	0	0
Reddened	0	0	0	0	0	1	0	0	0	0	0	0
Thickened wall	0	0	[1]	0	[4]	[4]	0	0	[10]	[5]	[8]	[9]

[a] MK-0431D combination of MK-0733 (simvastatin)/MK-0431 (sitagliptin).
[c] Control animals were dosed with MK-0733 vehicle immediately followed by administration of MK-0431 vehicle.
[ ] – Treatment-related change based on incidence and/or severity.

Organ Weights

All animals at scheduled necropsies; absolute weight, weight as a percent of body weight, and weight as a percent of brain weight. Adrenals, brain, heart, ovaries, kidneys, liver, pituitary, prostate, spleen, testes, thyroids, and thymus.

Liver

A dose-related increase in liver weight (16-48% ↑) occurred in females administered simvastatin with and without sitagliptin (60/0, 30/180, and 60/180 mg/kg); sitagliptin administered alone did not cause an increase in liver weight. In previous toxicology studies conducted under NDA 19-766, simvastatin caused a treatment-related increase in hepatic weight in female rats. The increase in liver weight when sitagliptin was co-administered with simvastatin (LD and HD) was slightly greater compared to the increase caused by simvastatin administered alone; however, the co-administration of the two drugs did caused a marked additional effect. The increase in liver weight in the females administered the simvastatin HD with and without sitagliptin corresponds to the histopathological finding of hepatocellular hypertrophy.

Thyroid

There was an increase in thyroid weight in males (25-33% ↑) and females (41-63% ↑) dosed at 60/0, 30/180, and 60/180 mg/kg; there was no increase in animals administered sitagliptin alone. The co-administration of the two drugs did not produce a marked additive effect on the increase in thyroid weight. An increase in thyroid weight was previously noted in female rats administered simvastatin in subchronic and chronic toxicity studies conducted under NDA 19-766. The histopathological finding of thyroid follicular epithelial hypertrophy associated with simvastatin treatment is consistent with the increase in thyroid weight.

Female: Organ Weights				
Dose (mg/kg)	Liver		Thyroid	
	Grams	% Br Wt	Grams	% Br Wt
0	6.1	314	0.02	0.92
30/0	7	363	0.02	1.1
60/0	8.2	408	0.03	1.3
0/180	7	365	0.02	0.92
30/180	7.8	397	0.03	1.4
60/180	8.9	465	0.3	1.5

Shaded values indicate $p < 0.05$ compared to control

Male: Organ Weights				
Dose (mg/kg)	Liver		Thyroid	
	Grams	% Br Wt	Grams	% Br Wt
0	10.5	518	0.03	1.2
30/0	10.2	499	0.03	1.3
60/0	10.6	519	0.03	1.6
0/180	11.6	573	0.02	1.2
30/180	10.9	541	0.03	1.3
60/180	10.7	527	0.03	1.5

Shaded values indicate $p < 0.05$ compared to control

Histopathology

Control and 60/180 mg/kg groups: refer to the table below
0/60 mg/kg group: stomach, thyroid gland, and liver
0/180 mg/kg group: liver
30/180 mg/kg group (males): liver
30/180 mg/kg (females) and 0/30 mg/kg groups: no organs/tissues examined

Histopathology Inventory (Sponsor's Table)

brain (including cerebral cortex, subcortical white matter, basal ganglia, thalamus, hippocampus, midbrain, cerebellum, and medulla oblongata)
spinal cord (cervical)
peripheral nerve (sciatic)
eye
optic nerve
pituitary
adrenals
thyroids
parathyroids
Harderian gland
salivary gland (submandibular/sublingual)
heart
aorta
skeletal muscle (quadriceps)
small intestine (duodenum, jejunum, and ileum)
Peyer's patches
esophagus
large intestine (colon and cecum)
stomach (glandular and nonglandular portions)
kidneys
urinary bladder
skin (from inguinal mammary region)
mammary gland
liver
lungs
trachea
spleen
thymus
prostate
seminal vesicles
lymph nodes (mesenteric and cervical)
pancreas
testes
epididymides
uterus
cervix
ovaries
vagina
bone (femur, tibia, and femorotibial joint)
bone marrow (in bone section)
Parathyroids, optic nerve, trachea, Peyer's patches, aorta, lymph nodes, and mammary gland (males) were evaluated when present in section.

