# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 219008Orig1s000

# PRODUCT QUALITY REVIEW(S)

| | |
|---|---|
| Title: | NDA IQA Template Title Page- EXEC SUMMARY |
| Document ID: | OPQ-ALL-TEM-0040 |
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*Template Revision: 03*

# Office of Pharmaceutical Quality

## New Drug Application (NDA)
## Integrated Quality Assessment Template

# NDA Executive Summary

## 1. Application/Product Information

| | | | |
|---|---|---|---|
| **NDA Number** | 219008 | | |
| **Applicant Name** | JANSSEN BIOTECH INC | | |
| **Drug Product Name** | Lazcluze (lazertinib) | | |
| **Dosage Form** | Tablet | | |
| **Proposed Strength(s)** | 80 mg and 240 mg | | |
| **NDA Classification** | Type 1 - NME | | |
| **Route of Administration** | Oral | | |
| **Maximum Daily Dose** | 240 mg | | |
| **Rx/OTC Dispensed** | Rx | | |
| **Proposed Indication** | LAZCLUZE, a kinase inhibitor, is indicated in combination with amivantamab for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test | | |
| **Drug Product Description** | 80 mg tablets: yellow, oval film-coated tablet, debossed with “LZ” on one side and “80” on the other side.<br>240 mg tablets: reddish purple, oval film-coated tablet, debossed with “LZ” on one side and “240” on the other side. | | |
| **Co-packaged product information** | N/A | | |
| **Device information** | N/A | | |
| **Storage Temperature/ Conditions** | Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature] | | |
| **Review Team** | **Discipline** | **Primary** | **Secondary** |

| | | | |
|---|---|---|---|
| | *Drug Substance* | Sivakoteswara Rao Mandadapu | Haripada Sarker |
| | *Drug Product/ Labeling* | Xiao Hong Chen | Xing Wang |
| | *Manufacturing* | Diane Goll<br>Huiquan Wu | Chunsheng Cai |
| | *Biopharmaceutics* | Jing Li | Anitha Govada |
| | *Microbiology* | Diane Goll | Chunsheng Cai |
| | *Other (specify)* | N/A | |
| | *RBPM* | Janell Artis | |
| | *ATL* | Xing Wang | |
| **Consults** | None | | |

**2. Final Overall Recommendation - Approval**

**3. Action Letter Information**

**a. Expiration Dating:**

**An expiration dating period of 24 months may be granted when stored at the proposed storage conditions.**

**b. Additional Comments for Action**

**N/A**

**4. Basis for Recommendation:**

**a. Summary of Rationale for Recommendation:**

*Lazertinib 80mg and 240mg tablets are produced* (b) (4) (b) (4) (b) (4) *Numerous issues were identified from both technical and regulatory perspectives during the assessment process* (b) (4) *Five sets of IRs were issued. All those issues were resolved after assessment of IR responses.*

*The original submission lacked data to support the uniformity of dissolution*

(b) (4)

[redacted]

*A PAI by 704(a)(4) has been conducted at the DP manufacturing site, Janssen Cilag SpA, (FEI 3003164454) lead by OPMA, and the recommendation is Approve. All other facilities are recommended for approval.*

*Overall, the applicant has provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. All associated manufacturing, testing, packaging facilities were deemed acceptable. Based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommends APPROVAL of NDA 219008 for LAZCLUZE™ (lazertinib) tablets, for oral use*

**b. Is the overall recommendation in agreement with the individual discipline recommendations?** Yes

**Recommendation by Subdiscipline:**

| | | |
|---|---|---|
| **Drug Substance** | **-** | **Adequate** |
| **Drug Product** | **-** | **Adequate** |
| **Quality Labeling** | **-** | **Adequate** |
| **Manufacturing** | **-** | **Adequate** |
| **Biopharmaceutics** | **-** | **Adequate** |
| **Microbiology** | **-** | **Adequate** |

**Environmental Assessment:** Categorical Exclusion - Adequate
**QPA for EA(s):** No

**5. Life-Cycle Considerations**
**Established Conditions per ICH Q12: No**
**Comments**:

**Comparability Protocols (PACMP): No**
**Comments:**

**Additional Lifecycle Comments: None**

***Application Technical Lead Name and Date:***
*Xing Wang, Ph.D.* *07/26/2024*

Xing Wang

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# CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

| | |
|---|---|
| **NDA Number** | 219008 |
| **Assessment Cycle Number** | 1 |
| **Drug Product Name** | Lazertinib |

