# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 216778Orig1s000

# NON-CLINICAL REVIEW(S)

**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

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| Application number: | NDA 216778 |
| Supporting document/s: | 7 |
| Applicant's letter date: | 9/22/2023 |
| CDER stamp date: | 9/22/2023 |
| Product: | sitagliptin and metformin hydrochloride extended-release tablets, 50 mg/500 mg, 50 mg/1000 mg, and 100 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: | Federica Basso, PhD |
| Division Director: | John Sharretts, MD |
| Project Manager: | Anne (Christine) Wright |

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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 extended-release 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, both are approved for treatment of type 2 diabetes. The applicant is relying on the FDA's previous finding of safety and effectiveness for the listed drug (LD), Janumet® XR (sitagliptin and metformin extended release HCl tablet, NDA 202270).

Compared to Janumet® XR, the proposed drug product, Sitagliptin and Metformin Hydrochloride Extended-Release Tablets, contains sitagliptin free base instead of sitagliptin phosphate monohydrate. The inactive ingredients differ from that of listed drug but are of no safety concerns. 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 and 100 mg/1000 mg) are identical to that of Janumet® XR.

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

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

## 1.2 Brief Discussion of Nonclinical Findings

To support this NDA, the sponsor is relying on FDA's previous findings of safety and efficacy for Janumet® XR.

The proposed product contains sitagliptin free base and metformin hydrochloride as the active ingredients. The free base instead of phosphate salt of sitagliptin used in JANUMET® XR (Merck Sharp and Dohme Corp, NDA# N202270) does not alter the absorption and pharmacokinetic profile of the drug. The salt form of metformin, i.e., metformin hydrochloride, in the proposed product is identical to that of the LD.

(b) (4) a (b) (4) impurity contained in the drug substance and product, exceeds ICH Q3B qualification threshold of not more than 1.5% (or 1.5 mg/day). To define a no-observed-adverse-effect level (NOAEL) of this impurity, Zydus conducted a 90-day oral toxicity study in rats, reviewed under NDA 211566. There were no remarkable toxicity findings observed in this study with (b) (4) up to the highest dose (b) (4) mg/kg/day PO) corresponding to (b) (4) fold maximum human exposure (based on body surface area comparison). Therefore, the Applicant's proposed specification limit for (b) (4) (not more than (b) (4) in shelf-life) is adequate.

There are no safety concerns regarding the presence of two potential nitrosamine impurities, [redacted] in metformin drug substance and [redacted] in sitagliptin drug product, as the total level of nitrosamines does not exceed the FDA's daily acceptable intake (AI) for the most potent nitrosamine ([redacted] ng/day for [redacted]), consistently with the Guidance for Industry: Recommended Acceptance Intake Limits for Nitrosamine Drug Substance-Related Impurities (August 2023)[1]. [redacted] was not detected [redacted] ppm) and [redacted] specification limit is no more than [redacted] ppm [redacted] ng/day for daily dose of 100 mg sitagliptin drug product). 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

Pharmacology/Toxicology recommends approval of this NDA for sitagliptin and metformin hydrochloride extended-release tablets.

#### 1.3.2 Additional Non-Clinical Recommendations

None

#### 1.3.3 Labeling

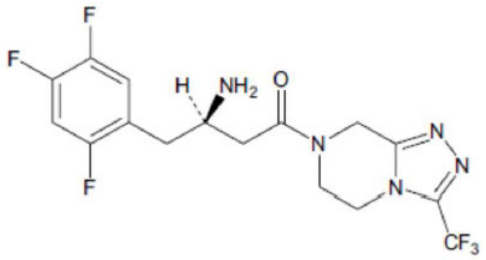
Product labeling should be identical to the PLLR compliant labeling for the LD, (Janumet XR), with the exception of the product Trade names (Sitagliptin and Metformin Hydrochloride Extended-Release Tablets).

## 2 Drug Information

### 2.1 Drug

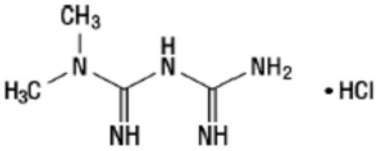
**Sitagliptin**
7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine

[1] Guidance for Industry: Recommended Acceptance Intake Limits for Nitrosamine Drug Substance-Related Impurities, August 2023



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

NDA 202270, Janumet XR, sitagliptin and metformin hydrochloride extended-release tablets, Merck.

