CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216778Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review and Summary Memo

Date	See digital signature
From	Patrick Archdeacon, MD Deputy Director Division of Diabetes, Lipid Disorders, and Obesity
NDA/BLA #	216778 (Original NDA submission)
Applicant	Zydus
Date of Submission	September 22, 2023
PDUFA Goal Date	July 22, 2024
Proprietary Name	Zituvimet XR
Established or Proper Name	Sitaglipin/Metformin hydrochloride (HCl) extended release (XR)
Dosage Form(s) and Strength(s)	Oral tablets 50mg/500mg, 50mg/1000mg, 100mg/1000mg
Applicant Proposed Indication(s)/Population(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)
Applicant Proposed Dosing Regimen(s)	Maximum recommended daily dose is 100 mg of sitagliptin and 2,000 mg of metformin HCl XR
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	As an adjunct to diet and exercise to improve glycemic control in adults with T2DM
Recommended Dosing Regimen(s) (if applicable)	Maximum recommended daily dose is 100 mg of sitagliptin and 2,000 mg of metformin HCl XR

1. Executive Summary

Zydus Worldwide DMCC (hereafter the Applicant) submitted NDA 216788 on September 22, 2023 proposing their fixed dose combination (FDC) of sitagliptin/metformin XR (to be marketed as Zituvimet XR) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitis (T2DM). The Applicant has previously submitted, and received approval for, NDA 211566 (sitagliptin, marketed as Zituvio, approved October 18, 2023) and NDA 216743 (sitagliptin/metformin IR, marketed as Zituvimet, approved November 3, 2023). Like NDAs 211644 and 216743, NDA 216788 is a 505(b)(2) application that proposes to rely on FDA's previous finding of safety and effectiveness for approved FDC sitagliptin/metformin products (NDA 021995, sitagliptin marketed as Januvia; NDA 022033, sitagliptin/metformin IR marketed as Janumet, and NDA 202270, sitagliptin/metformin XR marketed as Janumet XR, respectively). For this application, to justify reliance on FDA's previous finding of safety and effectiveness for Janumet XR, the Applicant conducted two relative bioavailability studies (one under fasting conditions and one under fed conditions), the results of which were used to demonstrate the bioequivalence of Zituvimet XR and Janumet XR. Based on review of the relative bioavailability studies, FDA concluded that bioequivalence had been demonstrated and that reliance on the previous finding of safety and effectiveness of Janumet XR was justified. Clinical review of the safety data collected during the conduct of the relative bioavailability studies (i.e., adverse event data) did not reveal any imbalances that would preclude the determination based on the finding on bioequivalence that it was appropriate to rely on the previous finding of safety and effectiveness of Janumet XR.

This cross-discipline team lead (CDTL) and division summary memo draws on the following reviews:

Office of Product Quality	Muthukumar Ramaswamy	June 12, 2024
Office of Study Integrity and Surveillance (OSIS)	James Lumalcuri	December 4, 2023
Nonclincal Pharmacology/Toxicology	Karen Hao, Federica Basso	June 5, 2024
Office of Clinical Pharmacology (OCP)	Deepa Rao, Edwin Chao	June 10, 2024
Division of Diabetes, Lipid Disorders, and Obesity (DDLO)	Susan Yuditskaya	July 18, 2024
Patient Labeling Team (Division of Medical Policy Programs)	Mary Carroll, Tierra Butler, Marcia Williams, LaShawn Griffiths	July 9, 2024
Division of Medical Error Prevention and Analysis (DMEPA)	Vraj Patel, Damon Birkemeier, Mishale Mistry	December 8, 2023; Amended July 12, 20024
Office of Prescription Drug Promotion (OPDP)	Tierra Butler	July 2, 2024

2. Background

T2DM is a disease of impaired glucose homeostasis resulting in chronic hyperglycemia and significant morbidity and mortality attributable to microvascular (retinopathy, nephropathy, peripheral neuropathy) and macrovascular disease (cardiovascular disease). Several classes of drugs have been approved to improve glycemic control in persons with T2DM. Treatments that improve glycemic control, as measured by hemoglobin A1c (A1C), have been demonstrated to reduce the risk of microvascular outcomes associated with T2DM. Some specific treatments (e.g., SGLT2 inhibitors and

GLP-1 receptor agonists) have also been shown in large cardiovascular outcome trials to reduce the risk of macrovascular outcomes associated with T2DM.

Metformin is a biguanide first approved by the FDA in 1994. Its indication is as an adjunct to diet and exercise to improve glycemic control in adults and children with T2DM. It is available in immediate release (IR) formulations and extended release (ER) formulations. Sitagliptin is a DPP-4 inhibitor first approved by the FDA in 2006. Its indication is as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Labeling of current sitaglipin-containing products, including Janumet XR, states that the safety and effectiveness has not been established in pediatric patients and describes efficacy analyses based on three studies conducted in a total of 410 pediatric studies in which the effect of treatment with sitagliptin was not significantly different from placebo. For that reason, Janumet XR is approved as as adjunct to diet and exercise to improve glycemic control in adults with T2DM, but is not approved for use in children with T2DM.

