# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 216778Orig1s000

# CLINICAL REVIEW(S)

# CLINICAL REVIEW

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| Application Type | NDA |
| Application Number(s) | 216778 |
| Priority or Standard | Standard |
| Submit Date(s) | 09/22/2023 |
| Received Date(s) | 09/22/2023 |
| PDUFA Goal Date | 07/22/2024 |
| Division/Office | DDLO/OND |
| Reviewer Name(s) | Susan Yuditskaya, MD |
| Review Completion Date | 07/18/2024 |
| Established/Proper Name | sitagliptin/metformin XR |
| (Proposed) Trade Name | Zituvimet XR |
| Applicant | Zydus |
| Dosage Form(s) | Oral |
| Applicant Proposed Dosing Regimen(s) | 50mg/500mg, 50mg/1000mg, 100mg/1000mg |
| Applicant Proposed Indication(s)/Population(s) | Zituvimet ER is a combination of sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride (HCl), a biguanide indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). |
| Recommendation on Regulatory Action | Approved |
| Recommended Indication(s)/Population(s) (if applicable) | Zituvimet ER is a combination of sitagliptin, a DPP-4 inhibitor, and metformin HCl, a biguanide indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. |

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## Glossary

| | |
|---|---|
| AE | Adverse event |
| BA | bioavailability |
| BE | bioequivalence |
| BRF | Benefit Risk Framework |
| CDER | Center for Drug Evaluation and Research |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| CRF | case report form |
| CRT | clinical review template |
| CV | cardiovascular |
| DPP-4 | dipeptidyl peptidase-4 |
| ECG | electrocardiogram |
| ER | Extended-release |
| eCTD | electronic common technical document |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| GCP | good clinical practice |
| GIP | glucose-dependent insulinotropic polypeptide |
| GLP-1 RA | glucagon-like peptide-1 receptor agonists |
| GMR | geometric mean ratio |
| GRMP | good review management practice |
| HDPE | high-density polyethylene |
| ICH | International Council for Harmonization |
| IID | Inactive Ingredients Database |
| IND | Investigational New Drug Application |
| iPSP | integrated pediatric study plan |
| IR | Immediate-release |
| MDD | maximal daily dose |
| NDA | new drug application |
| (b) (4) | (b) (4) |
| NME | new molecular entity |
| NOAEL | no-observed-adverse-effect level |
| (b) (4) | (b) (4) |
| OPQ | Office of Pharmaceutical Quality |
| OSI | Office of Scientific Investigation |

| | |
|---|---|
| OSIS | Office of Study Integrity and Surveillance |
| PD | pharmacodynamics |
| PI | prescribing information or package insert |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PP | per protocol |
| PPI | patient package insert |
| PREA | Pediatric Research Equity Act |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SGLT2 | sodium-glucose cotransporter-2 |
| T2DM | Type 2 Diabetes Mellitus |
| TZD | thiazolidinediones |
| WRO | written-response-only |
| XR | Extended-release |

# 1. Executive Summary

## 1.1. Product Introduction

Metformin is a biguanide used as a first-line treatment for T2DM. It was approved in 1994 in the US. It is currently available in both immediate release (IR) and extended release (ER) formulations in fixed-dose-combinations with sitagliptin.

Sitagliptin is a DPP-4 inhibitor which is used as a second-line treatment for T2DM. It was initially approved by the US FDA in October 2006 under the brand name Januvia (Merck & Co). Janumet (metformin/sitagliptin IR) was approved in 2007 and Janumet XR (metformin/sitagliptin XR) in 2012. Janumet XR was approved through a 505(b)(1) application because Januvia was Merck's own product and Merck also had a full right of reference to Glumetza, an extended-release metformin approved by FDA in 2005. Of note, the sitagliptin component of Janumet and Janumet XR is the salt form, sitagliptin phosphate monohydrate.

The applicant has developed a sitagliptin/metformin XR combination tablet in which the sitagliptin is a free base, rather than the phosphate monohydrate salt. The proposed trade name for the product is Zituvimet XR. The Applicant has proposed three strengths – 50 mg/500 mg, 50 mg/1000 mg, and 100 mg/1000 mg. The proposed dosing regimen is 1-2 tablets orally once daily with a meal. The applicant filed a 505(b)(2) application using Janumet XR as the reference listed drug.

