CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219122Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review and Summary Memo

Date	See digital signature
From	Kim Shimy, MD Clinical Team Lead Division of Diabetes, Lipid Disorders, and Obesity (DDLO) Patrick Archdeacon, MD (Signatory) Deputy Director DDLO
NDA #/BLA #	NDA 219122
Applicant	Azurity Pharmaceuticals, Inc.
Date of Submission Receipt	November 19, 2024
PDUFA Goal Date	January 17, 2025
Established or Proper Name	Sitagliptin
(Proposed) Trade name	Brynovin
Dosage forms / Strength	oral solution, 25 mg/mL strength
Applicant Proposed Indication(s)/Population(s) Recommended Action	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommendation on Regulatory Action	Approval

Material Reviewed/Consulted	
Office of Pharmaceutical Quality (OPQ) Integrated Quality Review (12/19/2024)	Daniel Jansen and Zhengfu Wang (Drug Substance), Dan Berger (Drug Product/Labeling), Naresh Pavurala and Erin Kim (Manufacturing), Xia Xu and Nandini Bhattacharya (Microbiology), Oluwafunmike Ajomale (RBPM), and Muthukumar Ramaswamy (Application Technical Lead/Drug Product/Labeling)
Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name Review (12/23/2024)	Vraj Patel, Damon Birkemeier
DMEPA) Labeling Review (12/16/2024)	Vraj Patel, Damon Birkemeier
Office of Prescription Drug Promotion (OPDP) Labeling Review (1/2/2025)	Tierra Butler
Division of Medical Policy Programs (DMPP)/OPDP Labeling Review: Medication Guide (1/2/2025)	Lonice Carter, Tierra Butler, Nyedra Booker, Lashawn Griffiths
Primary clinical review for original NDA submission (11/1/2024)	Lauren Wood Heickman
Division Director (DD)/Cross Discipline Team Lead (CDTL) Memo for original NDA submission (11/3/2024)	Patrick Archdeacon

1. Executive Summary

This document serves as the 'Summary Basis for Regulatory Action' memo for the Class 1 resubmission of a new drug application (NDA) for sitagliptin oral solution, NDA 219122. The Applicant resubmitted the application on November 18, 2024 with updated facility information in Form 356h and has indicated that the drug substance manufacturer has provided responses to the FDA inspection report on October 21, 2024.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) review team has determined that the compliance status of all facilities associated with this application are acceptable. The Office of Pharmaceutical Quality (OPQ) review team has reviewed this new information and recommends approval of this NDA from a quality perspective. Therefore, there are no outstanding deficiencies, and we recommend approval.

2. Introduction

On January 4, 2024, Azurity Pharmaceuticals, Inc. (hereafter the Applicant) submitted NDA 219122 under Section 505 (b)(2) of the Federal Food, Drug and Cosmetic Act seeking approval of sitagliptin hydrochloride oral solution 25 mg/mL as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2D). The Applicant proposed to rely on prior FDA findings of safety and effectiveness for Januvia (Sitagliptin phosphate monohydrate tablet, NDA 021995), marketed by Merck Sharp & Dohme Corp. The development program for this application is based on demonstration of bioequivalence to the listed drug, Januvia. A single bioavailability/bioequivalence study using Januvia as a reference was submitted, and the Office of Clinical Pharmacology (OCP) concluded that this study adequately demonstrated bioequivalence, hence establishing a scientific bridge between the two products. No new nonclinical or clinical data were submitted and no new claims are being sought with this application.

At the time of the original submission, all review disciplines supported approval, except for OPQ. Although OPQ did not identify any deficiencies related to drug substance, drug product, manufacturing process, labeling, and microbiology sections of the application, OPQ recommended a complete response (CR) on the basis of a (b) (4) current good manufacturing practice (CGMP) inspection of a manufacturing facility (b) (4) (b) (4) that led to an Official Action Indicated (OAI) regulatory action. On November 4, 2024, the FDA issued a CR for NDA 219122 citing the facilities inspection deficiencies.

On November 18th, 2024, the Applicant resubmitted NDA 219122. In the resubmission, the Applicant indicates that responses to the FDA's inspection report had been submitted by the manufacturing facility on October 21, 2024. The Applicant also provided updated labeling information and a clinical safety update. No additional new information was submitted. The remainder of this document only summarizes new findings from pertinent review disciplines for the NDA resubmission.