NDA 216743, Zituvimet, sitagliptin and metformin hydrochloride tablets, Zydus

NDA 211566, Zituvio, sitagliptin tablets, Zydus

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

## 2.3 Drug Formulation

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

**Table 1. Similarity between listed product and proposed drug product**

| Listed Drug Product | Proposed Drug Product | Function in proposed drug product |
|---|---|---|
| Sitagliptin Phosphate | Sitagliptin Free Base | Active Ingredient |
| Metformin Hydrochloride | Metformin Hydrochloride, USP | Active Ingredient |
| Povidone | Povidone (b) (4) (b) (4) | (b) (4) |
| Hypromellose | Hypromellose, USP (b) (4) (b) (4) | |
| Colloidal silicon dioxide | Colloidal Silicon Dioxide, (b) (4) (b) (4) | |
| Sodium stearyl fumarate | Sodium Stearyl Fumarate, NF (b) (4) | |
| Propyl gallate | --- | --- |
| Polyethylene glycol | --- | --- |
| Kaolin | --- | --- |
| Microcrystalline cellulose (50 mg/500 mg) | Microcrystalline Cellulose, NF (b) (4) (b) (4) | (b) (4) |
| --- | Dibasic Calcium Phosphate, USP Anhydrous (b) (4) | |
| --- | Croscarmellose Sodium, NF (b) (4) | |
| --- | Ferric Oxide, NF (Yellow) (b) (4) | |
| --- | Malic Acid, NF | |

| Listed Drug Product | Proposed Drug Product | Function in proposed drug product |
|---|---|---|
| --- | (b) (4) | (b) (4) |
| --- | Pregelatinized Starch (b) (4) NF | |
| --- | Magnesium Stearate, NF (b) (4) | |
| --- | (b) (4) | |
| **Film coating** | | |
| Hypromellose | --- | Film coating composition |
| Hydroxypropyl cellulose | --- | |
| Titanium dioxide | Titanium Dioxide, USP | |
| FD&C #2/Indigo Carmine Aluminum Lake | --- | |
| Carnauba wax | --- | |
| Yellow iron oxide (50 mg/1000 mg) | Iron Oxide Yellow, NF | |
| --- | Polyvinyl Alcohol-Partially Hydrolyzed, USP | |
| --- | Talc, USP | |
| --- | (b) (4) Polyethylene Glycol (b) (4) USP | |
| --- | Iron Oxide Red, NF (50 mg/500 mg and 100 mg/1000 mg) | |
| --- | FD&C yellow #6/ (b) (4) Aluminum Lake (50 mg/1000 mg and 100 mg/1000 mg) | |

**Table 2. Proposed drug product composition**

| Sr. No. | Name of Ingredient | 50 mg/500 mg | | | 50 mg/1000 mg | | | 100 mg/1000 mg | | | Function |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | mg/unit | %w/w+ | %w/w# | mg/unit | %w/w+ | %w/w# | mg/unit | %w/w+ | %w/w# | |
| | | | | | | | | | | | |

(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.

## Table 3. Excipients

| Inactive Ingredients | Listing in the IID | Quantity (mg / Unit) | | | Maximum Daily Intake (mg) | Levels recommended in IID (mg) (Oral Route) ¥ | | IID Compliance |
|---|---|---|---|---|---|---|---|---|
| | | 50 mg/ 500mg | 50 mg/ 1000mg | 100 mg/ 1000mg | | Maximum Potency per unit dose | Maximum daily exposure | |
| Microcrystalline Cellulose, NF (b) (4) (b) (4) | Yes | (b) (4) | | | (b) (4) | ---- | (b) (4) | Complies |
| Dibasic Calcium Phosphate, USP Anhydrous (b) (4) | Yes | | | | | --- | | Complies |
| Croscarmellose Sodium, NF (b) (4) (b) (4) | Yes | | | | | --- | | Complies |
| | | | | | | --- | | |
| | | | | | | --- | | |
| Ferric Oxide, NF (Yellow) (b) (4) (b) (4) | Yes | | | | | --- | | Complies |
| Povidone (b) (4) | Yes | | | | | --- | | Complies |
| Malic Acid, NF | Yes | | | | | --- | | Complies |