**Assessment Recommendation:** Adequate

| Item | Assessment Conclusion | SDN # where labeling is adequate ("N/A" otherwise) |
|---|---|---|
| Prescribing Information Labeling | Adequate | **#0003** |
| Patient Information | Adequate | **#0003** |
| Instruction for Use (IFU) | N/A | **NA** |
| Container Labels | Adequate | **#0003** |
| Carton Labeling | Adequate | **#0003** |

**Brief Description of Outstanding Issues: N/A**

**Submissions being reviewed:**

| Document Reviewed (eCTD #, SDN #) | Date Received | Information Provided |
|---|---|---|
| **#0003** | 12/20/2023 | PI and container carton labels |
| **#0045** | 06/17/2024 | Response to IRs |
| **#0048** | 06/20/2024 | Updated container carton labels |

## 1.0 PRESCRIBING INFORMATION[1]

**Assessment of Product Quality Related Aspects of the Prescribing Information:**

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

## 1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

*(copy of proposed text)*

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| **Product Title in Highlights[2] [21 CFR 201.57(a)(2)]** | | |
| Established name(s)[3] | Adequate | LAZCLUZE™ (lazertinib) tablets |
| Route(s) of administration | Adequate | For oral use |
| Controlled drug substance symbol (if applicable) | N/A | |
| Initial U.S. Approval [§201.57(a)(3)] | Adequate | |
| **Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]** | | |
| Dosage form(s)[4] and strength(s) in metric system[5] | Adequate | Tablets: 80 mg and 240 mg |
| If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6] | Adequate | |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7] | N/A | |

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)
[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).
[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline
[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>
[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.[8] | N/A | |

**Assessment:** *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

## 1.2 FULL PRESCRIBING INFORMATION

### 1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(*copy of proposed text*)

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| **DOSAGE AND ADMINISTRATION section** | | |
| Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product). | N/A | |

[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)

[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food). | Adequate | |
| For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11] | N/A | |
| If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11). | N/A | |
| For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug | N/A | |
| For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs." | N/A | |

**Assessment:** *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition

### 1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

(*copy of proposed text*)

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| **DOSAGE FORMS AND STRENGTHS section** | | |
| Available dosage form(s) | Adequate | Tablets |
| Strength(s) in metric system | Adequate | 80 mg and 240 mg |
| If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement. | Adequate | |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable. | Adequate | Tablets<br>• 80 mg: yellow oval film-coated tablet, debossed with "LZ" on one side and "80" on the other side. Each tablet contains 80 mg of lazertinib.<br>• 240 mg: reddish purple oval film-coated tablet, debossed with "LZ" on one side and "240" on the other side. Each tablet contains 240 mg of lazertinib. |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored." | N/A | |
| For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and | N/A | |

[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| imaging bulk package (see USP <659>). | | |

**Assessment:** *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

### 1.2.3 Section 11 (DESCRIPTION)[14]

(*copy of proposed text*)

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| **DESCRIPTION section** | | |
| Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)]. | Adequate | LAZCLUZE™ (lazertinib) tablets |
| Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)]. | Adequate | LAZCLUZE™ (lazertinib) tablets, for oral use |
| If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)]. | Adequate | The equivalency statement is edited to remove (b) (4) per current Agency thinking and to be consistent in the practice. It reads as following: LAZCLUZE™ (lazertinib) film-coated tablets contain 80 mg or 240 mg of lazertinib (active ingredient), equivalent to (b) (4) 93 (b) (4) and (b) (4) 281. (b) (4) mg (calculated on anhydrous basis) (b) (4) respectively. |

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)]. | Adequate | All inactive ingredients are listed but not in alphabetical order. The edit has been made so that they are provided in alphabetical order. |
| For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)]. | N/A | |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)]. | N/A | |
| Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)]. | N/A | |
| Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)]. | Adequate | Lazertinib is a kinase inhibitor. |
| Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)]. | Adequate | |
| If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)]. | N/A | |

