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APPLICATION NUMBER:

216743Orig1s000

NON-CLINICAL REVIEW(S)

Memorandum to the File

Date: October 3, 2023

From: Patricia Brundage, Lead Interdisciplinary Scientist, DPT-OCHEN

To: NDA 216743

Re: Nitrosamine Impurities in Sitagliptin and Metformin Hydrochloride Tablets

Zydus Worldwide DMCC (Zydus) is seeking marketing approval for Sitagliptin and Metformin Hydrochloride Tablets as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus under a 505(b)(2) application. Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor and metformin is a biguanide. The application is relying on the FDA's previous finding of safety and effectiveness for the listed drug (LD), Janumet® (sitagliptin phosphate monohydrate and metformin hydrochloride tablet, NDA 022044).

(b) (4)

Pharm/Tox concurs that the Applicant's control strategy is adequate to ensure the long-term safety of Sitagliptin and Metformin Hydrochloride Tablets with respect to (b) (4) (b) (4)

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/s/

PATRICIA M BRUNDAGE
10/03/2023 03:31:16 PM

CALVIN L ELMORE
10/03/2023 03:45:16 PM

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	216743
Supporting document/s:	0006, 0011
Applicant's letter date:	12/31/2022
CDER stamp date:	12/31/2022
Product:	Sitagliptin and Metformin Hydrochloride Tablets, 50 mg/500 mg and 50 mg/1000 mg
Indication:	Type 2 Diabetes Mellitus (T2DM)
Applicant:	Zydus Worldwide DMCC
Review Division:	Division of Diabetes, Lipid Disorders, and Obesity Products
Reviewer:	Karen Hao, PhD
Supervisor/Team Leader:	Patricia Brundage, PhD
Division Director:	John Sharretts, MD
Project Manager:	Anne (Christine) Wright

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 216743 are owned by Zydus Worldwide DMCC or are data for which Zydus Worldwide DMCC has obtained a written right of reference. Any information or data necessary for approval of NDA 216743 that Zydus Worldwide DMCC does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 216743.

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1 Executive Summary

1.1 Introduction

Zydus Worldwide DMCC (Zydus) submitted a 505(B)(2) application for Sitagliptin and Metformin Hydrochloride Tablets indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor and metformin is a biguanide. The application is relying on the FDA's previous finding of safety and effectiveness for the listed drug (LD), Janumet® (sitagliptin phosphate monohydrate and metformin hydrochloride tablet, NDA 022044).

Compared to Janumet®, the proposed product (Zituvimet) contains sitagliptin free base instead of sitagliptin phosphate and different inactive ingredients. The proposed indication, route of administration (oral), dosage form (tablet), and strengths of the proposed drug product (50 mg/500 mg; 50 mg/1000 mg) is same as that of Janumet®.

There are no nonclinical studies conducted under this NDA, nor changes in the label of nonclinical sections from Janumet®.

This review documents the nonclinical evaluation and recommendation of approvability of this NDA.

1.2 Brief Discussion of Nonclinical Findings

For the nonclinical toxicology data to support this NDA, the sponsor is relying on FDA's previous findings of safety and efficacy for Janumet®.

(b) (4), a process/degradation impurity contained in the drug substance and product, with the specification not more than (b) (4)% in drug product (or (b) (4) mg/day), exceeds ICH Q3B qualification threshold. To define a no-observed-adverse-effect level (NOAEL) to qualify the level of this impurity in the drug product, Zydus conducted a 90-Day oral toxicity study in rats. There were no remarkable toxicity findings observed in this study with (b) (4) at doses up to (b) (4) mg/kg/day PO (high dose). The NOAEL was concluded (b) (4) mg/kg/day, (b) (4)-fold maximum human exposure of this impurity (based on body surface area comparison). Therefore, there are no safety concerns for the Applicant's proposed specification limits of (b) (4).

(b) (4)

All inactive ingredients utilized in the product are listed in the FDA's Inactive Ingredient Database (IIG) within the range of approved orally administered drug products.

1.3 Recommendations

1.3.1 Approvability

This drug product is recommended to be approved from a nonclinical perspective.

1.3.2 Additional Non-Clinical Recommendations

None

1.3.3 Labeling

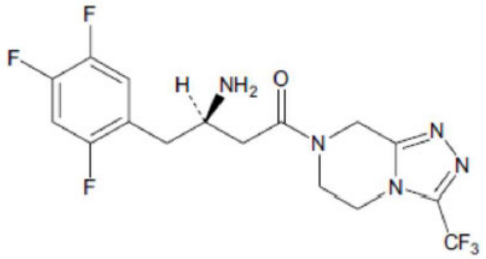
The sponsor's proposal of using the same Janumet® label information in nonclinical sections with the exception of the product Tradename is acceptable.

2 Drug Information

2.1 Drug

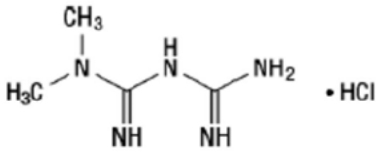
General information

Sitagliptin:
7-[(3R)-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



CAS #: 486460-32-6
Molecular Formula: C16H15F6N5O
MW: 407.31
Pharmacologic Class: dipeptidyl peptidase-4 (DPP-4) inhibitor

Metformin HCl:
N,N-dimethylimidodicarbonimidic diamide hydrochloride



CAS # 1115-70-4
Molecular formula: C4H11N5•HCl
MW: 165.62
Pharmacologic Class: biguanide

2.2 Relevant INDs, NDAs, BLAs and DMFs

LD NDA 022044
LD (Brand) Name and Strength(s): JANUMET® (sitagliptin and metformin hydrochloride)
Tablets, 50 mg/500 mg and 50 mg/1000 mg
Name of the LD NDA Holder: Merck Sharp and Dohme Corp

DMFs
(b) (4) -Sitagliptin Free Base
(b) (4) - Metformin Hydrochloride USP

2.3 Drug Formulation

Compared to the LD, Janumet®, the proposed product (Zituvimet) contains the same active ingredients, sitagliptin (free base instead of phosphate salt form in Janumet®) and metformin hydrochloride, and different excipients. See tables below.

