CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216743Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date of Consult Request:	June 23, 2023
From:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
To:	Division of Pediatric and Maternal Health (DPMH)
NDA:	216743
Drug:	sitagliptin and metformin hydrochloride tablets
Applicant:	Zydus Worldwide DMCC
Indication:	As an adjunct to diet and exercise to improve glycemic control in adults with T2DM

DDLO submitted a consult request to DPMH on June 23, 2023: "Provide input on pediatric information in Section 8.4 of the proposed labeling, which is protected by patent exclusivity (M-187 *PED, Exp. 6/4/2024) on the innovator product (Janumet, N022044). Of note, the proposed language in this NDA is similar to the language in N211566 (sitagliptin) which was found adequate by DPMH in 2021 (Tentatively approved)."

DPMH attended the internal labeling, team, and Pediatric Review Committee (PeRC) meetings and provided comments.

DPMH has no further comments at this time, thus, this memorandum will close out the consult request.

DPMH Pediatric MTL:	Mona Khurana
DPMH Pediatric reviewer:	Charlotte Jones
DPMH RPM:	Denise Pica-Branco
DPMH SCSO:	Rosemary Addy

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/s/

DENISE J PICA-BRANCO
10/19/2023 12:52:18 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 12, 2023
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 216743
Product Name, Dosage Form, and Strength:	Zituvimet (sitagliptin and metformin hydrochloride) tablets, 50 mg/500 mg and 50 mg/1,000 mg
Applicant/Sponsor Name:	Zydus Pharmaceuticals Inc. (Zydus)
TTT ID #:	2023-3228-4
DMEPA 1 Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

Zydus submitted revised Zituvimet container labels on October 10, 2023. The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the revised container labels for Zituvimet (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Zydus addressed and implemented all of our recommendations and we have no additional recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Conrad, A. Review of Revised Label and Labeling Memorandum for Zituvimet (NDA 216743). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Oct 4. TTT ID No.: 2023-3228-3.

Reference ID: 5259577

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/s/

ARIANE O CONRAD
10/12/2023 11:50:55 AM

IDALIA E RYCHLIK
10/12/2023 12:20:22 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 11, 2023

To: Michael Oyewole, PharmD, Regulatory Project Manager, Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Justin Penzenstadler, PharmD, Clinical Reviewer, DDLO

Melinda Wilson, PharmD, MPH, Associate Director for Labeling, DDLO

From: Tierra Butler, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sapna Shah, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZITUVIMET (sitagliptin and metformin hydrochloride) tablets, for oral use

NDA: 216743

Background:

In response to DDLO's consult request dated January 10, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original NDA submission for ZITUVIMET (sitagliptin and metformin hydrochloride) tablets, for oral use (Zituvimet).

PI/Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on September 26, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on October 5, 2023.

Carton and Container Labeling:
OPDP's review of the proposed container labeling is based on the draft labeling emailed to OPDP on September 26, 2023 and we do not have any comments at this time.

Reference ID: 5258694

Thank you for your consult. If you have any questions, please contact Tierra Butler at (301) 796-1368 or tierra.butler@fda.hhs.gov.

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/s/

TIERRA N BUTLER
10/11/2023 10:23:37 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 5, 2023
To:	Anne (Christine) Wright Regulatory Project Manager **Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Tierra Butler, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ZITUVIMET (sitagliptin and metformin hydrochloride)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 216743
Applicant:	Zydus Worldwide DMCC

1 INTRODUCTION

On January 3, 2023, Zydus Worldwide DMCC submitted for the Agency's review New Drug Application (NDA) #216743 for ZITUVIMET (sitagliptin and metformin hydrochloride). The proposed indication for ZITUVIMET (sitagliptin and metformin hydrochloride) is an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Diabetes, Lipid Disorders, and Obesity (DDLO), on January 11, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ZITUVIMET (sitagliptin and metformin hydrochloride) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft ZITUVIMET (sitagliptin and metformin hydrochloride) MG received by the Review Division on January 3, 2023, and received by DMPP and OPDP on September 26, 2023.
- Draft ZITUVIMET (sitagliptin and metformin hydrochloride) Prescribing Information (PI) received on January 3, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 26, 2023.
- Approved JANUMET comparator labeling dated June 21, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the IFU document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
10/05/2023 01:26:53 PM
DMPP-OPDP review of sitagliptin and metformin hydrochloride (ZITUVIMET) NDA 216743 MG