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)]. | Adequate | Lazertinib is soluble or practically insoluble in aqueous media, and slightly soluble to freely soluble in organic solvents over a wide range of pH values. |
| For oral prescription drug products, include gluten statement[19] (if applicable). | N/A | |
| Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"). | N/A | |
| If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2). | N/A | |

**Assessment:** *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

### 1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

(*copy of proposed text*)

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| **HOW SUPPLIED/STORAGE AND HANDLING section** | | |
| Available dosage form(s) [§ 201.57(c)(17)]. | Adequate | Tablets |

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)
[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety. No equivalency statement. | Adequate | 80 mg and 240 mg |
| Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)]. | Adequate | |
| Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)]. | Adequate | 80 mg tablets: Yellow, oval, film-coated, debossed with "LZ" on one side and "80" on the other side.<br>- Bottle of 60-tablets (NDC 57894-080-60).<br>(b) (4)<br>240 mg tablets: Reddish purple, oval, film-coated, debossed with "LZ" on one side and "240" on the other side.<br>- Bottle of 30-tablets (NDC 57894-240-30). |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored." | N/A | |
| For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>). | N/A | |

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)] | N/A | |
| Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>). | Adequate | Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*. |
| Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*[21] | N/A | |
| Include information about child-resistant packaging[22] (if chosen by manufacturer). | Adequate | |

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)
[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)

**Assessment:** *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

### 1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

### 1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

| Item | Item in Proposed Labeling (choose "Adequate" or "Inadequate") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| **Manufacturing Information After Section 17** | | |
| Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer. | Adequate | Name and location is provided but street address is not listed.<br><br>Product of Belgium<br>Manufactured for:<br>Janssen Biotech, Inc.<br>Horsham, PA 19044, USA |

**Assessment:** *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

## 2.0 PATIENT LABELING

[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)

**Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):**

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| Established name[24] | Adequate | |
| Special preparation instructions (if applicable). | N/A | |
| Storage and handling information (if applicable). | Adequate | |
| If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form. | N/A | |
| Active ingredient(s) (if applicable). | Adequate | |
| Alphabetical listing of inactive ingredients (if applicable). | Adequate | The applicant was asked to list inactive ingredients in alphabetical order. |
| Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer. | Adequate | |

**Assessment:** *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

## 3.0 CONTAINER AND CARTON LABELING[25]

### 3.1 Container Labels[26]

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this pag

[24] Established name = [Drug] [Route of Administration] [Dosage Form]
[25] Carton and Container Labeling Resources
[26] Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

| Item | Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A") | Is item in Container Labels same as that of Carton Labeling? | Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate) |
|---|---|---|---|
| Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)]. | Adequate | Yes | LAZCLUZE™ (lazertinib) tablets |
| Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28] | Adequate | Yes | 80 mg and 240 mg |
| Route(s) of administration, not required for oral use [§ 201.100(b)(3)]. | Adequate | Yes | Not provided. It is acceptable as this is optional for oral use. |
| If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>]. | Adequate | Yes | The equivalent statement should be based on anhydrous basis to be consistent with PI. Refer to section 11 of PI. |
| Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29] | Adequate | Yes | 60 (b) (4) count for 80 mg tablets; 30 count for 240 mg tablets |
| "Rx only" displayed on the principal display [§ 201.100(b)(1)]. | Adequate | Yes | |
| NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35]. | Adequate | Yes | |
| Lot number and expiration date [§ 201.18 & 201.17]. | Adequate | Yes | |
| Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD). | Adequate | Yes | Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) *[see* |

[27] Established name = [Drug] [Route of Administration] [Dosage Form]

[28] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

[29] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

| Item | Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A") | Is item in Container Labels same as that of Carton Labeling? | Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate) |
|---|---|---|---|
| | | | *USP Controlled Room Temperature]*. |
| For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>). | N/A | Choose an item. | |
| Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)]. | N/A | Choose an item. | |
| For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)]. | N/A | Choose an item. | |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)]. | N/A | Choose an item. | |
| Linear Bar code [§ 201.25(c)(2)].[30] | N/A | Choose an item. | |
| Adequate directions for use: "Recommended Dosage: See | Adequate | Yes | |

[30] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

| Item | Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A") | Is item in Container Labels same as that of Carton Labeling? | Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate) |
|---|---|---|---|
| Prescribing Information" [§ 201.5 & 201.55]. | | | |
| Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)]. | Adequate | Yes | |
| "Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)]. | Adequate | Yes | |
| If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient. | N/A | Choose an item. | |
| No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>). | N/A | Choose an item. | |
| If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. | N/A | Choose an item. | |
| When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.[31] | N/A | Choose an item. | |
| And others if space is available. | N/A | Choose an item. | |