Zydus proposed product formulation

Ingredient(s)	50 mg/500 mg		50 mg/1000 mg	
	mg/tablet	% w/w	mg/tablet	% w/w
(b) (4)				
Metformin Hydrochloride USP	500.00	(b) (4)	1000.00	(b) (4)
Microcrystalline Cellulose (b) (4)				
(b) (4)				
Croscarmellose Sodium (b) (4)				
(b) (4)				
Povidone (b) (4)				
(b) (4)				
				(b) (4)
Sitagliptin free base (b) (4)	50.00		50.00	
Low Substituted Hydroxypropylcellulose (b) (4)				
(b) (4)				
Malic Acid (b) (4)				
Colloidal Silicon Dioxide (b) (4)				
(b) (4)				
Sodium Stearyl Fumarate (b) (4)				
Magnesium Stearate (b) (4)				
Film Coating				
(b) (4)				
Total weight of film coated tablet (mg)				
(b) (4)				

2.4 Comments on Novel Excipients

All inactive ingredients utilized in the formulation are listed in the FDA's Inactive Ingredient Database (IIG) and are within or below the listed levels for orally administered products. See below.

Ingredient(s)	Listing In the Inactive Ingredients Database	Sitagliptin and Metformin Hydrochloride Tablets (mg/tablet)		mg/day*	Highest level recommended in IID# (mg) (Oral Route)	IID Compliance
		50 mg/ 500 mg	50 mg/ 1000 mg			
Microcrystalline Cellulose (b) (4) (b) (4)	Yes			(b) (4)	29520 mg@@	Complies
Croscarmellose Sodium (b) (4)	Yes				1875 mg	Complies
Povidone (b) (4) (b) (4)	Yes				(b) (4)	Complies
Low Substituted Hydroxypropylcellulose (b) (4)	Yes				370 mg	Complies
Malic Acid (b) (4)	Yes				16760 mg	Complies
Colloidal Silicon Dioxide (b) (4) (b) (4)	Yes				2553 mg^^	Complies
Sodium Stearyl Fumarate (b) (4)	Yes				435 mg	Complies
Magnesium Stearate (b) (4)	Yes				629 mg	Complies
(b) (4)	Yes				(b) (4)	Complies
						(b) (4)
Colloidal Silicon Dioxide (b) (4)	Yes			(b) (4)	2553 mg^^	Complies
Composition of				(b) (4)		
Polyvinyl Alcohol – (b) (4)	Yes			(b) (4)	165mg	Complies

Ingredient(s)	Listing In the Inactive Ingredients Database	Sitagliptin and Metformin Hydrochloride Tablets (mg/tablet)		mg/day*	Highest level recommended in IID# (mg) (Oral Route)	IID Compliance
		50 mg/ 500 mg	50 mg/ 1000 mg			
Polyethylene Glycol (b) (4)	Yes			(b) (4	(b) (4)	Complies
Titanium Dioxide (b) (4)	Yes				297mg	Complies
Talc (b) (4)	Yes				5119mg	Complies
Iron Oxide Yellow (b) (4)	Yes				24mg	Complies
Iron Oxide Red (b) (4)	Yes				31mg	Complies
FD&C Yellow #6/ (b) (4) (b) (4) Aluminum Lake	Yes				(b) (4)	Complies
(b) (4)						(b) (4)

*Based on maximum daily dose of 100 mg/2000 mg of Sitagliptin and Metformin Hydrochloride which is equivalent to 2 tablets.

(b) (4)

#Data Through: October 1, 2022; Database Last Updated: October 19, 2022.

According to 21 CFR 201.20, products containing FD&C Yellow No.6 as a color additive should be labeled to indicate the presence of this ingredient in section 11 (Description). The level of Yellow No.6 contained in the current product is very low ((b) (4) mg/day). Nonclinical team agreed with CMC reviewer (Dr. Dan Burger), inclusion of Yellow No.6 information in section 11 of the label is adequate and appropriate.

2.5 Comments on Impurities/Degradants of Concern

Zydus drug substance and drug product impurities comply with ICH Q3A/B requirements for qualification threshold except (b) (4) in the drug product. The proposed limit for (b) (4) (NMT (b) (4) %) was to address the increasing trend observed in stability studies for (b) (4) in the drug product under accelerated conditions at the 6-month time point. Therefore, Zydus performed a GLP compliant 90–day repeated dose toxicity study of (b) (4) in rats by oral route to evaluate the potential toxicity and establish a NOAEL.

This 90-day toxicity study has been reviewed under NDA 211566, submitted by Zydus for Sitagliptin Tablets (reviewed by Dr. Parvaheh Espandiari on 6/11/2021). There were

no remarkable toxicity findings observed in rats given (b) (4) at doses up to (b) (4) mg/kg/day PO (high dose). The NOAEL was concluded (b) (4) mg/kg/day, (b) (4)-fold maximum human exposure of this impurity.

(b) (4)

Regarding to the potential presence of (b) (4) in drug product, the CMC team agreed no routine testing of (b) (4) in drug product is necessary based on the sponsor's data that (b) (4) was below BQL in multiple drug product stability testing batches.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KAREN H HAO
09/20/2023 09:10:13 PM

PATRICIA M BRUNDAGE
09/25/2023 07:03:56 AM
I concur