3. Product Quality

The Office of Product Quality (OPQ) reviewed the Chemistry, Manufacuring, and Controls information for NDA 216778. The review of the DS was conducted by Ben Zhang and Zhengfu Wang, the review of the DP and labeling was conducted by Jennifer McChord and Muthu Ramaswamy, the review of the manufacturing process was conducted by Peter Krommenhoek and Aditi Thakur, the review of biopharmaceutics was conducted by Huang Modthan and Haritha Mandula, and Muthu Ramaswamy served as the assessment team leader (ATL). Based on their reviews, OPQ concluded (and I concur) that the NDA meets all applicable standards to support the quality and purity of the drug product; OPQ recommended approval of the NDA from a quality perspective.

Important issues covered in the OPQ review include a request for biowaiver and an evaluation of the potential of the DS and DP to form nitrosamine impurities.

- The proposed DP has three strengths of sitagliptin/metformin XR tablets: 50 mg/500 mg; 50 mg/1000 mg; 100 mg/1000 mg (dispected in 30 count or 60 count high density polyethylene bottles with dessicant). The Applicant conducted bioequivalence studies to bridge their proposed DP to Janumet XR tablets using the 100 mg/1000 mg tablets only. For that reason, the Applicant request biowaiver for the lower strengths on the basis that the proposed strength tables are proportionally similar in composition of their active and inactive ingredients and provided in vitro dissolution profile information. Based on the review of the biowaiver request, the biophamaceutics reviewer concluded (and I concur) that adequate information was provided to grant the biowaiver request.

- During the review, the potential for the Zituvimet XR drug substance (DS) and drug product (DP) to form nitrosamine impurities was assessed, as the potential for the formation of nitrosamine impurities had been identified with other sitagliptin-containing products. FDA concluded that NDA 216788 included adequate manufacturing and control information to meet FDA established acceptable intake (AI) limits for the identified nitrosamine impurities of interest. (b) (4)4) the labeling was informed by available stability data: a shelf-life of 18 month was granted for the 50mg/500mg, and 50mg/1000mg tablets packaged in sealed 30ct or 60ct bottles, when stored at 25°C/60% RH and Section 16 of the United States Prescribing Information (USPI) instructs to "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in a dry place with cap tightly closed. Keep ZITUVIMET XR in the original container to protect it from moisture. Use ZITUVIMET XR within 1 month of opening the bottle."

For additional details regarding the OPQ review, see the Integrated Quality Review dated June 12, 2024, signed by Dr. Muthu Ramaswamy.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review of NDA 216778 was conducted by Karen Hao and Federica Basso. Based on their review, the pharmacology/toxicology team recommended approval of the NDA from a nonclinical perspective. I concur with their recommendation.

The nonclinical review concludes that no new nonclinical studies are required under this 505(b)(2) NDA that is relying on FDA's previous finding of safety and effectiveness for Janumet XR. The nonclinical review notes that Janumet XR contains sitagliptin phosphate monohydrate whereas Zituvimet XR contains sitagliptin free base. However, the review also notes that the use of free base instead of phosphate salt does not alter the absorption and pharmacokinetic profile of sitagliptin. In addition, the review notes that the inactive ingredients of the two drug products are nonidentical, but reports that all inactive ingredients used in the Zituvimet XR formulation are listed in the FDA's Inactive Ingredients Database (IIG) and are within or below the listed levels for orally administered products. Finally, the nonclinical review notes that (b) (4), a (b) (4) impurity is contained in the Zituvimet DS and DP and exceeds ICH Q3B qualification threshold of not more than 1.5% (or 1.5 mg/day). However, (b) (4) was previously assessed in a 90 day oral toxicity study in rats reviewed under NDA 211566 (sitagliptin marketed as Zituvio): there were no remarkable toxicity findings observed in this study up to the highest dose (b) (4) mg/kg/day PO) corresponding to (b) (4) fold maximum human exposure. Therefore the Applicant's proposed specification limit for (b) (4) is adequate. The nonclincal review also notes the evaluation regarding the potential for nitrosamine impurities (described in greater detail in the OPQ review) and concurs that the potential nitrosamine impurities are not a safety concern that would preclude approval as the level of nitrosamines does not exceed the FDA's daily AI for these impurities.

For additional details regarding the nonclinical review, see the review dated June 5, 2024, signed by Dr. Karen Hao and Dr. Fede Basso.

5. Clinical Pharmacology

The clinical pharmacology review of NDA 216778 was conducted by Deepa Rao and Edwin Chow. Based on their review, the clinical pharmacology team finds that the submitted PK results are acceptable to support approval from a clinical pharmacology perspective. I concur with their findings.