| Inactive Ingredients | Listing in the IID | Quantity (mg / Unit) | | | Maximum Daily Intake (mg) | Levels recommended in IID (mg) (Oral Route) ¥ | | IID Compliance |
|---|---|---|---|---|---|---|---|---|
| | | 50 mg/ 500mg | 50 mg/ 1000mg | 100 mg/ 1000mg | | Maximum Potency per unit dose | Maximum daily exposure | |
| Colloidal Silicon Dioxide, NF (b) (4) | Yes | (b) (4) | | | (b) (4) | 5000 | --- | Complies |
| | | | | | | --- | (b) (4) | |
| Magnesium Stearate, NF (b) (4) | Yes | | | | | --- | | Complies |
| | | | | | | --- | | |
| Sodium Stearyl Fumarate, NF ( (b) (4) | Yes | | | | | --- | | Complies |
| Pregelatinized Starch (b) (4) NF | Yes | | | | | --- | | Complies |
| Povidone (b) (4) USP | Yes | | | | | --- | | Complies |
| Hypromellose, USP ( (b) (4) (b) (4) | Yes | | | | | --- | | Complies |
| | | | | | | | | (b) (4) |
| | | | | | | | | (b) (4) |

| Inactive Ingredients | Listing in the IID | Quantity (mg / Unit) | | | Maximum Daily Intake (mg) | Levels recommended in IID (mg) (Oral Route) ¥ | | IID Compliance |
|---|---|---|---|---|---|---|---|---|
| | | 50 mg/ 500mg | 50 mg/ 1000mg | 100 mg/ 1000mg | | Maximum Potency per unit dose | Maximum daily exposure | |
| (b) (4) | | | | | | | | |
| IIG Evaluation of all (b) (4) Coating Materials Composition | | | | | | | | |
| Polyvinyl Alcohol-Partially Hydrolyzed, USP | Yes | | | | (b) (4) | -- | (b) (4) | Complies |
| (b) (4) Polyethylene Glycol (b) (4) USP | Yes | | | | | --- | | Complies |
| Titanium Dioxide, USP | Yes | | | | | --- | | Complies |
| Talc, USP | Yes | | | | | --- | | Complies |
| Iron Oxide Yellow, NF/ (b) (4) | Yes | | | | | --- | | Complies |
| Iron Oxide Red, NF/ (b) (4) | Yes | | | | | --- | | Complies |
| FD&C yellow #6/ (b) (4) Aluminum Lake | No | | | | | --- | | Complies |

¥ eIID Database last updated July 21, 2023

(b) (4)

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. The level of Yellow No.6 contained in the current product is quite low (b) (4) mg/day). Consistent to the recommendation provided to NDA 216743 (sitagliptin/metformin from Zydus), inclusion of Yellow No.6 information in section 11 of the label is considered adequate.

## 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 for (b) (4) in the drug product. The proposed limit for (b) (4) (NMT (b) (4) %) was to address the increasing levels observed in stability studies under accelerated conditions at the 6-month time point. Therefore, Zydus performed a GLP compliant 90-day repeated dose toxicity study with (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, Zituvio, sitagliptin tablets from Zydus (Dr. Parvaneh Espandiari's review, 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 established at the high dose, (b) (4) mg/kg/day, (b) (4) fold maximum human exposure.

Additionally, there is the possibility of nitrosamine impurities (b) (4) (b) (4) in metformin drug substance and (b) (4) (b) (4) in sitagliptin drug product, which have been recently identified in marketed metformin and sitagliptin containing drug products[2,3]. If more than one nitrosamine impurity is identified, the total level of nitrosamines should not exceed the recommended AI limit for the most potent nitrosamine in the drug product based on the maximum daily dose. The sponsor tested multiple stability batches and reported that (b) (4) content is (b) (4) (b) (4) For (b) (4) the applicant's proposed control limit of NMT ``` ng/day ( ppm in drug product for daily dose of 100 mg sitagliptin) is acceptable based on FDA's current guidance[1]. The CMC team agrees that monitoring for (b) (4) only in the drug product is acceptable as (b) (4) levels are BQL in the samples of stability batches.

**Table 4 (b) (4) and (b) (4) specification limits**

(b) (4)

(b) (4)

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/s/

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KAREN H HAO
06/05/2024 04:21:01 PM

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06/05/2024 04:24:15 PM
I concur