The applicant is proposing the following indication:

"Zituvimet ER is a combination of sitagliptin, a DPP-4 inhibitor, and metformin HCl, a biguanide indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus."

Benefit-Risk Integrated Assessment

Diabetes mellitus is a serious disease that affects 22 million people in the United States. Diabetes mellitus can lead to macrovascular and microvascular complications that can reduce the quality of life and longevity of affected patients. There are currently 12 classes of diabetes medications approved for the treatment of type 2 diabetes mellitus including multiple metformin products.

The reference product Janumet XR has been approved in the US since 2012, and its safety and effectiveness have been well-characterized. The benefit-risk assessment for Zituvimet is based on the assessment that the data and information submitted constitute an adequate scientific bridge to the reference product, such that reliance on the safety and effectiveness of Janumet XR is justified.

Benefit-Risk Dimensions

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • In 2021, the Center for Disease Control estimated that 38.4 million people in the United States have diabetes mellitus. Of these, the American Diabetes Association estimated that 36.4 million people have T2DM.<br>• Diabetes mellitus is associated with multiple complications including macrovascular and microvascular complications which may shorten and affect the quality of life of patients.<br>• Studies have shown that improving glycemic control in patients with diabetes mellitus improved clinical outcomes (e.g., reduction in retinopathy).<br>• Many diabetic patients also have additional risk factors such as smoking, obesity, hypertension and hyperlipidemia which contribute to their overall health burden. | • Diabetes mellitus is highly prevalent in the United States and is a serious condition associated with chronic morbidity and premature death due to associated vascular complications.<br><br>• Glycemic control of diabetes mellitus improves microvascular complications. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Current Treatment Options | • Thirteen classes of drugs are FDA approved in the United States to improve glycemic control in patients T2DM.<br>• There are multiple metformin products, including immediate- and extended-release.<br>• Sitagliptin in combination with metformin XR is currently only available as Janumet XR | There are multiple effective treatment options available for the treatment of T2DM, including multiple IR and ER metformin formulations.<br><br>Janumet XR is currently the only fixed-dose combination product that consists of both sitagliptin and metformin XR. |
| Benefit | • Zituvimet XR is a fixed dose combination product that includes sitagliptin and metformin XR together in a single tablet.<br>• There is currently only one fixed dose combination product that includes sitagliptin and metformin XR on the market – Janumet XR. | Zituvimet XR would be only the second sitagliptin/metformin XR combination product on the market, which would increase accessibility by increasing availability.<br><br>Better access to a once-daily dosed medication that is a combination of two glucose-lowering medications could help simplify the glucose control medication regimens of more patients with T2DM, which could improve adherence. |
| Risk and Risk Management | • The safety of Zituvimet XR is expected to be similar to that of the reference drug Janumet XR | The data and information submitted comprise an adequate scientific bridge between Zituvimet XR and Janumet XR such that reliance on the safety and effectiveness of Janumet XR is justified. |

### 1.2. Patient Experience Data

Not applicable.

## 2. Therapeutic Context

### 2.1. Analysis of Condition

T2DM is a disease of impaired glucose homeostasis resulting in chronic hyperglycemia that is associated with significant morbidity and mortality due to microvascular and macrovascular pathologies, and is a major cause of hospitalization, blindness, renal failure, amputations and cardiovascular (CV) disease. Patients have varying degrees of insulin resistance and are unable to maintain euglycemia with endogenous insulin secretion.

### 2.2. Analysis of Current Treatment Options

There is no cure for T2DM, but therapies aimed at improving glycemic control are available. Currently approved therapies in T2DM aim to improve glycemic control by improving insulin resistance, enhancing insulin secretion, or increasing glucose excretion.

Several classes of drugs are currently approved for the treatment of T2DM, used either alone or in combination. These drug classes include:

- Biguanides (i.e. metformin)
- Sulfonylureas
- Thiazolidinediones (TZDs)
- Meglitinides
- DPP-4 inhibitors
- Glucagon-like peptide-1 receptor agonists (GLP-1 RA)
- GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) co-agonist (i.e. tirzepatide)
- Sodium-glucose cotransporter-2 (SGLT2) inhibitors
- Alpha-glucosidase inhibitors
- Amylin-mimetics

- Dopamine agonist (i.e. bromocriptine)
- Insulin and insulin analogues
- Bile acid sequestrants (i.e. colesevelam hydrochloride)

Despite the relatively large number of drugs available for the treatment of T2DM, a substantial proportion of patients either remain under poor glycemic control or experience deterioration of glycemic control after an initial period of successful treatment with an anti-diabetic drug.