3. Product Quality

Following a cGMP inspection of [redacted] (b) (4) in [redacted] (b) (4) the FDA conveyed deficiencies to the representative of the facility. During the original NDA review cycle, the compliance status of [redacted] (b) (4) was changed to "withhold due to potential Official Action Indicated alert (pOAI)" as of [redacted] (b) (4). According to OPQ (see Integrated Quality Assessment dated September 25, 2024 and updated on October 10, 2024) and as described in the subsequent November 4, 2024 CR letter, satisfactory responses from the facility and FDA determination that the facility has come into compliance with CGMP are needed before the application can be approved from a quality perspective.

Following the NDA resubmission, the OPQ review states that the OPMA facility reviewer has determined that the compliance status of the drug substance manufacturing facility is voluntary action indicated (VAI), and that the status of all facilities associated with this application are acceptable. As of December 12, 2024, the Overall Manufacturing Inspection recommendation for NDA 219122 is to approve. Overall, OPQ recommends approval for this NDA from a quality perspective. Refer to the Integrated Quality Assessment dated December 19, 2024, for additional details.

4. Nonclinical Pharmacology/Toxicology

No new information was submitted in this review cycle. Approval was recommended in the first submission (see nonclinical review dated October 8, 2024).

5. Clinical Pharmacology

No new information was submitted in this review cycle. Approval was recommended in the first submission (see clinical pharmacology review dated September 25, 2024).

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy and Safety

Approval was recommended in the first submission (see primary clinical review dated November 1, 2024 and DD/CDTL memo dated November 3, 2024). No new clinical studies with sitagliptin oral solution have been initiated since the original NDA submission. With the NDA resubmission, the Applicant submitted a clinical safety update report describing results of relevant clinical and non-clinical literature published between April 5, 2024 until November 7, 2024; no new safety concerns were identified based on review of available literature. There are no outstanding issues that preclude approval from a clinical perspective.

8. Advisory Committee Meeting

The application does not raise significant issues regarding the safety or effectiveness of the drug.

9. Pediatrics

The Pediatric Research Equity Act (PREA) was triggered with the original NDA submission, due to the change in the salt form of sitagliptin from sitagliptin phosphate monohydrate to sitagliptin hydrochloride and due to the change in the dose form from tablet to liquid formulation. During the first review cycle, the Pediatric Research Committee (PeRC) concluded there are no additional PREA studies for this product because the completed pediatric studies of the reference product (Januvia) did not establish efficacy in the pediatric population. The PeRC agreed that this product can be considered to have been assessed in the pediatric population.

10. Other Regulatory Issues

The Applicant has proposed the proprietary name Brynovin. This name was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and found to be acceptable. Refer to the DMEPA review dated December 23, 2024 for additional details.

11. Labeling

There are no outstanding labeling issues, and final agreed upon labeling will be included in the NDA approval letter. The label closely follows the medical and scientific content of the reference drug, Januvia (sitagliptin; NDA 021995). A statement was added to section 2 (Dosage and Administration) clarifying instructions for accurate measurement of the dosage with a calibrated oral syringe or oral dosing cup scored using metric units of measurements (i.e., mL). Based on stability testing and per OPQ recommendations, section 16 also includes appropriate storage instructions to protect from light and to avoid excessive heat and freezing.

The Office of Prescription Drug Promotion (OPDP), Division of Medical Policy Programs (DMPP) and DMEPA were formally consulted upon receipt of this NDA resubmission to review the labeling, medication guide, and the carton and container labeling. Each discipline has documented concurrence with the agreed upon labeling.

Recommended Regulatory Action: Approval

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.

/s/

KIM J SHIMY
01/15/2025 12:41:25 PM

PATRICK ARCHDEACON
01/15/2025 12:57:00 PM

Cross-Discipline Team Leader Review and Summary Memo

Date	See digital signature
From	Patrick Archdeacon, MD (Signatory) Deputy Director Division of Diabetes, Lipid Disorders, and Obesity
NDA #/BLA #	NDA 219122 (Original NDA submission)
Applicant	Azurity Pharmaceuticals, Inc.
Date of Submission Receipt	January 4, 2024
PDUFA Goal Date	November 4, 2024
Established or Proper Name	Sitagliptin oral solution, 25 mg/mL
(Proposed) Trade name	Brynovin
Dosage forms / Strength	oral liquid solution, 25 mg/mL strength
Applicant Proposed Indication(s)/Population(s) Recommended Action	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)
Recommendation on Regulatory Action	Complete Response

1. Executive Summary

This document serves as the 'Summary Basis for Regulatory Action' memo for the original new drug application (NDA) for an oral liquid solution for sitagliptin, NDA 219122.