[31] USP General Notices 3.20 Indicating Conformance

**Assessment of Carton Labels and Container Labeling:** *Adequate*

***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

## 4. OUTSTANDING ISSUES AND RECOMMENDATIONS

***Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See Carton/Container Labeling Specific Resources for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these issues in this section.***

*Primary Labeling Assessor Name and Date: Xiao Hong Chen June 25, 2024*

*Secondary Assessor Name and Date (and Secondary Summary, as needed): David Claffey*

Xiao Chen

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David Claffey

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# CHAPTER VI: BIOPHARMACEUTICS

| | |
|---|---|
| **Product Information** | Lazertinib |
| **NDA Number** | 219008-RTOR (for NME; SDN1, SDN2 and SDN3) |
| **Assessment Cycle Number** | 1 |
| **Drug Product Name/ Strength** | Lazcluze® (Lazertinib) Tablets/ 80 and 240 mg |
| **Route of Administration** | Oral |
| **Applicant Name** | Janssen Biotech Inc. |
| **Therapeutic Classification/ OND Division** | Anticancer/Division of Oncology 2 (DO2) |
| **Proposed Indication** | Lazertinib in combination with amivantamab for first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test. |

***Assessment Recommendation:*** **Adequate**

***Assessment Summary:***

**Background:**
Janssen Research & Development, LLC (Janssen) is submitting this 505(b)(1) New Drug Application (NDA) 219008 on behalf of Janssen Biotech, Inc. The NDA is a rolling submission, and the Quality module was submitted on 12/5/2023 (SDN 2). This NDA is reviewed under Real-Time Oncology Review (RTOR) project, a pilot project of the FDA Oncology Center of Excellence (OCE).

The proposed drug product contains a new molecular entity (NME) drug substance, Lazertinib. The drug product is an immediate release, oval shaped, film-coated (FC) tablet for oral administration, containing (b) (4) mg of (b) (4) which is equivalent to 80 or 240 mg of lazertinib free base, respectively. The tablet strengths are dose proportional and differentiated by color and debossing. The drug product is manufactured (b) (4)

This Biopharmaceutics review is focused on the evaluation of the following aspects:

- Dissolution methods and acceptance criteria,
- Dissolution uniformity [redacted], (b) (4)
- Bridging between the pivotal clinical product and the proposed commercial drug product.

***Reviewer's Assessment:***

Dissolution methods and acceptance criteria

The drug substance demonstrates pH-dependent solubility with the highest solubility in the acidic condition. [redacted] (b) (4)

[redacted] (b) (4)

In the current NDA, the Applicant proposed separate dissolution methods for each of the proposed strength, 80 and 240 mg, choosing a medium at pH 4.5 with addition of surfactant. Method development reports were submitted to support the selection of the testing parameters. The methods showed a trend of decreased dissolution as API particle size distribution (PSD) increases. Based on the in vivo study results, the methods were able to define a safe space in terms of API PSD. An alternative method requested by FDA using 0.1N HCl medium did not provide additional benefits compared to the currently proposed methods. Based on the totality of the information, the Applicant proposed dissolution methods, as shown in Table 1, are found acceptable.

Table 1. The approved dissolution methods and acceptance criteria for Lazertinib Tablet 80 mg and 240 mg

| Strength | Apparatus | RPM | Medium | pH | Volume | Temp. | Acceptance Criterion |
|---|---|---|---|---|---|---|---|
| 80 mg | USP 2 | 75 | 1.0% polysorbate 20 in 0.1M sodium citrate buffer | 4.5 | 900mL | 37.0 | Q= (b) (4) % in 45 min |
| 240 mg | USP 2 | 75 | 2.0% polysorbate 20 in 0.1M sodium citrate buffer | 4.5 | 900mL | 37.0 | Q= (b) (4) % in 45 min |

Dissolution Uniformity [redacted] (b) (4)

In the original submission, data to support the uniformity of dissolution [redacted] (b) (4) was lacking, and hence was requested by the FDA. [redacted] (b) (4)