Relevant to this application, sitagliptin and metformin are currently widely used both alone and in combination with each other and with a range of other oral hypoglycemic agents, for treatment of T2DM. The first-line treatment for T2DM, metformin, was approved by the US FDA in December 1994. There are currently over 100 metformin products currently on the market, including immediate-release (IR) and extended-release (XR or ER) formulations. There are currently four approved DPP-4 inhibitors in the US market, of which sitagliptin was the first, approved in October 2006. There is currently only one approved fixed-dose combination product containing both metformin XR and sitagliptin, and that is Janumet XR, approved by the US FDA in 2012.

# 3. Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

Table 1 Related Regulatory History Summary

| Drug | Regulatory Event | Approval Date |
|---|---|---|
| Metformin | IND 027966 opened Feb 1986 (Lipha Pharmaceuticals, Inc) | |
| | NDA 020357 opened 09/29/1993 | Approved 03/03/1995, as Glucophage (EMD Serono Inc) |
| Metformin XR | NDA 021202 opened 11/12/1999 | Approved 10/13/2000 as Glucophage XR (EMD Serono Inc) |
| Januvia (sitagliptin) | IND 065495 opened 08/12/2002 (Merck and Co Inc) | |
| | NDA 021995 opened 12/16/2015 | Approved 10/16/2006 as Januvia (Merck and Co Inc) |

| | | |
|---|---|---|
| Zituvio (sitagliptin) | NDA 211566 opened on 11/02/2020 as a 505(b)2 application (Zydus Lifesciences Global FZE) | Approved on 10/18/2023 |
| Zituvimet (sitagliptin/metformin) | NDA 216743 opened on 09/24/2021 as a 505(b)2 application (Zydus Lifesciences Global FZE) | Approved on 11/03/2023 |
| Zituvimet XR (sitagliptin/metformin extended-release) | NDA 216778 submitted on 09/22/2023 (Zydus Worldwide DMCC) | |

## 3.2. Summary of Presubmission/Submission Regulatory Activity

12/09/2021 - Type B Written Response Only (WRO) meeting

- A 505(b)2 application may be appropriate for Zituvimet XR given the long history of usage of sitagliptin and metformin hydrochloride-containing products.
- Additional nonclinical studies may be needed, depending upon review of the quality data
- The proposed relative bioavailability (BA) studies under fasting and fed conditions comparing the highest dose Zituvimet XR tablet (100/1000mg) to equivalent dose of the listed drug Janumet XR would be sufficient to establish a pharmacokinetic bridge.
- A bioequivalence waiver for the other tablet dosages (50mg/500mg and 50mg/1000mg) would depend upon the findings of a dose-proportionality study across the different strengths of the proposed drug product. Otherwise, bioequivalence should be demonstrated on the highest and lowest strengths, and biowaiver for the middle strength(s) contingent upon the comparison of the dissolution profiles of the middle strength(s) versus the highest and lowest strengths.
- Due to the change in form of sitagliptin from sitagliptin phosphate monohydrate to sitagliptin free base, Zituvimet XR would be subject to PREA requirements. However, partial waivers of PREA requirements could apply based on studies being impossible or highly impracticable in patients from birth to under 11 years of age, and sitagliptin having previously not demonstrated to be effective in the 11–17-year-old patient group.
- A minimum of 12 months of long-term and 6 months of accelerated stability data is necessary and should be in the NDA submission.

04/14/2022 – Type C WRO meeting to discuss questions about the responses in the 12/09/2021 Type B meeting.

- The Agency agreed that the proposed strengths (50 mg/500 mg and 50 mg/1000 mg) would be eligible for biowaiver if they fulfill the conditions of proportional similarity per the FDA

Draft Guidance for Industry, "Bioavailability Studies Submitted in NDAs or INDs – General Considerations" of formulation across all strengths, if there is acceptable bioequivalence studies on the 100 mg/1000 mg strength, and if dissolution profile similarity (e.g., f2) is demonstrated.