Liver

Bile duct hyperplasia was observed only in males co-administered the simvastatin HD and sitagliptin (60/180 mg/kg). No bile duct hyperplasia was noted in the livers of males co-administered the simvastatin LD and sitagliptin (30/180 mg/kg); the livers of females co-administered the simvastatin LD and sitagliptin were not examined. Bile duct proliferation/hyperplasia was noted in previous toxicology studies in rats conducted under NDA 21-995 (sitagliptin; 2-year study) and NDA 19-766 (simvastatin; 14-week study). The possibility that the bile duct hyperplasia in the current in study is due to the co-administration of the sitagliptin and simvastatin cannot be discounted due to of its absence in concurrent controls. The NOAEL for bile duct hyperplasia is 30/180 mg/kg.

In females, hepatocellular hypertrophy was observed in animals administered the simvastatin HD with and without sitagliptin (60/0 and 60/180 mg/kg); hypertrophy was not observed in animals administered sitagliptin alone (0/180 mg/kg). There was no increase in the incidence or

severity of the finding with the co-administration of the two drugs. This finding also corresponds to the increase in liver weight in females in the two simvastatin HD groups; both appear to be due to simvastatin administration. Given that the livers of the females administered the simvastatin LD with and without sitagliptin (30/0 mg/kg and 30/180 mg/kg) were not examined, a NOAEL for hepatocellular hypertrophy cannot be established.

Stomach
Acanthosis and/or hyperkeratosis of the stratified squamous mucosa (slight-marked) and inflammation and rare focal to multifocal mucosal vesiculation and/or focal superficial erosions of the nonglandular mucosa were observed in animals administered the simvastatin HD with and without sitagliptin (60/180 and 60/0 mg/kg); the stomachs of animals administered sitagliptin alone (0/180 mg/kg) were not examined. Co-administration of sitagliptin did not markedly increase in incidence or severity of the simvastatin-related histopathological findings. These findings are consistent with those observed in the rat in toxicology studies conducted under NDA 19-766 (simvastatin). Although a NOAEL for these finding was not established as the stomachs of the animals administered the simvastatin LD (30/0 mg/kg and 30/180 mg/kg) were not examined, these findings in the nonglandular stomach related to simvastatin treatment were determined to be unique to this anatomical structure of the rodent.

Thyroid
Follicular epithelial cell hypertrophy was observed in males and females administered the simvastatin HD with and without sitagliptin (60/180 and 60/0 mg/kg); the thyroids of animals administered sitagliptin alone (0/180 mg/kg) were not examined. There was no increase in the incidence or severity of the finding with the co-administration of the two drugs. Follicular cell hyperplasitc/neoplastic lesions were observed in rats administered similar doses of simvastatin in chronic toxicology studies conducted under NDA 19-766. Given that the thyroids of animals administered the simvastatin LD (30/0 and 30/180 mg/kg) were not examined, a NOAEL for follicular epithelial cell hypertrophy was not established. However, the follicular cell hypertrophy in rats due to simvastatin treatment has been attributed to elevated thyroid-stimulating hormone (TSH) levels as a result of enhancement of thyroid hormone clearance (Smith et al., 1991). This toxicity profile seems to be species-specific and does not occur in humans (Wu and Farrelly, 2006).

Histopathology (Dosing)									
Tissue/ Finding	Severity	Male (mg/kg)				Female (mg/kg)			
		0	60/0	0/180	60/180	0	60/0	0/180	60/180
		10	10	10	10	10	10	10	10
Thyroid									
Follicular cell hypertrophy	Very Slight/ Slight		4	NE	2		8	NE	8
Stomach (Nonglandular Mucosa)									
Acanthosis	Slight		7	NE	9		7	NE	7
	Moderate		2	NE	1		2	NE	3
	Marked		1	NE				NE	
Hyperkeratosis	Slight		6	NE	9		7	NE	6
	Moderate		3	NE	1		2	NE	4
Inflammation	Slight		5	NE	5		1	NE	4
Liver									
Centrilobular hypertrophy	Slight						10		10
Bile duct hyperplasia	Slight				6				

NE: not examined

Toxicokinetics

Week 13; 0.5, 1, 2, 4, 8, and 24 hours postdose. Sitagliptin, simvastatin, and L-654969 were measured.