TIERRA N BUTLER
10/05/2023 01:37:17 PM

MARCIA B WILLIAMS
10/05/2023 02:12:52 PM

LASHAWN M GRIFFITHS
10/05/2023 02:13:33 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 4, 2023
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 216743
Product Name, Dosage Form, and Strength:	Zituvimet (sitagliptin and metformin hydrochloride) tablets, 50 mg/500 mg and 50 mg/1,000 mg
Applicant/Sponsor Name:	Zydus Pharmaceuticals Inc. (Zydus)
TTT ID #:	2023-3228-3
DMEPA 1 Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

Zydus submitted revised Zituvimet container labels on September 28, 2023. The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the revised container labels for Zituvimet (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] We note that Zydus (b) (4) (b) (4)

2 CONCLUSION

We note that Zydus implemented our prior recommendations; however, we note that they also made additional modifications. Thus, our review of the revised container labels determined

[a] Conrad, A. Label and Labeling Review for Zituvimet (NDA 216743). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Sep 21. TTT ID No.: 2023-3228-2.

[b] Cover Letter Response to Information Request for sitagliptin and metformin hydrochloride (NDA 216743). Pennington (NJ): Zydus Pharmaceuticals (USA) Inc; 2021 Sep 21. Available from: \\CDSESUB1\EVSPROD\nda216743\0018\m1\us\cover-letter-0018-09212023.pdf.

Reference ID: 5255692

that they are unacceptable from a medication error perspective, and we have identified areas of improvement for Zydus to address in Section 3.

3 RECOMMENDATIONS FOR ZYDUS PHARMACEUTICALS INC.

We recommend the following be implemented prior to approval of this NDA:

A. We note that you have added the street address of the manufacturer and distributer to the bottle label per recommendations made by the Agency for the prescribing information. However, considering the space limitations on the bottle labels, we recommend removing this information from the label. Please note that the name of the manufacturer and distributor are required on the container label in accordance with 21 CFR 201.10(i) but the address information is not required.

B. To improve readability and prominence of the more important information on the side panel, we recommend removing the bold font from some of the information. Of note, consider removing the bold font from the following statements: "Recommended Dosage: See prescribing information", "This package is child-resistant. Keep this and all drugs out of the reach of children.", "Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F), [see USP Controlled Room Temperature]", "Mfg. by: Zydus Lifesciences Ltd., Pharmez, Matoda, Ahmedabad, India", and "Dist. by: Zydus Pharmaceuticals (USA) Inc. Route 31 North, Pennington, NJ 08534".

C. We note that you have revised the Medication Guide statement on the principal display panel to read "(b) (4) (b) (4) to combine the information regarding the medication guide that previously appeared on the side panel. However, we note that the document should be provided when dispensing the product and that the website information and telephone number are not required on the container label. Thus, we recommend reverting the Medication Guide statement back to its prior presentation "Dispense the enclosed Medication Guide to each patient." and omitting the prior statement (b) (4) (b) (4) Of note, you may include the website information and phone number on the side panel as space will allow.

D. We note that you have included a pink broken line box around the lines following "Discard 3 months after:"; however, it is unclear if this is for illustrative purposes only or if you intend to include these lines on the marketed label. Please clarify. If you do not intend to include these lines on the final label, please remove them from the mock-ups submitted for review.

E. Consider revising the statement "(b) (4) ." to read "This package is child resistant. Keep out of reach of children."

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/s/

ARIANE O CONRAD
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IDALIA E RYCHLIK
10/04/2023 03:34:51 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 21, 2023
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 216743
Product Name, Dosage Form, and Strength:	Zituvimet (sitagliptin and metformin hydrochloride) tablets, 50 mg/500 mg and 50 mg/1,000 mg
Applicant/Sponsor Name:	Zydus Pharmaceuticals Inc. (Zydus)
TTT ID #:	2023-3228-2
DMEPA 1 Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

Zydus submitted NDA 216743 via the 505(b)(2) pathway on January 3, 2023. We evaluated the proposed bottle labels and product labeling for Zituvimet in a prior review, and we determined that they were acceptable at that time.[a] On September 1, 2023, Zydus submitted updated bottle label mockups, which included a mockup for a (b) (4) presentation, and we were asked to review the revised labels (Appendix A).