- The Agency agreed that 6 months accelerated and 6 months long-term stability data for one exhibit batch of all strengths manufactured with alternate source API batch is acceptable for submission in the initial NDA due to the equivalence of the impurity profiles and physiochemical properties.

### 3.3. Foreign Regulatory Actions and Marketing History

Zituvimet XR is not yet approved for marketing in any country.

## 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

### 4.1. Office of Scientific Investigations (OSI)

Because the submission did not include clinical data other than the bioequivalence studies, OSI was not involved in the review of NDA 216778. Instead, the Office of Study Integrity and Surveillance (OSIS) was consulted regarding the bioequivalence studies. OSIS determined new on-site inspections were not needed for the clinical or analytic sites. ORA had previously inspected the clinical study site in July 2022 under ANDA (b) (4) and OSIS had previously conducted a Remote Regulatory Assessment (RRA) of the analytical site in (b) (4) under ANDAs (b) (4) and (b) (4) OSIS determined that the data from those reviewed studies submitted in ANDAs (b) (4), (b) (4), and (b) (4) were reliable. Based on the previous ORA inspection and the previous RRA, OSIS determined that inspections are not needed for either site for NDA 216778. Please refer to the OSIS review memo [CONSULT REV-DSI-05 (Bioequivalence Establishment Inspection Report Review)] dated 12/04/2023 for more details.

### 4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) Review team assessed the Chemistry, Manufacturing, and Controls (CMC) information for the NDA 216778 submission and determined that the NDA meets all applicable standards to support the quality and purity of the Zituvimet XR drug product. OPQ recommends approval of this NDA from a quality perspective.

This 505(b)(2) NDA, 216778 is for a [redacted]tablet containing sitagliptin free base [redacted] and metformin hydrochloride [redacted] provided as 50 mg/500mg, 50mg/1000mg and 100/1000mg in 30ct or 60ct high density polyethylene (HDPE) bottles with desiccant. The listed drug (LD) product, JANUMET® XR (sitagliptin and metformin hydrochloride extended release) tablets (NDA 202270) contains sitagliptin phosphate monohydrate and metformin HCl.

The manufacturing process involves species that could potentially form nitrosamine impurities, including [redacted] and [redacted]) so this was an important focus of the quality review. Evaluation found that no [redacted] are used in the manufacturing process of the drug substance, and the [redacted] impurity is controlled at NMT [redacted] ppm level in the drug substance, which based on the MDD of metformin hydrochloride of 2.0 gm/day, is well below the AI limit for [redacted] of NMT [redacted] ppm per the guidance for Control of Nitrosamine Impurity Drugs. It was also concluded that there is no potential for formation of nitrosamine impurity in the sitagliptin free base drug substance. [redacted] Based on 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. [redacted] Section 16 of the USPI includes instructions 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."

The applicant requested a biowaiver for the lower strengths (i.e., sitagliptin and metformin hydrochloride tablet, 50 mg/500 mg and 50mg/1000mg) on the basis that the proposed strength tablets are proportionally similar in composition of their active and inactive ingredients and provided in-vitro dissolution profile information. Biopharmaceutics review concluded that the information provided was satisfactory for the biowaiver request.

The different strengths of Zituvimet XR (50 mg/500 mg, 50 mg/1000 mg, and 100 mg/1000 mg sitagliptin/metformin, respectively) are distinguishable from one another based on size [redacted], color, and markings. The tablet strengths are consistent with approved metformin and sitagliptin products on the market. All excipients and coating components are compendial, in quantities present at acceptable levels for a maximum daily dose of 100 mg sitagliptin and 2000 mg metformin hydrochloride based on FDA's Inactive Ingredients Database (IID). Iron oxides are used in the coloring of the tablets [redacted]

The tablets are offered in HDPE bottles containing silica gel + activated carbon desiccant

sachets. The 50 mg/500 mg strength is offered in bottles of 60 tablets. The 50 mg/500 mg tablets are offered in bottles of 60 tablets. The 100 mg/1000 mg strength are offered in bottles of 30 tablets.

Below are the nomenclature, molecular structure, molecular formula, CAS number, molecular weight, and pharmacological class of each component of this fixed-combination drug product.