As described in the clinical pharmacology review, the clinical development program comprised two pivotal, single dose, relative bioavailability (BA)/ bioequivalence (BE) studies: a fasting BA/BE study (C1B01591) and a fed BA/BE study (C1B01592). Both studies were conducted with the 100 mg/1000 mg strengths of the Zituvimet XR and Janumet XR drug products. As previously described above, OPQ determined that a biowaviver was appropriate for the lower strength tablets. Both C1B01591 and C1B01592 demonstrated that the 90% confidence intervals and the geometric metan ratio of Zituvimet 100 mg/1000 mg are within the pre-specified limits of 80% to 125% for the primary PK endpoints (Cmax, AUC from time zero to time t, and AUC from time zero to infinity) for both sitagliptin and metformin. The clinical pharmacology review team concluded that Zituvimet XR and Janumet XR are bioequivalent.

The Office of Study Integrity and Surveillance (OSIS) was consulted. OSIS determined on-site inspections were not need for the clinical or analytic sites.

For additional details regarding the clinical pharmacology review, see the review dated June 10, 2024, signed by Dr. Deepa Rao and Dr. Edwin Chow. For additional details regarding the OSIS determination, see the review data January 4, 2023, signed by James Lumalcuri.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Not applicable. This 505(b)(2) NDA is relying on an adequate justification to rely on the previous finding of effectiveness for Janumet XR. The adequate justification is based on a demonstration of bioequivalence to Janumet XR in the relative BA/BE studies for the highest strength of Janumet XR and Zituvimet XR and the biowaiver for the lower strengths for the lower strengths of Zituvimet XR granted based on the review of in vitro dissolution profile data.

8. Safety

This 505(b)(2) NDA is relying on an adequate justification to rely on the previous finding of safety for Janumet XR. The adequate justification is based on a demonstration of bioequivalence to Janumet XR in the relative BA/BE studies for the highest strength of Janumet XR and Zituvimet XR and the biowaiver for the lower strengths for the lower strengths of Zituvimet XR granted based on the review of in vitro dissolution profile data.

In addition, a clinical review of NDA 216778 was conducted by Susan Yuditskaya. Based on her review, Dr. Susan Yuditskaya recommended approval of the NDA from clinical perspective. I concur with her recommendation.

Dr. Yuditskaya reviewed the safety data collected during the conduct of the two BA/BE studies, C1B01591 and C1B01592. Among the 64 healthy volunteers enrolled across both studies (32 subjects in each), no serious adverse events or deaths were observed and few adverse events(AE) were observed. The most common AE was mild vomiting, which was observed in a total of 5 subjects (three in the fasting BA/BE study and two in the fed BA/BE study). The distribution of the events was similar across the test (Zituvimet XR) and reference (Janumet XR) products and the events observed are consistent with the labeling of the reference product. Dr. Yuditskaya concluded (and I concur) that no findings from safety data reviewed precluded the conclusion that reliance on the previous finding of safety and effectiveness for Janumet XR is justified by the demonstration of bioequivalence between Zituvimet XR and Janumet XR in C1B01591 and C1B01592.

For additional details, see the clinical review dated July 18, 2024, signed by Dr. Susan Yuditskaya.

9. Advisory Committee Meeting

No issues were identified during the review that required input from an Advisory Committee.

10. Pediatrics

Because Zituvimet XR contains sitagliptin free base whereas Janumet XR contains sitagliptin phosphate monohydrate, PREA is triggered by NDA 216778. The Applicant requested (and was granted) a full waiver for pediatric studies because studies are highly impracticable for pediatrics individuals aged birth to less that 11 years of age (given that T2DM does not manifest in this age group) and because the sitaglipin component would not be expected to contribute to the effectiveness of Zituvimet XR, based the labeling of Janumet XR and other approved sitagllptin products.

Reference ID: 5415594

11. Labeling

The Patient Labeling Team from the Division of Medical Policy Programs, the Office of Prescription Drug Promotion, the Office of Product Quality, the Division of Medical Error Prevention and Analysis, and the Division of Diabetes and Lipid Disorders all participate in the review of labeling. As a 505(b)(2) application, the proposed labeling for Zituvimet XR was baed on the label of the listed drug, Janumet XR. Minor changes were made to the proposed labeling to comply with regulations and guidance, to remove redundancies, and to reflect updates made to modernize other metformin fixed dose combination products. Importantly, the labeling includes instruction specific to Zituvimet XR about its proper storage and handling: the labeling reflects that a shelf-life of 18 month was granted for the 50mg/500mg, and 50mg/1000mg tablets packaged in sealed 30ct or 60ct bottles, when stored at 25°C/60% RH and Section 16 of the United States Prescribing Information (USPI) instructs to "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in a dry place with cap tightly closed. Keep ZITUVIMET XR in the original container to protect it from moisture. Use ZITUVIMET XR within 1 month of opening the bottle."

12. Postmarketing Recommendations

No postmarketing requirements or commitments are recommended.

Reference ID: 5415594

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/s/

PATRICK ARCHDEACON
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