Both simvastatin and sitagliptin were rapidly absorbed in the plasma (0.5-2 h). The major active metabolite of simvastatin (simvastatin acid; L-654969) appeared rapidly in the plasma with mean maximum plasma concentrations by 0.5-2 hours postdose.

There were no significant sex differences in systemic exposure (AUC and Cmax) of sitagliptin. For simvastatin, the AUC and Cmax values of simvastatin and its metabolite L-654969 were generally higher (up to 3X) in females than in males. Plasma levels of L-654969 were also higher than simvastatin in all animals.

Simvastatin had no effect on sitagliptin mean systemic exposure (AUC) and peak plasma concentration. Exposure (AUC and Cmax values) to simvastatin and L-654969 were generally similar between groups administered simvastatin with and without sitagliptin except for animals administered the simvastatin LD (30/0 mg/kg and 30/180 mg/kg). Co-administration of the simvastatin LD and sitagliptin (30/180 mg/kg) decreased the systemic exposure (AUC) by ~3X in females compared to the simvastatin LD administered alone. Simvastatin peak exposure (Cmax) was also ~2-6X lower in animals (male and female) co-administered the simvastatin LD and sitagliptin (30/180 mg/kg) compared to those administered the simvastatin LD alone. Exposure (AUC and Cmax) to L-654969 was also lower (2-4X) in animals co-administered the simvastatin LD with sitagliptin.

Sitagliptin TK Parameters for MK-0431 (Sponsor's Table)

MK-0733/MK-0431 (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (μM•hr)	C_{max} (μM)	T_{max} (hr)
0/180	Female	171 ± 27.0	29.2 ± 3.39	2.0 ± NC
	Male	154 ± 8.16	26.6 ± 2.57	1.0 ± NC
	All	163 ± 13.8	27.5 ± 1.55	1.0 ± NC
30/180	Female	129 ± 11.0	22.7 ± 5.16	2.0 ± NC
	Male	256 ± 29.9	27.7 ± 8.29	2.0 ± NC
	All	193 ± 23.1	25.2 ± 4.62	2.0 ± NC
60/180	Female	191 ± 14.0	20.9 ± 4.13	2.0 ± NC
	Male	161 ± 20.5	29.9 ± 10.5	1.0 ± NC
	All	171 ± 15.7	22.6 ± 5.77	1.0 ± NC

NC = Not Calculated

Simvastatin TK Parameters for MK-0431 (Sponsor's Table)

MK-0733/ MK0431 (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (μM•hr)	C_{max} (μM)	T_{max} (hr)
30/0	Female	0.851 ± 0.207	0.550 ± 0.226	0.50 ± NC
	Male	0.237 ± 0.0306	0.121 ± 0.0147	0.50 ± NC
60/0	Female	1.60 ± 0.252	0.583 ± 0.130	2.0 ± NC
	Male	0.609 ± 0.123	0.154 ± 0.0215	1.0 ± NC
30/180	Female	0.347 ± 0.0645	0.0884 ± 0.0332	2.0 ± NC
	Male	0.254 ± 0.116	0.0629 ± 0.0117	0.50 ± NC
60/180	Female	1.68 ± 0.407	0.192 ± 0.0747	0.50 ± NC
	Male	0.686 ± 0.215	0.278 ± 0.121	0.50 ± NC

[a]Drug concentrations in plasma from all control group animals for simvastatin were below the LLQ of the bioanalytical method (LLQ = 0.012 μM).
NC = Not Calculated

L-654969 TK Parameters for MK-0431 (Sponsor's Table)

