# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 219122Orig1s000

# NON-CLINICAL REVIEW(S)

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

# PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

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| Application number: | NDA 219122 |
| Supporting document/s: | 0001, 0005, 0014 |
| Applicant's letter date: | 01/04/2024 |
| CDER stamp date: | 01/04/2024 |
| Product: | Sitagliptin hydrochloride oral solution, 25 mg/mL |
| Indication: | Type 2 Diabetes Mellitus (T2DM) |
| Applicant: | Azurity Pharmaceuticals, Inc. |
| Review Division: | Division of Diabetes, Lipid Disorders, and Obesity Products |
| Reviewer: | Amit Chaudhary, PhD |
| Supervisor/Team Leader: | Patricia Brundage, PhD |
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# 1 Executive Summary

## 1.1 Introduction

Azurity Pharmaceuticals, Inc. is seeking marketing approval of Sitagliptin hydrochloride oral solution for the treatment of type 2 diabetes mellitus as a 505(b)(2) new drug application (NDA). Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor. The Applicant is relying on the FDA's finding of safety and effectiveness for the U.S.- approved intended listed drug (LD) Januvia® (sitagliptin phosphate) under NDA 021995 (Sponsor: Merck Sharp and Dohme LLC, approved 2006). To establish a scientific bridge between the Sitagliptin hydrochloride oral solution and the LD, the sponsor conducted a bioavailability (BA) and bioequivalence (BE) study to provide a scientific bridge to rely on the safety and efficacy data of the LD. Compared to Januvia® (tablet strength: 25 mg, 50 mg, 100 mg), the proposed product is an oral solution (25 mg/mL), contains sitagliptin hydrochloride instead of sitagliptin phosphate, and contains different inactive ingredients. The proposed indication and route of administration (oral) is same as that of Januvia®.

This review documents the nonclinical evaluation and recommendation of approvability of this NDA.

## 1.2 Brief Discussion of Nonclinical Findings

There are no nonclinical studies conducted under this NDA. The sponsor conducted a BA and BE study to provide a scientific bridge and is relying on the nonclinical safety data for Januvia®.

A nitrosamine impurity, (b) (4) is controlled in drug substance (DS) specification at no more than (NMT) (b) (4) ppm ( (b) (4) ng/day) and in drug product (DP) specification at NMT (b) (4) ppm ( (b) (4) ng/day). (b) (4) (b) (4) the acceptable intake (AI) limit for (b) (4) is (b) (4) ng/day. From nonclinical perspectives, the DS and DP specifications for (b) (4) which do not exceed the (b) (4) limit of (b) (4) ng/day, are considered acceptable.

(b) (4)

## 1.3 Recommendations

### 1.3.1 Approvability

This drug product is recommended to be approved from a nonclinical perspective.

### 1.3.2 Additional Non Clinical Recommendations

NA

### 1.3.3 Labeling

The sponsor's proposal of using the same Januvia® label information in nonclinical sections with the exception of the product tradename is acceptable.

# 2 Drug Information

## 2.1 Drug

CAS Registry Number: 486459-71-6

Generic Name: Sitagliptin Hydrochloride

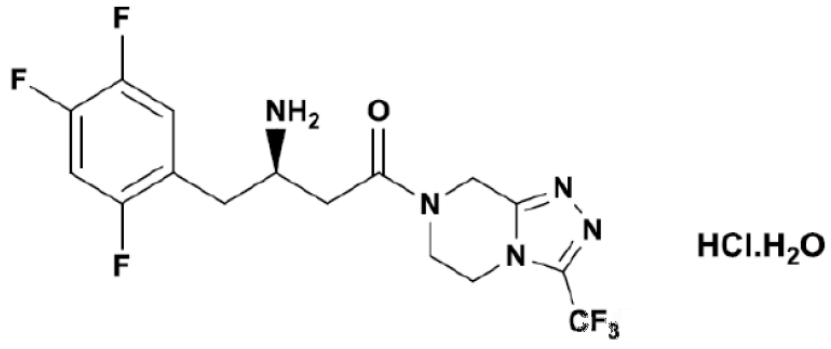
Code Name

Chemical Name: ((3R)-3-Amino-1-(3-(trifluoromethy1)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-y1)-4-(2,4,5-trifluorophenyl)butan-l-one hydrochloride monohydrate

Molecular Formula: C16H15F6N5O•HCl.H2O

Molecular Weight: 461.79

Structure:




Pharmacologic Class: Dipeptidyl peptidase-4 (DPP-4) inhibitor/ Oral antihyperglycemic/ Antidiabetic

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

Listed Drug : NDA 021995, JANUVIA® (sitagliptin) Tablets
Sponsor of Listed Drug: Merck & Co.