[redacted] Based on the dissolution data on the PPQ batches, dissolution uniformity [redacted] (b) (4) was demonstrated. In addition, dissolution testing on the final coated tablets for routine quality control is found acceptable, for the following reasons:

- (b) (4)
- (b) (4) Stratified sampling on the CQAs revealed minimal inter- or intra-batch variability, which provides assurance for dissolution consistency,

(b) (4)

Bridging between the pivotal clinical product and the proposed commercial drug product

The proposed commercial formulations (G004 and G005) are different from the pivotal clinical formulation (G002) in composition, and process (b) (4) A Bioequivalence study (study # 73841937NSC1009) was conducted to support the bridging between the proposed commercial formulations and the pivotal clinical formulation. The BE study is assessed by the Office of Clinical Pharmacology. From the pivotal BE batches of G004 and G005, to the commercial batches, there is no change in composition, manufacturing process, or manufacturing site (Latina site). (b) (4) Therefore, the bridging from clinical drug product to the proposed commercial formulation is adequately established, provided the Office of Clinical Pharmacology Review finds the bioequivalence study results adequate.

Overall, from a Biopharmaceutics perspective, NDA 219008 is recommended for APPROVAL.

| CQAs | Initial Risk Ranking | Comments | Updated Risk Ranking after Assessment Cycle #1 | Comments |
|---|---|---|---|---|
| Dissolution | Medium | DS Solubility is low and pH-dependent, with decreased solubility as pH is increased. DP is manufactured (b) (4) (b) (4) | Low | The risk is mitigated with the implementation of the approved dissolution method and acceptance criterion. Dissolution uniformity (b) (4) was demonstrated. |

**List Submissions Being Assessed:**

| Document(s) Assessed | Date Received |
|---|---|
| Original NDA (SDN 2)<br><br>RTOR submissions<br>SDN 3: \\CDSESUB1\evsprod\NDA219008\0003 - received December 21, 2023<br>SDN 2: \\CDSESUB1\evsprod\NDA219008\0002 - received December 5, 2023<br>SDN 1 \\CDSESUB1\evsprod\NDA219008\0001 - received November 22, 2023 | 12/05/2023 |
| Response to Biopharm IR (SDN-25) | 4/11/2024 |
| Response to Biopharm IR (SDN-47) | 6/20/2024 |

**Highlight Key Issues from Last Cycle and Their Resolution: None**

**Concise Description of Outstanding Issues *(list bullet points with key information and update as needed)*: None**

## B.1 BCS DESIGNATION

**Assessment: Adequate**

**Solubility:** The drug substance demonstrates pH-dependent solubility. The highest solubility is obtained in acidic condition and solubility decreases as pH increases.

Table 2. Drug Substance Solubility in Aqueous Media of Different pH at 37 °C after 72h Expressed as Free Form Equivalent

| Medium | Solubility (g/100 mL) | pH of Solution |
|---|---|---|
| 0.1 M HCl | 4.61 | 1.2 |
| 0.1 M Sodium Citrate buffer pH 4.5 | 0.0099 | 4.4 |
| 0.05 M Sodium Phosphate buffer pH 6.8 | <QL[a] | 6.8 |

[a] QL = quantitation limit
Sink conditions: 0.027 g/100 mL (3 x 80 mg/900 mL)

**Permeability:** The Applicant noted that the permeability of Lazertinib is moderate based on in vitro Caco-2 cell monolayer study[1]. As per the proposed USPI[2], following a single oral dose of radiolabeled lazertinib, approximately

[1] Drug Substance properties. \\CDSESUB1\EVSPROD\nda219008\0002\m3\32-body-data\32s-drug-sub\lazertinib-msoh-all\32s1-gen-info\general-properties.pdf
[2] Proposed USPI. \\CDSESUB1\EVSPROD\nda219008\0003\m1\us\114-labeling\draft\labeling\uspi-draft-labeling-text-clean-pdf.pdf

86% of the dose was recovered in feces (<5% as unchanged) and 4% in urine (<0.2% as unchanged), which indicates the permeability is unlikely to be high.

**Dissolution:** See details in the following section of "**DISSOLUTION METHOD AND ACCEPTANCE CRITERIA**".

## B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

**Assessment: Adequate**

The Applicant proposed separate dissolution methods for each of the proposed strengths, 80 and 240 mg. The following summarizes the dissolution method development report for each strength.