MK-0733/ MK0431 (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (μM•hr)	C_{max} (μM)	T_{max} (hr)
30/0	Female	9.02 ± 3.22	3.52 ± 2.09	2.0 ± NC
	Male	2.98 ± 0.373	1.01 ± 0.244	2.0 ± NC
60/0	Female	15.5 ± 2.73	7.04 ± 1.69	2.0 ± NC
	Male	6.23 ± 1.28	1.86 ± 0.645	2.0 ± NC
30/180	Female	4.71 ± 0.734	0.930 ± 0.235	2.0 ± NC
	Male	4.74 ± 1.83	0.390 ± 0.0487	0.50 ± NC
60/180	Female	13.6 ± 3.36	1.76 ± 0.895	0.50 ± NC
	Male	5.59 ± 1.17	1.12 ± 0.249	1.0 ± NC

[a]Drug concentrations in plasma from all control group animals for L-000654969 were below the LLQ of the bioanalytical method (LLQ = 0.011 μM).
NC = Not Calculated

7 Genetic Toxicology

No genotoxicity studies with the FDC of sitagliptin and simvastatin (MK-0431D) were conducted for this submission. The genetic toxicology of sitagliptin and simvastatin were previously

established individually under NDA 21-995 (sitagliptin) and NDA 19-766 (simvastatin). Neither sitagliptin nor simvastatin was found to be mutagenic or clastogenic.

Sitagliptin
According to the label for Januvia® (sitagliptin):

> 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.

Simvastatin
According to the labeling information for Zocor® (simvastatin):

> No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

8 Carcinogenicity

No carcinogenicity studies with the FDC of sitagliptin and simvastatin (MK-0431D) were conducted for this submission. The carcinogenic potential of sitagliptin and simvastatin were each previously established individually in two rodent species (mouse and rat) under NDA 21-995 (sitagliptin) and NDA 19-766 (simvastatin).

Sitagliptin
According to the labeling information for Januvia® (sitagliptin):

> 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.

The NOEL for liver tumors in the rat is 150 mg/kg (~20X MHRD of 100 mg sitagliptin; based on AUC). The increased incidence of liver tumors in rats is presumably due to non-genotoxic, chronic hepatotoxicity, although the supporting evidence for a plausible mechanism is weak. No mechanistic studies were conducted, but the sponsor cited hepatotoxicity (hypertrophy, ↑ liver weight, ↑ ALT and ALP) in the 13-week rat study as predictive evidence of liver tumorigenesis. The severity of the hepatocellular injury in the 2-year study, which consisted of basophilic/eosinophilic cellular alterations (both sexes) or cystic degeneration (males only), did not correlate with the presence of tumors. The basophilic/eosinophilic alterations may reflect peroxisome proliferation.

Simvastatin

In the initial carcinogenicity assessment, simvastatin was administered to rats for 105 weeks and to mice for 92 weeks at dosage levels of 1, 5, and 25 mg/kg for both species. Additional high dose carcinogenicity studies were conducted with simvastatin in both rats and mice at the request of the Agency.

According to the labeling information for Zocor® (simvastatin):

> In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately [2, 8, and 16 times] higher than the mean human plasma drug level, respectively (as total inhibitory activity based on AUC) after an [40 mg] oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day.
>
> In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were [2 times] higher than humans given [40 mg] simvastatin as measured by AUC).
>
> In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately [22 times] higher levels of simvastatin than in humans given [40 mg] simvastatin (as measured by AUC).
>
> A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other statins. These treatment levels represented plasma drug levels (AUC) of approximately [14 and 30 times] (males) and [44 and 50 times] (females) the mean human plasma drug exposure after an [40 milligram] daily dose.

In mice, a NOEL of 20 mg/kg (~2X MHRD of 40 mg simvastatin; based on AUC) was established for liver and lung adenomas. The NOEL of 25 mg/kg for liver tumors (adenomas/carcinomas) in the rat is ~22X the MHRD of 40 mg simvastatin (based on AUC); the increase hepatocellular tumors in the rat may be due to peroxisome proliferation at doses greater than 25 mg/kg. Although a NOEL was not established for thyroid follicular cell adenomas/carcinomas in the rat (>25 mg/kg), the mechanism of this hyperplastic effect was described in subsequent studies to be the result of treatment-related increases in circulating serum TSH levels specific to rats.