In addition, based on data reviewed by the Office of Product Quality (OPQ)/Chemistry, Manufacturing, and Controls (CMC), we were notified of product quality issues impacting product storage and expiration. Based on the information reviewed, their position regarding Zydus's sitagliptin labeling is as follows:

1. "*The expiration date will be set for 12 months when packaged in the original container with a desiccant.*
2. *Once the container is opened, the drug should be used within 3 months. The expiry date will be 3 months after first use (or being dispensed in a container without desiccant).*
3. *Expiry period will be up to 3 months after first opening or 12 months from date of manufacture, whichever comes first.*

[a] Conrad, A. Review of Revised Label and Labeling Memorandum for Zituvimet (NDA 216743). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 May 10. RCM No.: 2023-3228-1.

Reference ID: 5248246

4. [redacted] (b) (4)

Therefore, the "*12 month expiry date will be stamped on the bottle (all configurations) by the manufacturer. Once a user opens the bottle, they have up to 3 months to use it provided that this 3 months does not exceed the stamped expiry date. We would recommend adding a statement along these lines:*

Use within 3 months after first use. Date of opening: Expiry date: 3 months after first use."

2 DISCUSSION

We note that Zydus proposes to market 60 count, 180 count, [redacted] (b) (4) bottle presentations for this sitagliptin and metformin product. However, considering that Zydus's [redacted] (b) (4) We have no concerns regarding the proposed unit dose 60 count and 180 count bottles.

Thus, based on our discussions with the OPQ/CMC reviewer, we proposed the following to the review team for consideration:

1. Per CMC, the 12-month expiration date will be stamped on the bottle (all configurations) by the manufacturer. In addition, the product should be used within 3 months of opening the bottle.
2. Removal of the [redacted] (b) (4) from the proposed label and retention of the unit-dose 60 count and 180 count bottles only.
3. Addition of a statement on the 60 count and 180 count bottles indicating that the product should be dispensed in the original container and add a notation on the bottles to indicate the expiration date after opening the bottle (See Section 5).

Following discussion of these concerns with the review team, the Office of Product Quality (OPQ)/Chemistry, Manufacturing, and Controls (CMC) formally communicated to Zydus that [redacted] (b) (4)

[b] Wright, A. FDA Communication: NDA 216743/Zituvimet (sitagliptin and metformin hydrochloride) tablets Information Request. Silver Spring (MD): FDA, CDER, OND, DDLO (US); 2023 Sep 18. NDA 216743. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806f5554.

Thus, we provide labeling recommendations below in Section 4 for the remaining bottle presentations (60 count and 180 count) to address this concern.

3 CONCLUSION

We note that Zydus has been advised to remove the each of [redacted] (b) (4) from the Zituvimet product labeling. The 60 count and 180 count bottle presentations for Zituvimet are unacceptable from a medication error perspective because they contain inadequate information necessary for the safe use and storage of the product. We provide recommendations in Section 4.

4 RECOMMENDATIONS FOR DIVISION OF DIABETES, LIPID DISORDERS, AND OBESITY (DDLO)

A. Prescribing Information
    1. How Supplied/Storage and Handling Section 16
        a. For additional clarity regarding the storage instructions, we recommend adding the statements "Dispense in original container to protect from moisture. Once the bottle has been opened, the product must be used within 3 months." so that the storage information reads as follows: "Store at 20° to 25°C (68° to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F), [see USP Controlled Room Temperature]. Dispense in original container to protect from moisture. Once the bottle has been opened, the product must be used within 3 months."