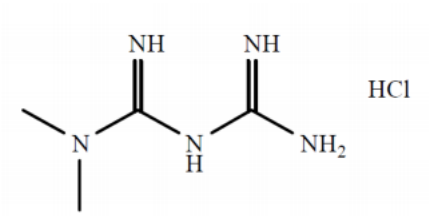
Metformin Hydrochloride

USAN: Metformin Hydrochloride

CAS No.: 1115-70-4

Chemical Names: 1,1-Dimethylbiguanide monohydrochloride

General properties:




**Metformin Hydrochloride, USP**

Molecular Formula: $C_4H_{11}N_5 \cdot HCl$

Molecular weight: 165.62 g/mol

Metformin Hydrochloride is a white, crystalline free flowing powder. It is an achiral molecule, freely soluble in water. The substance is slightly hygroscopic, and the partition coefficient is 1.43.

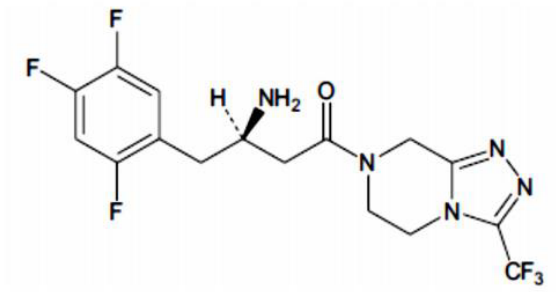
Sitagliptin Free Base

USAN: Sitagliptin

CAS No.: 486460-32-6

Chemical Names: (R)-3-Amino-1-(3-(trifluoromethyl)-5,6-dihydro [1,2,4] triazolo [4,3-a]pyrazine-7(8H)-yl)-4-(2,4,5-trifluorophenyl)butan-1-one

General properties:




**Sitagliptin Free Base**

Molecular Formula: C16H15F6N5O

Molecular weight: 407.31 g/mol

Sitagliptin is a white to off-white powder. It is a single enantiomer, highly soluble in aqueous media. The substance is non- hygroscopic, and the partition coefficient is 1.95. XRPD data demonstrate that the drug substance obtained from Zydus Lifesciences Limited only exist as (b) (4)

For more details on the product quality review please refer to REV-QUALITY-25 (Integrated Quality Review) dated 06/12/2024 by Dr. Muthukumar Ramaswamy.

## 4.3. Clinical Microbiology

Not applicable.

## 4.4. Nonclinical Pharmacology/Toxicology

Two types of impurities were the main subjects of the nonclinical pharmacology/toxicology review:

a) (b) (4), a (b) (4) impurity contained in the drug substance and product, was noted to exceed the 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 [Zituvio (sitagliptin free base)]. No remarkable toxicity of (b) (4) was observed in this study, up to the highest dose ((b) (4) mg/kg/day PO) corresponding to (b) (4) fold maximum human exposure (based on body surface area). Therefore, the reviewer's conclusion is that the Applicant's proposed specification limit for (b) (4) (b) (4) (not more than (b) (4) in shelf-life) is adequate.

b) Nitrosamines:

a. [redacted] in the metformin drug substance was not detected [redacted] ppm). The sponsor tested multiple stability batches and reported that [redacted] content is [redacted]

b. [redacted] in the sitagliptin drug product did not exceed the specification limit of [redacted] ppm ([redacted] ng/day for daily dose of 100 mg sitagliptin drug product). The applicant's [redacted] oposed control limit of [redacted] ng/day [redacted] ppm in drug product for daily dose of 100 mg sitagliptin) is acceptable based on FDA's current guidance.

**Table 2 [redacted] and [redacted] specification limits**

[redacted]

The review concluded that, based on these findings, the safety concerns regarding the presence of the two potential nitrosamine impurities [redacted] and [redacted] were adequately addressed in the NDA submission.

Please refer to the Nonclinical review memo by Dr. Karen Hao dated 06/05/2024 for more details.

## 4.5. Clinical Pharmacology

Clinical Pharmacology review concludes that the submitted pharmacokinetic (PK) results of the bioequivalence (BE) studies performed by the Sponsor are acceptable to support approval of Zituvimet XR from a clinical pharmacology perspective. The main conclusions are:

- The results of Study C1B01591, the pivotal single-dose fasting study, indicate that Zituvimet XR 100 mg/1000 mg (Test; T) is bioequivalent to Merck's JANUMET® XR 100 mg/1000mg (Reference; R) under **fasted conditions**, based on the 90% CI of the

geometric mean ratios (GMRs) for Cmax, AUCt and AUCi of sitagliptin and metformin for T and R being within the FDA-defined BE acceptance criteria of 80 – 125%.

