18 October 2023

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

CITIZEN PETITION

Requesting That FDA Take Certain Actions with Respect to Sitagliptin Drug Substance and Sitagliptin Containing Drug Product

Dear Sir or Madam:

On behalf of Zydus Pharmaceuticals (USA) Inc. the undersigned submits this Citizen Petition pursuant to the Federal Food, Drug and Cosmetic Act (the "FD&C Act") and in accordance with 21 C.F.R. §§ 10.25, 10.30, 10.31 and 314.70 to request that the Commissioner of Food and Drugs take certain actions with respect to current approved RLD Januvia® Tablets (NDA no. N021995), Janumet® Tablets (NDA no. N022044), Janumet XR® Tablets (NDA no. N202270), Steglujan® Tablets (NDA no. N209805) and Sitagliptin as Drug Substance.[1]

As discussed below, considering the risks associated with Nitrosamine impurities in medications exceeding established limits and given the therapeutic utility of Sitagliptin containing medications, FDA should ensure below requested action.

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1. Drugs@FDA "Sitagliptin"

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A. ACTIONS REQUESTED

Petitioner respectfully requests that FDA take the following actions considering the risks presented by Nitrosamine impurities in Sitagliptin containing products:

(1) FDA should withdraw the allowed interim acceptable intake levels of up to 246.7 ng per day as per information published by FDA on August 9, 2022 and set it to the level at the 37 ng per day level which presents minimal additional cancer risk when compared to a lifetime of exposure to Nitroso-STG-19 (known as NTTP) as per published guidance "Control of Nitrosamine Impurities in Human Drugs Guidance for Industry" on February, 2021 by U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Pharmaceutical Quality/ Manufacturing Standards/ Current Good Manufacturing Practice (CGMP) once the therapeutic equivalent generic ANDA or 505(b)(2) application is approved which is complying to the limits set in the guidance.

Upon availability of equivalent generic ANDA or 505(b)(2) FDA approved alternatives which will ensure the availability of the products to patients and avoid risk of shortages

- FDA should recall and withdraw current marketed products containing Sitagliptin as Drug Substance if it fails to comply with 37 ng per day level acceptable intake levels
- FDA should issue advisory stating details of contaminated lots to patients and issue quantifying current odds of cancer occurrence in patients exposed to contaminated lots.

(2) FDA should update and evaluate the data for Sitagliptin containing drug products FDA Adverse Event Reporting System (FAERS) to determine the severity and occurrence of carcinogenicity. If high number of cases are found than requesting FDA to take immediate action to ensure public health safety

(3) FDA should ensure that drug product manufacturers update their labeling to include nitrosamine impurities associated carcinogenicity risk as black box warning.

(4) FDA should ask manufacturer of Sitagliptin containing drug product to develop a Risk

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Evaluation and Mitigation Strategy (REMS) designed to reinforce medication use behaviors and actions that support the safe use of Sitagliptin containing medication.

(5) FDA should ask to manufacturer about trend data of all manufactured batches with respect to nitrosamine impurity. FDA should ensure that manufacturer establish supplier qualification program that considers potential nitrite impurities across any starting material, intermediates, solvents excipient suppliers and excipient lots to reduce the risk of nitrosamine formation in the drug product.

- FDA should ask 3rd party assessment to monitor overall quality functions like release and sourcing of starting materials, solvents, intermediates, excipients, drug substance and drug product specifically with respect to nitrosamine risk prior to release of drug product in market

(6) FDA should ask to manufacturer to submit and publish the information related to AMES test, mutagenicity potential and chromosomal results submitted to respond assessment report of the European Medicines Agency CHMP and Health Canada. USFDA should ask manufacturer about the reason of delays if any in reporting and details of submitted information to other agencies like CHMP and EMEA.

B. STATEMENTS OF GROUNDS

1. Factual Background

Sitagliptin is a prescription drug used to control high blood sugar in patients with type 2 diabetes mellitus. It could be dangerous for patients with this condition to stop taking their sitagliptin without first talking to their health care professional. FDA recommends prescribers continue to use sitagliptin when clinically appropriate to prevent a gap in patient treatment.