9 Reproductive and Developmental Toxicology

No nonclinical reproductive toxicology studies with the FDC of sitagliptin and simvastatin (MK-0431D) were conducted for this submission. The reproductive and developmental toxicity of sitagliptin and simvastatin were previously established individually under NDA 21-995

(sitagliptin) and NDA 19-766 (simvastatin). The proposed Pregnancy Category X labeling for the FDC of sitagliptin and simvastatin (MK-0431D) is based on the pregnancy category X classification of simvastatin.

Sitagliptin

Sitagliptin is classified in Pregnancy Category B based on a series of reproductive toxicity studies in rats and rabbits. According to the labeling information for Januvia® (sitagliptin):

> 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.
>
> In rat fertility studies with oral gavage doses of 125, 250, and 1000 mg/kg, males were treated for 4 weeks prior to mating, during mating, up to scheduled termination (approximately 8 weeks total) and females were treated 2 weeks prior to mating through gestation day 7. No adverse effect on fertility was observed at 125 mg/kg (approximately 12 times human exposure at the MRHD of 100 mg/day based on AUC comparisons). At higher doses, nondose-related increased resorptions in females were observed (approximately 25 and 100 times human exposure at the MRHD based on AUC comparison).

Simvastatin

Simvastatin is classified in Pregnancy Category X because lipids lowering drugs offer no benefit during pregnancy when cholesterol and cholesterol derivatives are needed for normal fetal development. A series of reproductive toxicity studies in rats and rabbits showed no evidence of teratogenicity.

According to the labeling information for Zocor® (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.
>
> There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight ([8 times] the maximum human exposure level, based on AUC, in patients receiving [40 mg/day]); however, this effect was not observed during a

subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, (which produces exposure levels [44 times] higher than those in humans taking [40 mg/day] based on surface area, mg/m^2), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day, (approximately [4 times] the human exposure, based on AUC, at [40 mg/day]). The clinical significance of these findings is unclear.

11 Integrated Summary and Safety Evaluation

This is a 505(b)(1) application for the fixed dose combination (FDC) drug product of sitagliptin and simvastatin (MK-0431D) for the treatment of patients with type 2 diabetes mellitus (T2DM) and hyperlipedemia. Based on the ICH Guidance M3 (R2) and agreement from the FDA, the nonclinical data previously submitted to support the NDAs for sitagliptin (Januvia®; Merck; NDA 21-995) and simvastatin (Zocor®; Merck; NDA 19-766) support the NDA for this FDC. Both drugs are approved for chronic use and the proposed dosages in the FDC are consistent with the labeling for the individual drug products.

In support of this application, the sponsor conducted a 3-month oral toxicity study in rats co-administered sitagliptin and simvastatin to determine the potential toxicity due to co-administration as well as the toxicokinetic profile of sitagliptin, simvastatin, and L-654969 (simvastatin active metabolite; simvastatin acid). No nonclinical pharmacology, ADME, genetic, reproductive or carcinogenicity studies were conducted with the sitagliptin and simvastatin FDC (MK-0431D).

Pharmacology

Sitagliptin is an approved oral anti-hyperglycemic agent, and simvastatin is an approved lipid-altering agent. 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. Simvastatin is a selective inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which catalyzes the conversion of HMG-CoA to mevalonate and is the rate-limiting step in cholesterol biosynthesis. In addition, simvastatin reduces VLDL and TG and increases HDL-C. There is no apparent overlap in the mechanisms of action of sitagliptin and simvastatin.

ADME/PK

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

In the 3-month rat co-administration study, simvastatin had no effect on sitagliptin systemic exposure (AUC and Cmax). Although simvastatin and simvastatin acid (L-654969) systemic exposure (AUC and Cmax) decreased slightly in rats co-administered the low dose of simvastatin (30 mg/kg) and sitagliptin compared to animals administered the simvastatin low dose alone, a similar decrease in systemic exposure was not observed in rats co-administered the simvastatin high dose (60 mg/kg) and sitagliptin. Likewise, clinically, there were no meaningful differences in the plasma $AUC_{0\text{-last}}$, Cmax, or Tmax of simvastatin or simvastatin

acid after administration of a single oral 20 mg dose of simvastatin in healthy subjects administered sitagliptin (200 mg/day; 5 days).