5 RECOMMENDATIONS FOR ZYDUS PHARMACEUTICALS INC.

We recommend the following be implemented prior to approval of this NDA:

A. We note that the stability data for this product indicates that the product must be used within 3 months after removal of the desiccant from the manufacturer bottle and that you have been advised to withdraw the [redacted] (b) (4) from the Zituvimet labeling. Thus, our labeling recommendations apply to the 60 count and 180 count bottles only.
    A. To improve communication of the storage recommendations, add the statement "Dispense in Original Container-Use within 3 months of opening" to the principal display panel (PDP).
    B. Considering the stability data, we recommend revising the storage information to read as follows: "Store at 20° to 25°C (68° to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F), [see USP Controlled Room Temperature]. Store in original container to protect from moisture. Once the bottle has been opened, the product must be used within 3 months."
    C. Because the product has a different beyond-use date after opening the bottle, we note that the label should have a designated space and format for the end-user to write the beyond-use date to minimize the risk of deteriorated drug medication errors. Thus, we recommend including space for end users to write

the beyond-use date on the side panel of the container label. For example: “Discard 3 months after ___/____/____”.

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/s/

ARIANE O CONRAD
09/21/2023 09:06:58 AM

IDALIA E RYCHLIK
09/21/2023 02:46:27 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 10, 2023
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 216743
Product Name, Dosage Form, and Strength:	Zituvimet (sitagliptin and metformin hydrochloride) tablets, 50 mg/500 mg and 50 mg/1,000 mg
Applicant/Sponsor Name:	Zydus Pharmaceuticals Inc. (Zydus)
TTT ID #:	2023-3228-1
DMEPA 1 Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels for Zituvimet on May 2, 2023. The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the revised container labels for Zituvimet (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] Of note, Zydus responded to each labeling recommendation and provided their rationale for any alternative changes made to the labels.[b]

2 CONCLUSION

The Applicant implemented our recommendations and we have no additional recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Conrad, A. Label and Labeling Review for Zituvimet (NDA 216743). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Apr 19. TTT ID No.: 2023-3228.
[b] Response to Information Request for Zituvimet (NDA 216743). Pennington (NJ): Zydus Pharmaceuticals (USA) Inc.; 2023 May 2. Available from: \\CDSESUB1\EVSPROD\nda216743\0012\m1\us\cover-letter-0012-05022023.pdf.

Reference ID: 5172027

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/s/

ARIANE O CONRAD
05/10/2023 06:12:49 PM

IDALIA E RYCHLIK
05/11/2023 09:03:28 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 19, 2023
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 216743
Product Name, Dosage Form, and Strength:	Zituvimet[a] (sitagliptin and metformin hydrochloride) tablets, 50 mg/500 mg and 50 mg/1,000 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Zydus Pharmaceuticals Inc. (Zydus)
FDA Received Date:	January 3, 2023; April 10, 2023
TTT ID #:	2023-3228
DMEPA 1 Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

[a] The proposed proprietary name, Zituvimet, was found conditionally acceptable by DMEPA on March 27, 2023 (PNR ID# 2023-1044724917).

Reference ID: 5161099

1 REASON FOR REVIEW

As part of the approval process for Zituvimet (sitagliptin and metformin hydrochloride) tablets, the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the proposed Zituvimet prescribing information and container labels for areas of vulnerability that may lead to medication errors. Zydus submitted NDA 216743 via the 505(b)(2) pathway and the reference listed drug is Janumet (sitagliptin and metformin hydrochloride, NDA 022044), which was approved on March 30, 2007.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters*	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	B

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed prescribing information (PI) and container labels for Zituvimet to identify areas of vulnerability that may lead to medication errors and other areas of improvement. The proposed PI is acceptable; however, we identified some areas of concern for the proposed container labels, and we provide our recommendations below in Section 4.1 for Zydus.

4 CONCLUSION & RECOMMENDATIONS

The proposed labels for Zituvimet are not acceptable from a medication error perspective and we have provided recommendations to improve clarity below in Section 4.1.

4.1 RECOMMENDATIONS FOR ZYDUS PHARMACEUTICALS INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. We note that your planned format for the expiration date is defined as "DDMMMYYYY". FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.

2. We note that the (b) (4) used for the proposed Zituvimet container labels is the (b) (4) as that used for your proposed Zituvio (sitagliptin) product and this design similarity may contribute to selection errors between these products. We recommend that you consider using (b) (4) some other means to further distinguish the Zituvimet label from the Zituvio label. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.

3. Decrease the prominence of the statement "Rx Only" by removing the bold font as this information appears as prominent as other more important information on the principal display panel.