## 2.3 Drug Formulation

The unit composition of Sitagliptin Hydrochloride Oral Solution, 25 mg/mL is listed in Table 1.

**Table 1. Unit Composition of Sitagliptin Hydrochloride Oral Solution, 25 mg/mL**

| Formula Ingredient | Pharmaceutical Function | mg/mL | %w/v | mg/dose |
|---|---|---|---|---|
| Sitagliptin Hydrochloride | Active | 27.24[a] | 0.27 | 27.24[a] |
| Butylated Hydroxyanisole, NF | (b) (4) | | | |
| Edetate Disodium, USP | | | | |
| Sodium Citrate Dihydrate, USP | | | | |
| Methylparaben Sodium, NF | | | | |
| Citric Acid Anhydrous, USP | | | | |
| Polysorbate 80, NF (b) (4) | | | | |
| (b) (4) | Sweetener/ Flavoring Agent | | | (b) (4) |
| Hydroxyethyl Cellulose, NF (b) (4) | | | | (b) (4) |
| Purified Water, USP | | | | |

QS = Quantity Sufficient
[a] 27.24 mg/mL of Sitagliptin Hydrochloride equivalent to 25 mg/mL of Sitagliptin Base
[b] 1 mL of the proposed product delivers 25 mg of the active

Composition (b) (4) flavor is listed in Table 2 and Table 3, respectively.

**Table 2. Quantitative Composition of (b) (4)**

| Component | %w/w |
|---|---|
| | (b) (4) |

**Table 3. (b) (4) – Compliance to Regulations**

| Ingredients | CAS # | %w/w | Maximum daily intake in mg | IID limit in mg | CFR Reference | UNII | FEMA No. | JECFA No. | Other References |
|---|---|---|---|---|---|---|---|---|---|
| (b) (4) | | | | | | | | | |

## 2.4 Comments on Novel Excipients

All inactive ingredients utilized in the formulation are listed in the FDA's Inactive Ingredient Database (IID) and are within or below the listed levels for orally administered products Table 4. Most components used in (b) (4) flavors are identified in the Code of Federal Regulations (CFR) as cleared food additives (e.g., 21 CFR part 172, subpart F) or as generally recognized as safe (GRAS) for use in food (21 CFR parts 182 and 184). (b) (4) are listed as GRAS in The Flavor and Extract Manufacturers Association of the United States (FEMA) and Joint FAO/WHO Expert Committee on Food Additives (JECFA).

**Table 4. Inactive Ingredients and Amounts Appropriate per IIG**

| Ingredients | mg/unit (1 mL) | Amount based on the MDD (mg) (4mL) | IIG Limit as per FDA's IID (Data through December 11, 2023) Route of Administration/ Dosage Form | Maximum Daily Exposure |
|---|---|---|---|---|
| Butylated Hydroxyanisole (BHA) | | (b) (4) | ORAL/LIQUID | 8 mg |
| Edetate Disodium | | | ORAL/SOLUTION | 420 mg |
| Sodium Citrate Dihydrate | | | ORAL/ SOLUTION | 750 mg |
| Methylparaben Sodium | | | ORAL/SOLUTION | 346 mg |
| Citric Acid Anhydrous | | | ORAL/ SOLUTION | 743 mg |
| Polysorbate 80 | | | ORAL/ SOLUTION | 432 mg |
| (b) (4) | | | | |
| Hydroxyethyl Cellulose | | (b) (4) | ORAL/SUSPENSION | (b) (4) |

## 2.5 Comments on Impurities/Degradants of Concern

The maximum daily dose (MDD) of the proposed drug product is 100 mg/day. Based on MDD, the ICH Q3A qualification threshold (QT) is not more than (NMT) 0.15% and ICH Q3B QT is NMT 200 µg/day or 0.02%.

Specified impurities (b) (4) are controlled in DS at NMT (b) (4)%. (b) (4) are controlled in DP at NMT (b) (4)%. From nonclinical perspective, the proposed DS and DP specification for specified impurities comply with ICH Q3A QT and ICH Q3B QT, respectively.

(b) (4) impurity, is controlled in DS at NMT (b) (4) ppm (b) (4) ng/day) and in DP at NMT (b) (4) ppm (b) (4) ng/day), which does not exceed the (b) (4)

limit of (b) (4) ng/day. [2,3] The recommended (b) (4) limit for (b) (4) uses the carcinogenic potency categorization approach (CPCA) method, which results in assignment of (b) (4) to potency category (PC) (b) (4) with an associated recommended (b) (4) limit of (b) (4) ng/day.

(b) (4)

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/s/

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10/08/2024 03:50:47 PM

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I concur