Azurity Pharmaceuticals, Inc. (hereafter the Applicant) submitted NDA 219122 on January 4, 2024 proposing their oral liquid solution formulation of sitagliptin 25 mg/mL (to be marketed as Brynovin) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

NDA 219122 is a 505(b)(2) application that proposes to rely on FDA's previous finding of safety and effectiveness for NDA 021995, sitagliptin marketed as Januvia. For this application, to justify reliance on FDA's previous finding of safety and effectiveness for Januvia, the Applicant submitted a Chemistry, Manufacturing, and Control (CMC) package and a single relative bioavailability (BA) and food effect study. Based on review of the relative BA study, the Office of Clinical Pharmacology (OCP) concluded that bioequivalence (BE) had been demonstrated for Sitagliptin Oral Solution (25 mg/mL) and that therefore a bridge between Azurity sitagliptin oral solution and Januvia tablet is established. Although a food effect not previously observed with Januvia was observed with Azurity sitagliptin oral solution, OCP concluded that the food effect is not clinically meaningful. Clinical review of the safety data collected during the conduct of the relative bioavailability study (i.e., adverse event data) did not reveal any findings that would preclude the determination that it was appropriate to rely on the previous finding of safety and effectiveness of Januvia through an established scientific bridge. Although NDA 219122 was determined to include sufficient data and information to bridge to the listed drug, the Office of Pharmaceutical Quality (OPQ) determined that the CMC package was not adequate to meet all applicable standards to support approval. Specifically, following a cGMP inspection of (b) (4) FDA conveyed deficiencies to the representative of the facility. As of (b) (4), the compliance status of (b) (4) is changed to withhold due to potential official action indicated alert (pOAI). Therefore, the OPMA facility assessment recommendation for NDA 219122 is "inadequate".

Subject	Author	Date
Office of Product Quality	Daniel Jansen (Drug Substance), Dan Berger (Drug Product), Naresh Pavurala (Manufacturing), Xia Xu (Microbiology), Oluwafunmike Funke Ajomale (RBPM), Muthukumar Ramaswamy (Application Technical Lead)	September 25, 2024 Amended October 10, 2024
Nonclincal Pharmacology/Toxicology	Amit M Chaudhary, Patricia Brundage	October 8, 2024

Office of Clinical Pharmacology (OCP)	Lin Zhou, Edwin Chow	September 25, 2024
Division of Diabetes, Lipid Disorders, and Obesity (DDLO)	Lauren Wood Heickman	November 1, 2024
Division of Medication Error Prevention and Analysis (DMEPA)	Vraj K Patel, Damon Birkemeier, Mishale Mistry	March 15, 2024 Amended April 2, 2024
Patient Labeling Review	Mary Carroll	October 8, 2024
Labeling Consult Review	Tierra N Butler	October 7, 2024
Office of Study Integrity and Surveillance (OSIS)	Felecia P Hagood	April 29, 2024

2. Background

Type 2 diabetes mellitus (T2DM) is a disease of abnormal glucose homeostasis which results in chronic hyperglycemia. Change from baseline A1C, demonstrating improved glycemic control, is an accepted surrogate endpoint for therapies as studies have shown that improved glycemic control reduces the risk of microvascular disease (retinopathy, nephropathy, neuropathy).

Sitagliptin is an DPP-4 enzyme inhibitor, initially approved in the US in 2006 as Januvia (NDA 021995) for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. It inhibits the metabolism and elimination of incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), prolonging endogenous incretin actions in glucose homeostasis, and thereby lowers plasma glucose levels. The Applicant has developed sitagliptin oral liquid solution (25 mg/mL) which differs from Januvia in dosage form (oral solution versus tablet) and salt form (hydrochloride versus phosphate).

This NDA consists of Chemistry, Manufacturing, and Controls (CMC) data and a single bioavailability (BA)/bioequivalence (BE) study. The NDA also relies on safety and efficacy data presented in the package insert of Januvia (i.e., sitagliptin phosphate). The Applicant uses the submitted PK data in the single pivotal relative BA/BE study to support reliance on the efficacy and safety data of the listed drug, Januvia.