- The results of Study C1B01592, the pivotal single-dose fed study, indicate that Zituvimet XR 100 mg/1000 mg (T) is BE to Merck's JANUMET® XR 100 mg/1000mg (R) under fed conditions as well, based on the 90% CI of the GMRs for Cmax, AUCt and AUCi of sitagliptin and metformin for T and R being within the FDA-defined BE acceptance criteria of 80 – 125%.

Please refer to the Clinical Pharmacology review dated 6/10/2024 by Dr. Deepa Rao for more details.

### 4.6. Devices and Companion Diagnostic Issues

Not applicable

### 4.7. Consumer Study Reviews

The Division of Medication Error Prevention and Analysis (DMEPA) proprietary name review did not identify any names that represent a potential source of drug name confusion and maintained its previous finding that the proposed proprietary name, Zituvimet XR, is conditionally acceptable. Please review to Proprietary Name Memorandum dated December 8, 2023 by Dr. Vraj Patel.

## 5. Sources of Clinical Data and Review Strategy

### 5.1. Table of Clinical Studies

Table 3 Summary of Clinical Studies

| Trial Identity | Trial Design | Regimen/ schedule/ route | Study Endpoints | Treatment Duration/ Follow Up | No. of patients enrolled (completed) | Study Population |
|---|---|---|---|---|---|---|
| Bioequivalence study – fasting (C1B01591) | Open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study in healthy adult human subjects after overnight fast of at least 10 hours. | Reference product: Janumet XR (sitagliptin phosphate monohydrate/metformin XR) 100mg /1000mg oral tablet<br><br>Test product: Zituvimet XR (sitagliptin free base/metformin XR) 100mg/1000mg oral tablet | PK parameters | Duration: single-dose<br><br>Follow-up: 9-10 day washout period between the R and T product dosing.<br><br>48 hour observation period post-dose | 32 (30) | Healthy adults age 18 to 45 with BMI 18.5 to 30.0 $kg/m^2$ |
| Bioequivalence study – fed (C1B01592) | Open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study in healthy adult human subjects, dosed 30 minutes after a standardized high-fat & high-calorie breakfast served after an overnight fast of at least 10 hours. | Reference product: Janumet XR (sitagliptin phosphate monohydrate/metformin XR) 100mg /1000mg oral tablet<br><br>Test product: Zituvimet XR (sitagliptin free base/metformin XR) 100mg/1000mg oral tablet | PK parameters | Duration: single-dose<br><br>Follow-up: 9-10 day washout period between the R and T product dosing.<br><br>48 hour observation period post-dose | 32 (28) | Healthy adults age 18 to 45 with BMI 18.5 to 30.0 $kg/m^2$ |

### 5.2. Review Strategy

The clinical program only involved two clinical pharmacology bioequivalence studies bridging the proposed Zituvimet XR product to Janumet XR as the reference listed drug. The studies are summarized in section 5.1, and a detailed review can be found in the Clinical Pharmacology review by Dr Deepa Rao. The Applicant has proposed to rely on FDA's finding of safety and effectiveness for Janumet XR (NDA 202270) in this 505(b)(2) application. To justify the reliance, the Applicant demonstrated bioequivalence of Zituvimet XR to Janumet XR. The clinical review of NDA 216778 is therefore limited to review of the adverse event, clinical laboratory, and vital sign data from the two bioequivalence studies to confirm that no clinical safety issues were observed in these studies that would preclude the conclusion of safety based on the reliance on Janumet XR.

## 6. Review of Relevant Individual Trials Used to Support Efficacy

### 6.1. Assessment of Efficacy Across Trials

Efficacy is based on FDA's previous findings of safety and effectiveness for Janumet XR. See the Clinical Pharmacology review by Dr. Deepa Rao for discussion of the adequacy of the BA/BE studies to comprise a scientific bridge.