JANUVIA® Tablets is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Product was first approved by FDA on Oct 16, 2006.[2] A significant evolution has happened in areas of impurity identification, quantification and associated toxicity post product approval. Maximum daily dose is 100 mg once a day. [2]

JANUMET® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both Sitagliptin and Metformin is appropriate. Recommended dosage is twice daily.[2]

JANUMET® XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both Sitagliptin and Metformin extended-release is appropriate. Recommended daily dose is once a daily.[2]

STEGLUJAN® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both Ertugliflozin and Sitagliptin is appropriate. Recommended daily dose is once a daily.[2]

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The table below summarizes the details on the approved products containing Sitagliptin, listed in the Orange Book[3]:

Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	RLD	RS	Applicant Holder	Approval date
SITAGLIPTIN PHOSPHATE	JANUVIA	N021995	TABLET	ORAL	EQ 25MG BASE	RLD		MERCK SHARP AND DOHME CORP	Oct 16, 2006
					EQ 50MG BASE	RLD			
					EQ 100MG BASE	RLD	RS		
METFORMIN HYDROCHLORIDE; SITAGLIPTIN PHOSPHATE	JANUMET	N022044	TABLET	ORAL	500MG; EQ 50MG BASE	RLD			Mar 30, 2007
					1GM; EQ 50MG BASE	RLD	RS		
METFORMIN HYDROCHLORIDE; SITAGLIPTIN PHOSPHATE	JANUMET XR	N202270	TABLET, EXTENDED RELEASE	ORAL	500MG; EQ 50MG BASE	RLD			Feb 2, 2012
					1GM; EQ 50MG BASE	RLD			
					1GM; EQ 100MG BASE	RLD	RS		
ERTUGLIFLOZIN; SITAGLIPTIN PHOSPHATE	STEGLUJAN	N209805	TABLET	ORAL	5MG; EQ 100MG BASE	RLD		MERCK SHARP AND DOHME LLC A SUB OF MERCK AND CO INC	Dec 19, 2017
					15MG; EQ 100MG BASE	RLD	RS		
					5MG; EQ 100MG BASE	RLD			

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2. Drugs FDA Label "Januvia Tablets, Janumet Tablet, Janumet XR Tablet, Steglujan Tablet"
3. Orange book FDA

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2. Statement of grounds

NTTP belongs to the nitrosamine class of compounds, some of which are classified as probable or possible human carcinogens (substances that could cause cancer), based on laboratory tests. Although there are no data available to directly evaluate the carcinogenic potential of NTTP, FDA used information available on closely related nitrosamine compounds to calculate lifetime exposure limits for NTTP.

2 a. Summary of events on Nitrosamines by various regulatory authorities:

USA[4,5]:

On February, 2021 U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Pharmaceutical Quality/ Manufacturing Standards/ Current Good Manufacturing Practice (CGMP) published guidance on "Control of Nitrosamine Impurities in Human Drugs Guidance for Industry" This guidance recommends steps manufacturers of APIs and drug products should take to detect and prevent unacceptable levels of nitrosamine impurities in pharmaceutical products. The guidance also describes conditions that may introduce nitrosamine impurities. The recent unexpected finding of nitrosamine impurities, which are probable human carcinogens in drugs.

FDA recommended guidance has made clear the need for a risk assessment strategy for potential nitrosamines in any pharmaceutical product at risk for their presence.

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4. Control of Nitrosamine Impurities in Human Drugs Guidance for Industry U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) February 2021 Rev.1
5. FDA works to avoid shortage of sitagliptin following detection of nitrosamine impurity | FDA

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On August 9, 2022, FDA published information stating that recently became aware of a nitrosamine impurity, Nitroso-STG-19 (known as NTTP), in certain samples of sitagliptin, a medicine used to treat type 2 diabetes mellitus. To avoid a shortage and help ensure patients have access to an adequate supply of the medicine, FDA will not object to the temporary distribution of sitagliptin containing NTTP above the acceptable intake limit of 37 ng per day, and up to 246.7 ng per day.

The manufacturer of a marketed product that contains sitagliptin should contact the Center for Drug Evaluation and Research's Drug Shortages Staff when its testing shows levels of NTTP that exceed 37 ng per day. FDA will determine on a case-by-case basis whether those drugs should be released for distribution.