3. Product Quality

The Office of Product Quality (OPQ) reviewed the Chemistry, Manufacturing, and Controls (CMC) information for NDA 219122. The recommendation from OPQ is that the information included in the Application is inadequate to support the approval of NDA 219122 related to facilities deficiencies identified during inspection of (b) (4)

The review of the drug substance (DS) was conducted by Daniel Jansen , the review of the drug product (DP) (including drug product composition, excipient compatibility, batch analysis, container closure system, and stability information) was conducted by Dan Berger, the review of drug manufacturing process data (including facility assessment and process assessment) was conducted by Naresh Pavurala, the review of microbiology data (b) (4) was conducted by Xia Xu, and Muthu Ramaswamy served as the assessment team leader (ATL).

The evaluation of nitrosamine impurities in oral sitagliptin solution (25 mg/mL) was an important issue covered in the OPQ review, as the potential for the formation of nitrosamine impurities had been identified with other sitagliptin-containing products. The applicant provided manufacturing and control information for the nitrosamine impurity, (b) (4) (b) (4) which indicated that the proposed manufacturing and control strategy for the drug substance and drug product is adequate to meet the FDA established lifetime acceptable intake (AI) limit of (b) (4) ng/day for (b) (4) in the drug product, at release and when stored through 12 months at 2-8°C. FDA concluded that NDA 219122 included adequate manufacturing and control information to meet FDA established acceptable intake (AI) limits for nitrosamine impurities of interest.

A deficiency was identified following a Current Good Manufacturing Practice (CGMP) facility inspection of the (b) (4) manufacturing facility that led to OPQ recommending complete response for this application. I concur with their conclusions. Other than the facilities deficiency, the OPQ review team concluded that there were no outstanding deficiencies related to drug substance, drug product, process, microbiology, or container and carton label.

For additional details regarding the OPQ review see the Integrated Quality Assessment dated September 25, 2024 and updated on October 10, 2024, signed by Dr. Muthu Ramaswamy.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review of NDA 219122 was conducted by Amit M Chaudhary and Patricia Brundage.

The nonclinical review concludes that no new nonclinical studies are required under this 505(b)(2) NDA that is relying on FDA's previous finding of safety and effectiveness for Januvia. The nonclinical review notes that Januvia contains sitagliptin phosphate whereas sitagliptin oral solution (25 mg/mL) contains sitagliptin hydrochloride salt. However, as long as the hydrochloride instead of phosphate salt does not alter the absorption and pharmacokinetic profile of sitagliptin the nonclinical safety findings from the sitagliptin phosphate salt (Januvia) were considered to be applicable to the oral sitagliptin solution

(25 mg/mL) containing the sitagliptin hydrochloride salt form. The review notes that the inactive ingredients of the two drug products are nonidentical, but reports that all inactive ingredients used in the sitagliptin oral solution (25 mg/mL) formulation are listed in the FDA's Inactive Ingredients Database (IIG) and are within or below the listed levels for orally administered products.

The nonclinical review also notes the evaluation regarding the potential for the nitrosamine impurity (b) (4) (described in greater detail in the OPQ review) and concurs that the potential nitrosamine impurities are not a safety concern that would preclude approval from a nonclinical perspective as the Applicant has a control limit for (b) (4) in the sitagliptin oral liquid solution drug substance of not more than (NMT) (b) (4) ppb (b) (4) ng/day based on maximum daily dose of 100 mg sitagliptin) which is below the FDA's current acceptable intake (AI) limit for (b) (4) of (b) (4) ng/day, (b) (4)

For additional details regarding the nonclinical review, see the review dated October 8, 2024 signed by Amit M Chaudhary and Patricia Brundage.

5. Clinical Pharmacology

The clinical pharmacology review of NDA 219122 was conducted by Lin Zhou and Edwin Chow. Based on their review, the clinical pharmacology team finds that the submitted PK results are acceptable to support the conclusion that oral sitagliptin solution (25 mg/mL) is bioequivalent to Januvia. The clinical pharmacology study showed a food effect, such that Cmax was reduced and Tmax was delayed under fed conditions; such a food effect has not been observed for the listed drug (Januvia). However, the clinical pharmacology team concluded based on the totality of the evidence that the food effect is not clinically meaningful. I concur with their findings.