(b) (4)

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(b) (4)

Overall, based on the totality of the information, the Applicant proposed dissolution methods for 80-mg and 240-mg strengths respectively are acceptable.

**DISSOLUTION ACCEPTANCE CRITERION: *ADEQUATE***

The Applicant provided the dissolution profile data for the representative batches (including the development batches, pivotal clinical batches and primary stability batches) for the 80-mg strength and 240-mg respectively. The results, which are summarized in Figure 16 and 17, supported the proposed dissolution acceptance criterion for both strengths: Q= (b) (4)% in 45 min.

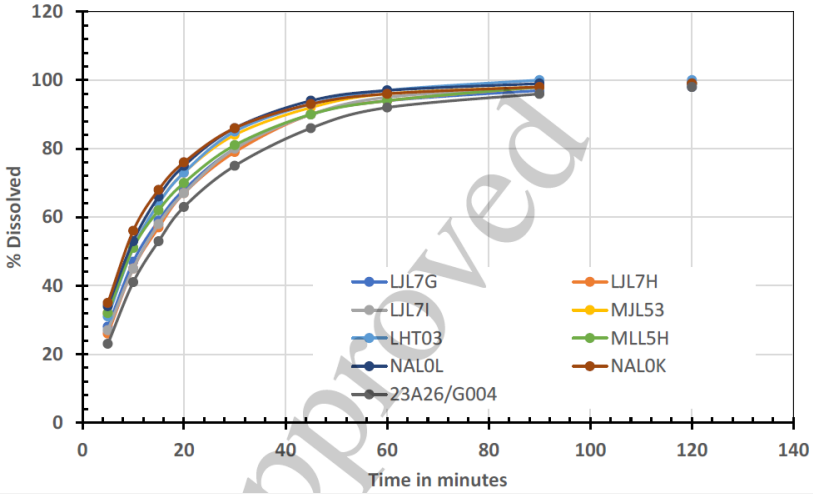


Figure 16. Dissolution Profiles for Representative 80 mg (G004) Batches (n=12)

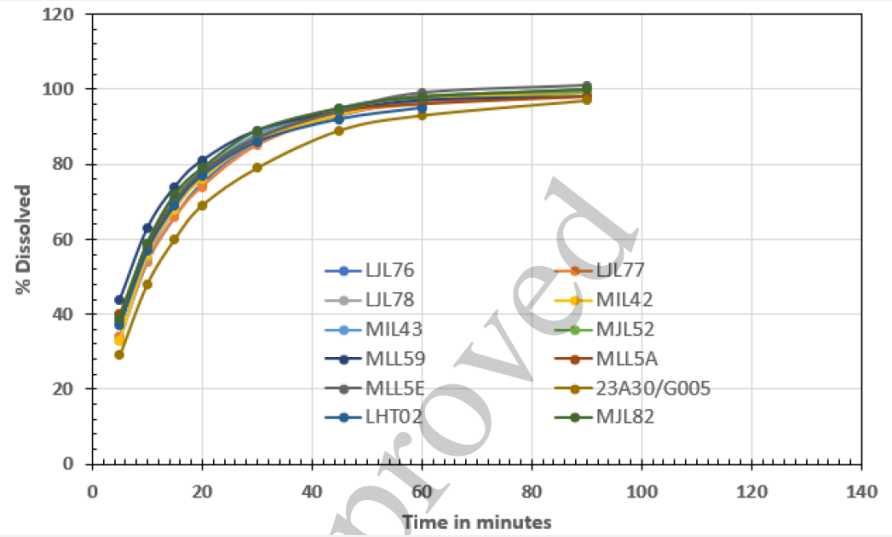


Figure 17. Dissolution Profiles for Representative 240 mg (G005) Batches (n=12)

## DISSOLUTION UNIFORMITY (b) (4)

(b) (4)

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(b) (4)

Based on the data provide for the PPQ batches, dissolution uniformity (b) (4) was demonstrated.

## B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA

**Assessment: Adequate.**

- **Particle Size Distribution:**

Study 73841937NSC1002 was performed at a dose of 240 mg (3 x 80 mg) in healthy subjects to evaluate the bioavailability of the 80 mg clinical drug product (G002) batches with different drug substance particle size distributions of dv50 values of (b) (4) and (b) (4) µm. The batches used in the study and the API PSD are summarized in Table 10.