Toxicology

Given the skeletal muscle degeneration in rats at simvastatin doses similar to or moderately above clinical exposure as well as the skeletal muscle toxicity (myalgia and rhabdomyolysis) reported in human subjects, 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. The dose of sitagliptin (180 mg/kg; 163-193 μM•h [AUC]) administered provided a safety margin of approximately 20 times the exposure at the clinical dose (100 mg/day; 8.5 μM•hr [AUC]), and was an established NOEL in rats orally administered sitagliptin for up to 6 months. The low and high doses of simvastatin (30 and 60 mg/kg) selected provided safety margins of approximately 20-66 times (3-10 μM•h [AUC]) and 47-114 times (7-17 μM•h [AUC]), respectively, the combined simvastatin and simvastatin acid exposure at the maximum clinical dose of 40 mg/day (0.15 μM•hr [AUC]). The simvastatin high dose (60 mg/kg) was expected to produce very slight or no skeletal muscle degeneration in rats following 3-month oral administration. However, administration of a higher dose of simvastatin dose closer to that previously found to produce skeletal muscle degeneration (e.g., 180 mg/kg in the 14-week rat study) would have been optimal to better examine possible interactions of the two drugs on with regard to myotoxicity.

In the 3-month study, 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 co-administration of sitagliptin and simvastatin did not cause adverse muscle or pancreas effects, adverse liver effects were slightly exacerbated by the co-administration of the two drugs. Adverse treatment-related effects associated with simvastatin were also noted in the stomach and thymus.

Administration of the simvastatin high dose (60 mg/kg; ~47-114X MHRD) caused an increase in liver weight and hepatocellular hypertrophy in females, as well as an increase in ALT levels (~2-3X ↑ compared to controls) in males and females. Similar adverse liver effects were noted in simvastatin toxicology studies conducted under NDA 19-766. Although these effects were not observed in animals administered sitagliptin alone, the co-administration of sitagliptin (180 mg/kg; ~20X MHRD) and simvastatin caused a slightly greater increase in liver weight (females only) and ALT levels with both the low (30 mg/kg; ~20-66X MHRD) and high (60 mg/kg; ~47-114X MHRD) simvastatin doses suggesting a possible drug-drug interaction between sitagliptin and simvastatin with regards to liver toxicity. There was no increase in the severity of the hepatocellular hypertrophy associated with the co-administration of the two drugs. Although the sponsor did not establish a NOAEL for the additional increase in liver weight and ALT levels, these adverse liver effects are clinically monitorable.

Bile duct hyperplasia was also noted in male rats (6/10) co-administered the simvastatin high dose (60 mg/kg; ~47X MHRD) and sitagliptin (180 mg/kg; ~20X MHRD). There were no similar findings in animals administered the simvastatin high dose or sitagliptin alone suggesting a potential drug-drug interaction. Bile duct proliferation/hyperplasia was previously observed in rats in studies conducted under NDA 21-995 (sitagliptin) and NDA 19-766 (simvastatin). In the 2-year sitagliptin rat study, bile duct hyperplasia was found at a very low frequency at 50 mg/kg (1/50) and 150 mg/kg (2/50), but not at 500 mg/kg. In addition, a single male rat at 150 mg/kg had a carcinoma of the bile duct. In a 3-month simvastatin rat study, bile duct proliferation and

cellular atypia occurred in females at 20 mg/kg. However, in the 3-month co-administration study, bile duct hyperplasia was not noted in males co-administered sitagliptin and the simvastatin low dose (30 mg/kg; ~20-66X MHRD) establishing a NOEL with an adequate margin of safety for this finding.

The adverse effects in the nonglandular stomach included increased wall thickness, acanthosis and/or hyperkeratosis of the mucosa, and inflammation. These effects, which are consistent with simvastatin-related effects in previous in toxicology studies in rats and mice, are thought to be pharmacologically-mediated (i.e., related to inhibition of the target enzyme) as the changes were reversible by supplementation with mevalonate, the product of HMG-CoA reductase activity. There was no marked increase in the incidence or severity of these findings associated co-administration of sitagliptin and simvastatin. Moreover, these simvastatin-related effects are considered to be limited to this unique anatomical structure of the rodent and have not been observed in the gastrointestinal tract of chronically treated monkeys (up to 62 weeks) or dogs (up to 33 weeks).

