CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216743Orig1s000

SUMMARY REVIEW

Division Summary Memo for Regulatory Action and CDTL review

Date	October 25, 2023
From	Patrick Archdeacon, MD (Signatory, Deputy Division Director) Edwin Chiu Yuen Chow, PhD (CDTL, Clinical Pharmacology Team Leader DCEP)
NDA # / Sequence #:	NDA 216743 S-0006
Applicant	Zydus Worldwide DMCC
Date of Submission Receipt	December 31, 2022
PDUFA Goal Date	November 3, 2023
Proprietary Name / Established (USAN) names	Sitagliptin + Metformin hydrochloride (HCl)
(Proposed) Trade name	ZITUVIMET
Dosage forms / Strength	The Applicant is seeking approval of film-coated tablets containing the following sitagliptin/metformin hydrocholoride dosage strengths: • 50 mg/500 mg • 50 mg/1000 mg
Recommended Action	Approval
New Recommended Indication(s)/Populations(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

1. Introduction

This document serves as the 'Summary Basis for Regulatory Action' memo for the original new drug application (NDA) for a fixed combination drug product (FCDP) comprising sitagliptin (free base) and metformin hydrochloride. Each of these components of the proposed FCDP is indicated to improve glycemic control in patients with type 2 diabetes mellitus (T2D). This memo references the following documents/sources:

Subject	Author	Date
Quality Assessment	Daniel Jansen (Drug Substance), Dan Berger (Drug Product), Naresh Pavurala (Manufacturing), Rebecca Moody (Biopharmaceutics), Oluwafunmike (Funke) Ajomale (RBPM), Muthu Ramaswamy (Application Technical Lead)	October 4, 2023
Pharmacology/Toxicology	Patricia Brundage	October 3, 2023
Clinical Pharmacology	Yaning Sun	October 4, 2023
Clinical	Justin Penzenstadler	October 31, 2023
Division of Medication Error Prevention and Analysis (DMEPA)	Ariane O Conrad	09/21/2023 10/04/2023 10/12/2023
Patient Labeling Review	Maria T Nguyen (Patient Labeling Reviewer), Tierra N Butler (Regulatory Reviewer)	October 5, 2023
Labeling Consult Review	Tierra N Butler	October 11, 2023
Clinical/Bioanalytical Inspections	James J Lumalcuri	March 28, 2023

2. Background

Type 2 diabetes (T2D) is a disease of abnormal glucose homeostasis which results in hyperglycemia. Improved glycemic control, measured by change from baseline A1C, has been the accepted target for therapies as studies have shown that improved glycemic controlreduces the risk of microvascular disease (retinopathy, nephropathy, neuropathy).

Sitagliptin is an DPP-4 enzyme inhibitor, approved for use as an adjunct to diet and exercise to improve glycemic control in adults with T2D. It inhibits the metabolism and elimination of incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), prolonging endogenous incretin actions in glucose homeostasis, and lower plasmas glucose levels.

Metformin is a biguanide approved for use as an adjunct to diet and exercise to improve glycemic control in adults and children with T2D. It lowers plasma glucose level through decreasing hepatic gluconeogenesis and improving peripheral insulin sensitivity.

This NDA consists of CMC data (including dissolution studies supporting a biowaiver) and three bioavailability (BA)/bioequivalence (BE) studies (one pilot and two pivotal). The NDA also relies on safety and efficacy data presented in the package insert of JANUMET (i.e., sitagliptin phosphate monohydrate and metformin). The Applicant uses the submitted PK data in the two pivotal relative BA BE studies to support bridging for the efficacy and safety data of the listed product, JANUMET.