Table 10. Drug Product Batches Used to Study the Clinical Relevance of the Proposed Commercial Dissolution Method (73841937NSC1002)

| DP Batch | Formulation | DP Manufacturing site | DS Batch (%DS used) | Particle Size (µm) | | |
|---|---|---|---|---|---|---|
| | | | | $d_v10$ | $d_v50$ | $d_v90$ |
| JLL16 | G002 | JSC Latina | A19HD1985 (b) (4)<br>A19HD1986<br>A19ID2109 | (b) (4) | | |
| 3180253R | G002 | (b) (4) | PP-1030B-9003 (b) (4) | | | |

DP = Drug Product; DS = Drug Substance

The clinical results indicated that batch JLL16 is comparable to batch 3180253R in bioavailability, as the 90% CI for the geometric mean ratios of $C_{max}$ and $AUC_{0\text{-}72h}$ fall within the 80.00% to 125.00% criteria.
Two sets of dissolution profiles of the drug product batches evaluated in study 73841937NSC1002 are collected: (1) measured on single unit with the

Proposed Commercial Dissolution Method – 80 mg (N = 6), which is presented in Figure 22(A). (2) measured at a dose of 240 mg (3 x 80 mg) with the proposed commercial dissolution method -240 mg (N=12), which is presented in Figure 22(B). The results both showed that the dissolution profiles of the 80 mg clinical drug product (G002) batches with API PSD of dv50 values of (b) (4) and (b) (4) µm are significantly different [f2=32 (80-mg) and f2=31 (3x80-mg) as per Applicant's calculation].

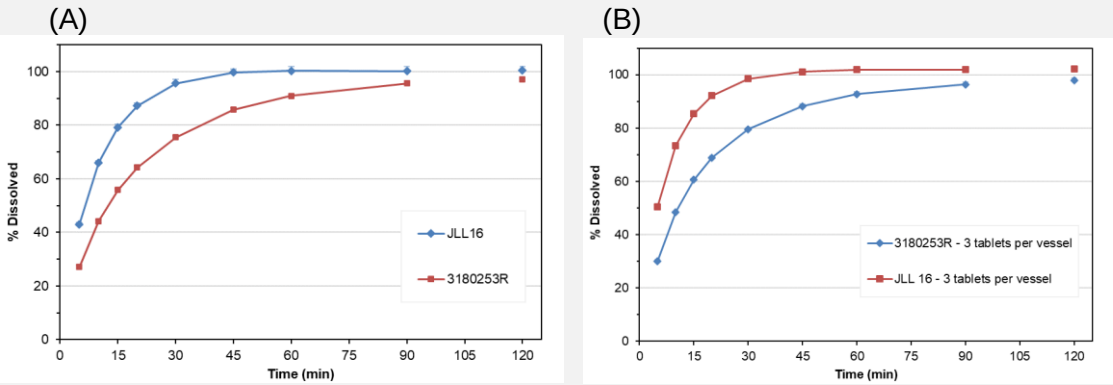


Figure 22. Average Dissolution Profiles of Drug Product Batches JLL16 and 3180253R (A). Measured with the Proposed Commercial Dissolution Method-80-mg (N = 6); (B). Measured with the Proposed Commercial Dissolution Method-240-mg at a Dose of 240 mg (N = 12)

Based on the results, it is concluded that the trend of decreased dissolution rate as API PSD increases has no in vivo relevance within the tested range. On the other hand, because DP batches made with API particle size of d50 from (b) (4) µm and d90 from (b) (4) µm resulted in comparable in vivo performance, a safe space could be established within the tested range.

- **Bioequivalence Study:**

Table 11 and 12 summarize the batches used in the pivotal bioequivalence study (73841937NSC1009), aiming to demonstrate the bioequivalence of the 80 mg clinical drug product (G002) drug product vs. the 80 mg proposed commercial drug product (G004) and the 240 mg commercial drug product (G005).