The clinical development program consists of a single clinical study (AZ17.001), a single dose, three-way crossover pivotal bioequivalence study intended to establish the PK bridge between Azurity's sitagliptin oral solution, 25 mg/mL, in the dose of 100 mg (4 mL) (proposed product) and Januvia, sitagliptin phosphate tablet, 100 mg (listed drug (LD)) in healthy adults under fed and fasted conditions. The three-way comparison was Azurtiy sitagliptin 100 mg under fasted conditions, Azurity sitagliptin 100 mg under fed conditions, and Januvia 100 mg under fasted conditions. Januvia was not studied in AZ17.001 under fed conditions.

Study AZ17.001 showed the proposed product and LD product are bioequivalent during fasting conditions as the 90% confidence intervals and the geometric mean ratios are within the pre-specified bioequivalence acceptance criteria limits of 80% to 125% for the primary PK endpoints (Cmax, AUC from time zero to time t, and AUC from time zero to infinity) of sitagliptin between test product and LD product.

For Azurity sitagliptin dosed under fed conditions, the 90% confidence intervals and the

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

geometric mean ratios are also within the pre-specified bioequivalence acceptance criteria limits of 80% to 125% for the AUC-based PK endpoints (AUC from time zero to time t, and AUC from time zero to infinity) of sitagliptin between test product and LD product. However, the steady-state Cmax was decreased by ~28% and the Tmax was delayed by 2.5 hours (from 1.5 hours to 4 hours) for the oral sitagliptin solution during fed conditions compared to the LD product during fasting conditions. The clinical pharmacology review evaluated the difference in Tmax and Cmax for any anticipated impact on clinical efficacy. The review team concluded that (1) food did not appear to impact AUC-based PK endpoints and (2) PK-modelling predicted no difference in simulated steady-state concentrations (Cavg) between fasted and fed conditions. The clinical pharmacology review further described that sitagliptin's pharmacodynamic effect, inhibition of plasma DPP-4 activity is primarily due to plasma sitagliptin concentration alone (Cavg) and furthermore, is independent of time (Tmax) based on experience with sitagliptin products (Januvia). Therefore, the clinical pharmacology team concluded that the reduced Cmax or delayed Tmax observed with fed conditions do not have a significant impact on clinical efficacy.

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

For additional details regarding the clinical pharmacology review, see the review dated September 25, 2024, signed by Lin Zhou and Edwin Chow. For additional details regarding the OSIS determination, see the review dated April 29, 2024, signed by Felecia Hagood.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy and Safety

This 505(b)(2) NDA is relying on an adequate justification to rely on the previous finding of efficacy and safety for Januvia. The adequate justification is based on a demonstration of bioequivalence to Januvia in the relative BA/BE study AZ17.001.

In addition, a clinical review of NDA 219122 was conducted by Lauren Wood Heickman, who reviewed the safety data collected during the conduct of study AZ17.001. Among the 30 healthy volunteers enrolled, no serious adverse events or deaths were observed and few adverse events (AE) were observed. The limited safety data collected during the conduct of Study AZ71.001 were inspected only to ensure that these data did not conflict with the conclusion of biosimilarity. Review of these limited safety data did not suggest any differences in the safety profiles of sitagliptin oral solution (25 mg/mL) and Januvia.

Dr. Wood Heickman concluded (and I concur) that no findings from the safety data reviewed precluded the conclusion that reliance on the previous finding of safety and effectiveness for Januvia is justified by the demonstration of bioequivalence between Sitagliptin oral solution (25 mg/mL) and Januvia in study AZ17.001.

For additional details, see the clinical review dated November 1, 2024, signed by Dr. Lauren Wood Heickman.

8. Advisory Committee Meeting

No new efficacy or safety issue rose to the level of requiring the input from an advisory panel.

Therefore, an advisory committee meeting was *not* convened for this NDA.

9. Pediatrics

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. After consultation with the Pediatric Research Committee (PeRC), CDER concluded that there are no additional studies required for this product because the pediatric studies of sitagliptin did not establish efficacy in the pediatric population. For that reason, sitagliptin products can be considered to have been assessed in the pediatric population.

10. Labeling

The labeling for submitted by the Applicant was based on approved labeling for Januvia (sitagliptin; NDA 021995). Because the NDA is receiving a Complete Response due to the facilities deficiencies, labeling is deferred until the next review cycle.

11. Recommendations

Complete Response due to the facilities deficiencies. Decisions about post-marketing requirements are deferred until the next review cycle.

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.

/s/

PATRICK ARCHDEACON
11/03/2024 10:55:59 PM