4. As currently presented, we note that there are two barcodes (linear barcode and Quick Response Code) on the label. Since the drug barcode is often used as an additional verification before drug administration in the inpatient setting, the presence of multiple barcodes is confusing to the healthcare providers. Therefore, we recommend you ensure that the barcode that does not contain the NDC number is presented in a size that does not compete with, distract from the presentation of other required or recommended information on the label.

5. We note that the statements "(b) (4) (b) (4)", "This package is child-resistant", and "Medication Guide available at www.zydususa.com/medguides or call 1-877-993-8779" are on the side panel. However, considering that the side panel appears crowded with information that is not required, we recommend that you consider the need for these statements and remove them from the side panel. If you choose to retain these statements, please provide your rationale for retaining each statement you intend to keep.

6. For improved clarity, we recommend revising the storage statement to include the degree symbol as follows: "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]".

7. In June 2021, FDA finalized guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers,

respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. The guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zituvimet received on April 10, 2023 from Zydus Pharmaceuticals Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Zituvimet and the Listed Drug		
Product Name	Zituvimet	Janumet[b]
Initial Approval Date	N/A	03/30/2007
Active Ingredient	sitagliptin and metformin hydrochloride	
Indication	an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	
Route of Administration	oral	
Dosage Form	tablets	
Strength	50 mg/500 mg and 50 mg/1,000 mg	
Dose and Frequency	• Take orally twice daily with meals. The maximum recommended daily dose is 100 mg of sitagliptin and 2000 mg of metformin HCl. • The recommended starting dose in patients not currently treated with metformin is 50 mg sitagliptin and 500 mg metformin HCl twice daily, with gradual dose escalation recommended to reduce gastrointestinal side effects associated with metformin. • The starting dose in patients already treated with metformin should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and the dose of metformin already being taken. For patients taking metformin HCl 850 mg twice daily, the recommended starting dose of is 50 mg sitagliptin and 1000 mg metformin HCl twice daily. • Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR) o Do not use in patients with eGFR below 30 mL/min/1.73 m^2. o Not recommended in patients with eGFR between 30 and less than 45 mL/min/1.73 m^2.	

[b] Janumet [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2023 Apr 17. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022044s052lbl.pdf.

How Supplied	50 mg/500 mg and 50 mg/1,000 mg: • bottles of 60 or 180 tablets with child-resistant closures	50 mg/500 mg and 50 mg/1,000 mg: • unit-of-use bottles of 60 or 180 tablets • bulk bottles of 1000 tablets
Storage	Store at 20-25°C (68-77°F)	

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Zituvimet labels and labeling submitted by Zydus Pharmaceuticals Inc.

- Container labels received on April 10, 2023
  - \\CDSESUB1\EVSPROD\nda216743\0011\m1\us\draft-container-labels.pdf
- Prescribing Information and Medication Guide received on April 10, 2023
  - \\CDSESUB1\EVSPROD\nda216743\0011\m1\us\draft-pi-doc.doc

B.2 Label and Labeling Images

50 mg/500 mg:

(b) (4)

[redacted]

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ARIANE O CONRAD
04/19/2023 04:48:59 PM

IDALIA E RYCHLIK
04/19/2023 05:30:17 PM

M E M O R A N D U M

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

DATE: 3/28/2023

TO: Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct on-site inspections**

RE: NDA 216743

The Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed for the site listed below. The rationale for this decision is noted below.

Rationale

Cliantha, Ahmedabad: The Office of Regulatory Affairs (ORA) inspected the clinical site in (b) (4). The inspection was conducted under the following submission: (b) (4).

The following item was discussed with the site:

- Informed consent did not inform subjects about unforeseeable risks from receiving the test drug product.

After review of the inspection findings, OSIS concluded that data from the reviewed studies were reliable.

(b) (4) OSIS conducted a Remote Regulatory Assessment (RRA) for the analytical site in (b) (4). The RRA was conducted under the following submissions: (b) (4) and (b) (4)

OSIS concluded that data from the reviewed studies were reliable.

Site

Facility Type	Facility Name	Facility Address
Clinical	Cliantha Research, Ltd.	Cliantha Corporate, TP 86, FP 28/1, Off S.P. Ring Road, Sarkhej, Ahmedabad, Gujarat, India
Analytical	(b) (4)	

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/s/

JAMES J LUMALCURI
03/28/2023 11:37:21 AM