3. CMC

The recommendation from the Office of Pharmaceutical Quality (OPQ) is that the CMC information is adequate to support the approval of NDA 216743. Dr. Daniel Jansen reviewed the Drug Substance information for metformin hydrochloride and sitagliptin; Dr. Dan Berger reviewed the Drug Product information (including drug product composition, excipient compatibility, batch analysis, container closure system, and stability information), Dr. Naresh Pavurala reviewed the drug manufacturing process data (including facility assessment and process assessment), Dr. Rebecca Moody reviewed the biopharmaceutical data (including the dissolution method, supporting dissolution data, dissolution acceptance criteria, and the biowaiver request). Dr. Muthu Ramaswamy performed a risk assessment for the finished product critical quality attributes. Together, the OPQ review team concluded that there are no outstanding deficiencies related to drug substance, drug product, process, facilities, biopharmaceutics, or container and carton label. Please see the integrated OPQ review for additional details (see Dr. Ramaswamy's Integrated Quality Assessment dated 9/29/2023 in DARRTS). I concur with their conclusions.

ZITUVIMET (sitagliptin/metformin HCl) immediate release tables are manufactured as film-coated oval shaped tablets in 2 different strengths:

- 50 mg sitagliptin/500 mg metformin hydrochloride
- 50 mg sitagliptin/1000 mg metformin hydrochloride

The ZITUVIMET tablet manufacturing process uses (b) (4) (b) (4) (b) (4). Tablet strengths of the drug products are distinguishable by size, color and debossing.

The acceptability of the final product formulation was established based on data available from BA/BE studies and from available dissolution data. Based on dissolution data of available strengths, over (b) (4)% drug release was observed in (b) (4)min. An acceptance criterion of NLT (b) (4)% release of sitagliptin and metformin HCl in 30 minutes was accepted. The BA/BE studies under fasted and fed conditions used the highest (50 mg/1000 mg) strength sitagliptin/metformin HCl immediate release tablets. The Applicant requested a biowaiver for the low strength (50 mg/500 mg). Dr. Moody concluded that the dissolution profiles of the low

strength tablets were similar to the dissolution profiles of the high strength tablet. For that reason, the biowaiver for the lower strength tablet was deemed appropriate.

(b) (4)

Based on available stability data, a shelf-life of 12 month was granted for the 50mg/500mg, and 50mg/1000mg tablets packaged in sealed 60ct and 180ct bottles, when stored at 25°C/60% RH. Per FDA recommendation, the applicant removed (b) (4)

(b) (4)

(b) (4)

4. Nonclinical Pharmacology/Toxicology

Dr. Patricia Brundage from the DPT-CHEN reviewed the nonclinical data supporting NDA 216743 and recommends approval. Please see Dr. Brundage's review for additional details (dated 10/03/2023 in DARRTS). I concur with her conclusions.

(b) (4)

5. Clinical Pharmacology/Biopharmaceutics

Dr. Yaning Sun from the Division of Cardiometabolic Endocrine and Pharmacology (DCEP) in the Office of Clinical Pharmacology reviewed the clinical pharmacology data supporting NDA 216743. He concluded that the data support approval. Please see Dr. Sun's review for additional details (dated 10/04/2023 in DARRTS). I concur with his conclusions.

The clinical development program consists of 3 clinical studies, i.e., a pilot fasting relative BABE study (C1B01291), a pivotal single-dose fasting relative BA/BE study (C1B01510) and a pivotal single-dose fed relative BA/BE study (C1B01511) to establish the PK bridge between the proposed drug product (ZITUVIMET) and the listed product (JANUMET) at their highest strength, i.e., Sitagliptin and Metformin Hydrochloride, 50 mg/1000 mg. Studies C1B01510

and C1B01511 are the pivotal BA/BE studies. A biowaiver request for the lower strength, i.e., sitagliptin and metformin hydrochloride, 50 mg/500 mg, was submitted.