## 7. Review of Safety

### 7.1. Safety Review Approach

Results of two clinical BA/BE studies were submitted with this NDA application, to establish a scientific bridge between Zituvimet XR and the reference listed drug, Janumet XR. Both studies were open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose studies; one of the studies was done under fasting conditions (C1b01591), and the other study done under fed conditions (C1B01592). Each study enrolled 32 patients, for a total of 64 patients across both studies. It should be noted that bioequivalence studies are not generally intended for evaluation of safety, however there was a limited amount of safety data collected in these studies, including laboratories, vital signs, and adverse events (AEs). I reviewed all AEs, serious adverse events, and deaths in the two clinical studies. There were no serious adverse events or deaths. There were 6 AEs in the fasting study, which were vomiting

and increased eosinophil count. There were 5 AEs in the fed study, which were mostly vomiting. All case report forms (CRFs) of subjects with AEs were reviewed. One of the subjects with vomiting also had increased transaminases. Review of the case report form for this subject revealed that in this case, these AEs occurred outside of the washout period of Zituvimet XR, just prior to being dosed with the reference drug. Therefore, I concluded that this subject's vomiting and transaminitis were unlikely to be related to the drug. All AEs were mild in severity, and were evenly distributed between Zituvimet XR and Janumet XR.

None of these data precludes relying on the conclusion that the demonstration of bioequivalence justifies reliance on FDA's previous finding of Janumet XR.

#### 7.1.1. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

### 7.2. Safety in the Postmarket Setting

#### 7.2.1. Safety Concerns Identified Through Postmarket Experience

Zituvimet XR is not approved in any country.

#### 7.2.2. Expectations on Safety in the Postmarket Setting

The safety of Zituvimet XR is expected to be similar to the safety of the reference product Janumet XR.

#### 7.2.1. Additional Safety Issues From Other Disciplines

None.

### 7.3. Integrated Assessment of Safety

No safety-focused clinical studies were performed by the applicant in support of this application. Review of adverse events (AEs) from the single-dose crossover BE studies was conducted. Of the 64 healthy volunteers who enrolled across both studies (32 subjects in the fed study, 32 subjects in the fasting study), there were no serious adverse events (SAE), and no deaths. The most common type of AE was mild vomiting in 5 subjects (3 subjects in the fasting study and 2 subjects in the fed study), which resulted in those subjects' discontinuation from the respective studies, and was evenly distributed between the test and reference product. In 1 of the subjects in the fed study who experienced vomiting, the vomiting occurred just prior to receiving the crossover dose (which in this case was the reference product), after the washout period for the test product had already elapsed, and was therefore thought to be unlikely to be related to the study drug. In conclusion, there are no new safety concerns arose in the two BE studies performed, and the events observed are all consistent with the labeling of the reference

product.

I conclude that Zituvimet XR is safe in adults with T2D, based on a reliance on FDA's previous finding of safety for Janumet XR in adults with T2D. The reliance is justified by the scientific bridge between Zituvimet XR and Janumet XR established by the demonstration of BE. No safety data collected in Studies C1B01591 or C1B01592 preclude this conclusion.

## 8. Advisory Committee Meeting and Other External Consultations

Not applicable.

## 9. Labeling Recommendations

### 9.1. Prescription Drug Labeling

The applicant submitted a label based on the label of the reference drug, Janumet XR. The following changes were made to the Prescribing Information:

- Edits to bring label into compliance with existing regulations and guidances
- Corrected the "Initial US Approval" date from (b) (4) to 2007 to reflect the date of the first approval of a combination of sitagliptin and metformin.
- Revised language for consistency with the Zituvimet PI and for consistency with the draft guidance for industry: Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (July 2018)
- Deleted information about (b) (4) from Section 6 (Adverse events) since it is already stated in the Warnings and Precautions section and for consistency with other metformin fixed dose combination product labeling.
- Included information about the child-resistant closure

### 9.2. Nonprescription Drug Labeling

Not applicable.

## 10. Risk Evaluation and Mitigation Strategies (REMS)

No REMS was recommended for this application.

# 11. Postmarketing Requirements and Commitments

No postmarketing requirements or commitments are recommended for this application.

# 12. Appendices

## 12.1. References

None

## 12.2. Financial Disclosure

The bioequivalence studies were conducted at a single site, with only one investigator.

Covered Clinical Study (Name and/or Number): Fasting Study #C1b01591
Fed Study #C1b01592

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 1 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): None | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): Form 3455 not submitted because Sponsor stated it was not applicable | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>Sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) None | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

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**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.**

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/s/

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SUSAN J YUDITSKAYA
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07/18/2024 06:36:09 AM