In August , 2023 FDA published final guidance titled as "Recommended "Acceptable Intake (AI)" Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs) for Industry" for immediate implementation.

Table 2: FDA Recommended AI Limits for Certain NDSRIs Based on Compound-Specific Data or Read-Across Analysis from a Surrogate (last updated 8/4/2023) also specifies the limits for 7-Nitroso-3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo-[4,3-a]pyrazine (NTTP) of Sitagliptin API at recommended AI limit of 37 ng/day. [6]

Europe[7]:

Prior to USFDA publication on July 29, 2022, assessment report of the European Medicines Agency (EMA) CHMP's Article 5(3) of Regulation (EC) No 726/2004 opinion on

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6. Questions and answers for marketing authorization holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products. 31 January 2022 EMA/409815/2020 Rev.7
7. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/updated-information-recommended-acceptable-intake-limits-nitrosamine-drug-substance-related

nitrosamine impurities in human medicinal products provides general guidance and recommendations on mitigating and preventing the presence of nitrosamines in human medicinal products established 7-Nitroso-3-(trifluoromethyl)-5,6,7,8-tetrahydro [1,2,4] triazolo- [4,3-a]pyrazine (Nitroso impurity of Sitagliptin) limit to control at 37 ng/day.CHMP asked Marketing authorization holders should complete the confirmatory testing and submit their variation applications by:

1 October 2023 for chemical medicines;

1 July 2023 for biological medicines.

The CHMP and CMDh extended the deadline for submitting variation applications for chemical medicines from 26 September 2022 to 1 October 2023 in July 2022.

Canada[8]:

Summary from guidance representing Health Canada's current thinking and recommendations on issues related to N-nitrosamine impurities (nitrosamine impurities or nitrosamines).

The request in Health Canada's call for review to evaluate the risk of the presence of nitrosamine impurities outlined in the October 2, 2019, letter applies to human pharmaceutical products with a drug identification number (DIN) containing chemically synthesized and semi-synthetic APIs. This includes:

- prescription and non-prescription (over-the-counter) drug products
- chemically synthesized excipients and raw materials used in the manufacturing of drug products

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8. Nitrosamine impurities in medications: Guidance - Canada.ca

The request for conducting risk assessments for the potential presence of nitrosamine impurities was extended to all biological and radiopharmaceutical products for human use. This was outlined in Health Canada's letter dated December 15, 2020.

Timelines for completing risk assessments (Step 1), confirmatory testing (Step 2) and changes to the market authorization (Step 3)

As communicated to MAHs on August 10, 2020, for drug products containing chemically synthesized and semi-synthetic APIs, the steps for actions relating to nitrosamines are expected to be completed as follows:

Step 1: risk assessments by March 31, 2021
Step 2: confirmatory testing by October 1, 2022
Step 3: changes to the market authorization by October 1, 2022

Based on above established facts below conclusion are drawn:

- Current manufacturer of Sitagliptin containing drug product is available in other than USA markets like Europe and Canada
- Health Canada asked to submit risk assessment report by March 31, 2021 in the published guidance
- European Medicines Agency CHMP already identified and established limit for nitrosamine impurity for Sitagliptin containing products

Summary of last update in CMC section[1]:

- We also referred and compiled latest revision of Manufacturing (CMC) supplement for various Sitagliptin containing drug products. No revision is submitted any of the products containing Sitagliptin post findings of overall Nitrosamine impurities related findings.

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Active Ingredient	Proprietary Name	Appl. No.	Manufacturing (CMC) latest supplement
SITAGLIPTIN PHOSPHATE	JANUVIA®	N021995	January 11, 2016
METFORMIN HYDROCHLORIDE; SITAGLIPTIN PHOSPHATE	JANUMET®	N022044	June 12, 2015
METFORMIN HYDROCHLORIDE; SITAGLIPTIN PHOSPHATE	JANUMET XR®	N202270	September 19, 2014
ERTUGLIFLOZIN; SITAGLIPTIN PHOSPHATE	STEGLUJAN®	N209805	December 19, 2017

Based on above facts USFDA should ask manufacturer about the reason of delays in reporting and details of submitted information in order to comply stated requirements and timelines by Health Canada and European Medicines Agency