The increased thyroid weight and follicular epithelial hypertrophy in animals administered the simvastatin high dose with and without sitagliptin is consistent with the thyroid hyperplasia/neoplasia in the rat observed in the simvastatin carcinogenicity studies conducted in support of NDA 19-766. The sponsor opted not to examine the simvastatin low dose groups so a NOAEL could not be established for the follicular epithelial hypertrophy. However, the follicular cell hypertrophy in rats due to simvastatin treatment are not considered to be indicative of human risk as they were considered secondary to changes in thyroxine homeostasis and not representative a primary carcinogenic effect.

The reproductive toxicity, genotoxicity, and carcinogenicity studies were conducted in support of NDA 21-995 (sitagliptin) and NDA 19-766 (simvastatin) supporting the chronic administration of MK-0431D.

Simvastatin carries pregnancy category X labeling warranting the same labeling for the FDC of sitagliptin and simvastatin (MK-0431D). Although a series of reproductive toxicity studies in rats and rabbits showed no evidence of teratogenicity related to simvastatin treatment, simvastatin is classified in pregnancy category X because lipids lowering drugs offer no benefit during pregnancy when cholesterol and cholesterol derivatives are needed for normal fetal development.

12 References

Smith PF, Grossman SJ, Gerson RJ, Gordon LR, Deluca JG, Majka JA, Wang RW, Germershausen JI, MacDonald JS. Studies on the mechanism of simvastatin-induced thyroid hypertrophy and follicular cell adenoma in the rat. Toxicol Pathol. 1991;19(3):197-205.

Wu KM, Farrelly JG. Preclinical development of new drugs that enhance thyroid hormone metabolism and clearance: inadequacy of using rats as an animal model for predicting human risks in an IND and NDA. Am J Ther. 2006 Mar-Apr;13(2):141-4.

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/s/

PATRICIA M BRUNDAGE
07/18/2011

TODD M BOURCIER
07/20/2011
PT supports Approval

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 202343 **Applicant:** Merck **Stamp Date:** 07 Dec 2010

Drug Name: MK-0431D **NDA Type:** NDA 505(b)(1)

Based on the ICH Guidance M3 (R2) and agreement from the FDA, the nonclinical data previously submitted to support the NDAs for sitagliptin (JANUVIA™; Merck; NDA 21-995) and simvastatin (ZOCOR™; Merck; NDA 19-766) support the NDA for the fixed-dose combination (FDC) containing sitagliptin and simvastatin (MK-0431D). A 3-month oral toxicity study was conducted in the rat with co-administration of sitagliptin and simvastatin to support registration of the MK-0431D FDC; the study was conducted to determine the potential toxicity and toxicologic interaction and toxicokinetic profile of co-administration of sitagliptin and simvastatin, as well as the toxicokinetic profile of L-000654969 (an active metabolite of simvastatin [simvastatin acid]).

On **initial** overview of the NDA 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		The sponsor submitted a 3-month oral toxicity study in the rat with co-administration of sitagliptin and simvastatin. Sponsor also submitted Simvastatin NDA 19-766 Nonclinical Summary of General Toxicity and Simvastatin Expert Report. No nonclinical study summaries of sitagliptin were submitted.
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).			Certificate of analysis for drug lots used in 3-month oral toxicity study not provided; unable to determine if the formulation to be marketed is highly similar to formulation used in the nonclinical study.
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 submitted a rationale to justify the alternative route?	X		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A; no studies requested.
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		Degradation product (b) (4) (b) (4) identified by CMC as exceeding the ICH qualification threshold is a known (b) (4); the proposed limit is acceptable.
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.

- Please submit or direct us to the Certificate of Analysis for drug lots of sitagliptin and simvastatin used in the 3-month oral combination toxicity study in rats (TT #09-1083).

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

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/s/

PATRICIA M BRUNDAGE
02/01/2011

TODD M BOURCIER
02/02/2011
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