Table 11. Drug Product Batches Used to Study the Bioequivalence of the 80 mg Clinical Drug Product (G002) and the 80 mg Proposed Commercial Drug Product (G004) (73841937NSC1009)

| DP Batch | Formulation | DP Manufacturing site | DS Batch | Particle Size (µm) | | |
|---|---|---|---|---|---|---|
| | | | | $d_v10$ | $d_v50$ | $d_v90$ |
| 3201472R | G002 | (b) (4) | A21FD1597 | (b) (4) | | |
| LJL7G | G004 | JSC Latina | A21CD0918 | | | |

DP = Drug Product; DS = Drug Substance

Table 12. Drug Product Batches Used to Study the Bioequivalence of the 80 mg Clinical Drug Product (G002) and the 240 mg Proposed Commercial Drug Product (G005) (73841937NSC1009)

| DP Batch | Formulation | DP Manufacturing site | DS Batch (%DS used) | Particle Size (µm) | | |
|---|---|---|---|---|---|---|
| | | | | $d_v10$ | $d_v50$ | $d_v90$ |
| 3201472R | G002 | (b) (4) | A21FD1597 | | | (b) (4) |
| MJL82 | G005 | JSC Latina | A22FB1112 (b) (4) A22FB1118 | | | |

DP = Drug Product; DS = Drug Substance

The tested batches for G002, G004, and G005 showed comparable in vivo PK profile and similar in vitro dissolution profiles. The assessment of the bioequivalence study results will be conducted by Office of Clinical Pharmacology.
It is noteworthy that the API particles sizes of the batches used in the bioequivalence study are within the defined safe space in terms of API PSD, which is the range tested in Study 73841937NSC1002.

## B.12 BRIDGING OF FORMULATIONS

**Assessment: Adequate**

The initial clinical formulation, **G001**, was an immediate release 80 mg FC tablet for oral administration developed by Yuhan Corporation, South Korea.
The G001 formulation was optimized by the Applicant to the pivotal clinical 80 mg FC tablet formulation **G002** (b) (4) (b) (4) the pivotal clinical 80 mg FC tablet formulation (G002) was further optimized to a 240 mg tablet (**G005**) of acceptable size. Subsequently, a dose-proportional 80 mg tablet (**G004**) was developed using this further optimized formulation (b) (4)

In comparison to G002 (pivotal clinical formulation), the G004 (80mg) and G005 (240mg) formulations (proposed commercial formulation) are different in:

(1) Composition. (b) (4) An overview of the composition of the proposed formulations throughout the development is provided in the Table below:

Table 13. Composition of the Initial Clinical 80 mg (G001), Pivotal Clinical 80 mg (G002), and Proposed Commercial 80 mg (G004) and 240 mg (G005) FC Tablet

(b) (4)

(2) Process. The clinical 80 mg FC tablet formulation (G002) was manufactured by (b) (4), while (b) (4) was used to manufacture the commercial drug product batches.

In order to demonstrate equivalency in the quality and performance of the pivotal clinical product (G002 formulation, (b) (4)) and the proposed commercial product (G004 and G005 formulations, (b) (4)), bioequivalence (BE) study 73841937NSC1009 has been conducted. The bridging between the 80 mg (G004) and 240 mg (G005) commercial formulations and the pivotal clinical 80 mg (G002) formulation is established from a Biopharmaceutics perspective, provided the Office of Clinical Pharmacology Review finds the bioequivalence study results adequate.

(b) (4)

Therefore, the bridging between the clinical drug product (b) (4) to the proposed commercial drug product by (b) (4) is adequately established by bioequivalence studies. Adequacy of BE studies to support the bridge is pending assessment by the Office of Clinical Pharmacology review team.

[8] Manufacturing process development. \\CDSESUB1\EVSPROD\nda219008\0039\m3\32-body-data\32p-drug-prod\active-film-coated-tablet-all\32p2-pharm-dev\pharmaceutical-development.pdf

## B. 13 BIOWAIVER REQUEST

**Assessment:** N/A

## R. REGIONAL INFORMATION

Comparability Protocols

**Assessment:** N/A

Post-Approval Commitments

**Assessment:** N/A

Lifecycle Management Considerations

**N/A**

## BIOPHARMACEUTICS LIST OF DEFICIENCIES

**None.**

*Primary Biopharmaceutics Assessor's Name and Date: Jing Li, Ph.D. 7/5/2024*

*Secondary Assessor Name and Date (and Secondary Summary, as needed): Anitha Govada, Ph.D. 7/12/2024*

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