2 b. <u>Boxed warning and REMS implementation:</u>

As per FDA published guidance for Industry "Warnings and Precautions Contraindications, and Boxed Warning Sections of Labelling for Human Prescription Drug and Biological Products and Content and Format" published by USFDA Center for Drug Evaluation and Research (CDER) in October 2011 states that

Boxed Warning can be for prescribers one of the following situations:

- There is an adverse reaction so serious in proportion to the potential benefit from (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it be considered in assessing the risks and benefits of using the drug OR

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• There is a serious adverse reaction that can be prevented or reduced in frequency severity by appropriate use of the drug (e.g., patient selection, careful mon certain concomitant therapy, addition of another drug or managing patient manner, avoiding use in a specific clinical situation)

Infrequently, a boxed warning can also be used in other situations to highlight warning information that is especially important to the prescriber.[9]

Sitagliptin is marketed as combination product with Metformin as brand name of JANUMET® and JANUMET XR®. In metformin containing drug products already multiple recalls were done by various drug product manufacturer for failure to complying nitrosamine impurities acceptance criteria.[10] Considering the previous experience of Metformin and additionally nitrosamine impurities from Sitagliptin increases the occurrence of carcinogenic potential in combination products

As per USFDA Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

REMS are designed to reinforce medication use behaviors and actions that support the safe use of that medication. While all medications have labeling that informs health care stakeholders about medication risks, only a few medications require a REMS.

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9. FDA published guidance for Industry "Warnings and Precautions Contraindications, and Boxed Warning Sections of Labelling for Human Prescription Drug and Biological Products and Content and Format" published by USFDA Center for Drug Evaluation and Research (CDER) in October 2011
10. Search list of recalled metformin products | FDA

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REMS are not designed to mitigate all the adverse events of a medication, these are communicated to health care providers in the medication's prescribing information. Rather, REMS focus on preventing, monitoring and/or managing a specific serious risk by informing, educating and/or reinforcing actions to reduce the frequency and/or severity of the event.

FDA allowed Sitagliptin formulation with the intermittent limit than the established limit which possess risk of mutagenicity and carcinogenicity that should be part of boxed label warning and it should be listed and monitored by REMS.[11]

2 c. <u>Sitagliptin tablets Nitrosamine Impurities Assessment:</u>

We have developed method and performed analysis of multiple lots of RLD (i.e. Januvia Tablets) over the current year. It has been observed that all the lots of Januvia tested so far are still complying to the interim limits (246.7 ng/day) and none of the batches are complying to the final limits (37 ng/day) prescribed by the agency.

Zydus product complies to the final limits at the stations tested so far and the trend data clearly depicts that the Zydus product will comply to the final limits at 24 months as well based on the extrapolation of data using MiniTab statistical software version 18. Our current proposed shelf-life is 18 months based on available accrued stability data; the same shall be extended based on generation of further stability data.

We have developed the analytical method to analyse the test product and same analytical method has been validated by suitable validation parameters (i.e. System Suitability and Precision, Filter Compatibility and Saturation, LOD and LOQ, Method Precision, Solution Stability, Linearity, Accuracy, Range, Intermediate Precision and Robustness).

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11. https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

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Summary of validated analytical method including sample preparation procedure is provided in **Annexure-I**. Further, we have also provided the Nitroso-STG-19 (NTTP) data of Reference Listed Drug products (Januvia® Tablets, USA) and Test product (Zydus product) in Annexure-II and Annexure-III respectively.

3. Conclusion

For the reasons described above, Petitioner respectfully requests that FDA grant the actions requested in this citizen petition considering the risks associated with mutagenic impurities and given the therapeutic utility of Sitagliptin containing formulation.

C. ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.31.

D. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), Petitioner will submit economic information upon the request by the Commissioner.

E. CERTIFICATION

The petitioner certifies that, to the best of knowledge and belief of Petitioner, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which is unfavorable to the petition.

Sincerely,

Digitally signed by Srinivas Gurram
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Annexure:

Annexure 1: Analytical method for estimation of NTTP in Sitagliptin Tablet

Annexure 2: NTTP data of Reference Listed Drug product Januvia® (Sitagliptin Tablets)

Annexure 3: NTTP data of Zydus Product on Long-term stability study (25 ± 2°C/ 60 ± 5% RH)

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