- **Study C1B01291** is a single dose, two-way crossover pilot BE study for ZWD's sitagliptin and metformin HCI tablets 50 mg/1000 mg (proposed product) and JANUMET® (sitagliptin and metformin HCl tablets) sitagliptin 50 mg / metformin HCl 1000 mg (LD product) in healthy men under fasting conditions. The maximum plasma concentration (C_{max}), area under the curve from zero to time (t) (AUC_t) and area under the curve from zero to infinity (AUC_i) of sitagliptin and metformin were assessed via average BE approach.
- **Study C1B01510** is a single dose, two-way crossover pivotal BE study for ZWD's sitagliptin and metformin HCI tablets, 50 mg/1000 mg (proposed product) and JANUMET®'s tablets, sitagliptin and metformin HCl, 50 mg / 1000 mg (LD product) in healthy men under **fasting** conditions. The results showed the proposed product and LD product are bioequivalent as the 90% CI of the ratios for C_{max}, AUC_t and AUC_i of sitagliptin and metformin between proposed product and LD product are within the BE acceptance criteria of 80%-125%.
- **Study C1B01511** is a single dose, two-way crossover pivotal BE study for ZWD's sitagliptin and metformin HCI tablets, 50 mg/1000 mg (proposed product) and JANUMET®'s tablets, sitagliptin and metformin HCl, 50 mg / 1000 mg (LD product) in healthy men under **fed** conditions. The results showed the proposed product and LD product are bioequivalent as the 90% CI of the ratios for C_{max}, AUC_t and AUC_i of sitagliptin and metformin between test product and LD product are within the BE acceptance criteria of 80%-125%.

Dr. Sun concluded that the results of Study C1B01510 and C1B01511 supported a finding of BE for the highest strength ZITUVIMET tablets. Dr. Sun noted that the Applicant had requested and received a biowaiver for the low strength ZITUVIMET tablets (see Dr. Moody's Biopharmaceutics review in the integrated review from the Office of Pharmaceutical Quality). Dr. Sun also noted that the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed for the clinical and bioanalytical sites (see Bioequivalence Establishment Inspection Report review dated 03/28/2023). OSIS had conducted a Remote Regulatory Assessment (RRA) for the clinical and analytical sites in (b) (4). OSIS concluded that data from the reviewed studies were reliable. In addition, Dr. Sun reviewed the bioanalytical method validations for sitagliptin and metformin plasma concentration determination in the studies and found them acceptable.

6. Clinical/Statistical- Efficacy

Clinical reviewer noted no outstanding issues and recommended approval. See Dr. Penzenstadler's clinical review (Dated 10/31/2023 in DARRTS). As discussed under Clinical Pharmacology, the relative BA studies provide the bridge to the efficacy findings of the listed drug, JANUMET, for the indication to improve glycemic control in adults with type 2 diabetes mellitus. I concur with his conclusions.

7. Safety

This application primarily relies on the Agency's previous determination of safety for the listed drug, JANUMET. Refer to the clinical recommendation in Section 6 above. I concur with his conclusions.

8. Advisory Committee Meeting

No new efficacy or safety issue rose to the level of requiring the input from an advisory panel. Therefore, an advisory committee meeting was *not* convened for this NDA.

9. Pediatrics

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. After consultation with the Pediatric Research Committee (PeRC), CDER concluded that there are no additional studies required for this product because the pediatric studies of sitagliptin did not establish efficacy in the pediatric population. For that reason, combination products that include sitagliptin can be considered to have been assessed in the pediatric population.

10. Labeling

The labeling for ZITUVIMET submitted by the Applicant was based on approved labeling for JANUMET (sitagliptin/metformin; NDA 022044).

During the review of NDA 216743, it was determined that the labeling for ZITUVIMET should be revised to address the following issues:

- Language from various sections were updated for consistency with the approved label of sitagliptin (ZITUVIO) and to be in compliance with existing regulations and labeling guidance.
- A statement regarding pediatric information describing clinical studies was included in Section 8.4 (Pediatric Use) to acknowledge exclusivity at this time.
- (b) (4)
- (b) (4) Additional information on storage conditions were also added.

11. Recommendations

- Recommended Regulatory Action

Approval:

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

Recommendation for other Postmarketing Requirements and Commitments

None

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/

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10/31/2023 04:11:36 PM

PATRICK ARCHDEACON
10/31/2023 04:22:00 PM