

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217759Orig1s000

PRODUCT QUALITY REVIEW(S)



| | | |
|-----------------|-------------------------------------------------------------------------|--------------|
| Title: | New Drug Application (NDA) Integrated Quality Assessment Template | |
| Document ID: | OPQ-ALL-TEM-0004 | |
| Effective Date: | 01 Aug 2022 | Revision: 08 |
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Office of Pharmaceutical Quality

New Drug Application (NDA) 217759 Integrated Quality Assessment Template



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RECOMMENDATION

| |
|------------------------------------------------------------------|
| <input checked="" type="checkbox"/> Approval |
| <input type="checkbox"/> Approval with Post-Marketing Commitment |
| <input type="checkbox"/> Complete Response |

NDA 217759 Assessment #1

| | |
|--------------------------------|------------------------------------------------------|
| Drug Product Name | Leniolisib Tablets |
| Dosage Form | Tablets |
| Strength | 70 mg/tablet (as free base) |
| Route of Administration | Oral |
| Rx/OTC Dispensed | Rx |
| Applicant | Pharming Technologies B.V. |
| US agent, if applicable | Jennifer Knicley, Senior Director Regulatory Affairs |

| Submission(s) Assessed | Document Date | Discipline(s) Affected |
|---------------------------|---------------|--------------------------|
| Original SD 1 | 7/29/2022 | All |
| Amendment SD 10 | 10/5/2022 | Biopharmaceutics |
| Amendment SD 21 | 11/14/2022 | Manufacturing |
| Amendment SD 22 | 11/21/2022 | Manufacturing |
| Amendment SD 23 | 11/28/2022 | Environmental Assessment |
| Amendment SD 27 | 12/2/2022 | Biopharmaceutics |
| Amendment SD 28 | 12/6/2022 | Drug Product |
| Amendment SD 29 | 12/8/2022 | Drug Product |
| Amendment SD 30 | 12/13/2022 | Manufacturing |



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QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

| DMF # | Type | Holder | Item Referenced | Status | Date Review Completed | Comments |
|---------|------|---------|-----------------|--------|-----------------------|-------------------------------|
| (b) (4) | III | (b) (4) | (b) (4) | N/A | | Sufficient information in NDA |
| | III | | | N/A | | Sufficient information in NDA |
| | IV | | | N/A | | Sufficient information in NDA |

B. OTHER DOCUMENTS: IND, RLD, RS, Approved NDA

| Document | Application Number | Description |
|----------|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| IND | (b) (4) | (b) (4) |
| IND | 124045 | Leniolisib capsules for Activated PI3 K δ Syndrome (APDS)/p110 δ -activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency (PASLI) |

2. CONSULTS

| Discipline | Status | Recommendation | Date | Assessor |
|-------------------------|--------|----------------|------|----------|
| Biostatistics | N/A | | | |
| Pharmacology/Toxicology | N/A | | | |
| CDRH | N/A | | | |
| Clinical | N/A | | | |
| Other | | | | |



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NDA Executive Summary

1. Application/Product Information

| | |
|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NDA Number. | 217759 |
| Applicant Name | Pharming Technologies B.V. |
| Drug Product Name | Leniolisib Tablets |
| Dosage Form. | Tablet |
| Proposed Strength(s) | 70 mg (as free base) per tablet |
| Route of Administration | Oral |
| Maximum Daily Dose | 140 mg |
| Rx/OTC Dispensed | Rx |
| Proposed Indication | Treatment of activated phosphoinositide 3-kinase delta (PI3K δ) syndrome (APDS) in adults and adolescents aged 12 or older |
| Drug Product Description | <p>Leniolisib (as the phosphate salt) is formulated as an immediate release film-coated tablet and it is said to be in BCS Class II (low solubility and high permeability). The drug is an NME and is an inhibitor of p110δ subunit of PI3K class IA, which is said to drive activated phosphoinositide 3-kinase-delta (P13K-δ) syndrome (APDS). Leniolisib is for APDS treatment in adults and adolescents 12 years and older. The dose is 70 mg BID. The drug substance has one chiral center (b) (4)</p> <p>The drug product is formulated with compendial grade excipients and is manufactured (b) (4)</p> |



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|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------|------------------|
| | <p style="text-align: right;">(b) (4)</p> <p>The stability data for the registration batches are not in line with Q1A recommendations: 12 months of long-term (25°C/60%RH) and intermediate (30°C/75%RH) data are provided for one batch, 9 months for a second batch, and 6 months for the third batch. All batches have 6 months of accelerated (40°C/75%RH) stability data. The registration batches are said to be commercial scale. However, there are supportive data from the intended commercial site (Skye Pharma; proposed commercial site) for one non-GMP commercial scale batch PFV2100019 (12 months of long-term (25°C/60%RH) and intermediate (30°C/75%RH) data and 6 months 40°C/75%RH). Additional supportive stability data are provided for a batch of drug product manufactured at Novartis (not the proposed commercial site) with the final formulation (1010016227) (b) (4), with up to 42 months of long term data. The applicant proposes a 24 month expiry period, which is supported by the totality of the stability data.</p> | | | |
| 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]. Do not refrigerate. Store and dispense in original container. | | | |
| Review Team | <table border="1" style="width: 100%;"> <tr> <td style="width: 33%;">Discipline</td> <td style="width: 33%;">Primary</td> <td style="width: 33%;">Secondary</td> </tr> </table> | Discipline | Primary | Secondary |
| Discipline | Primary | Secondary | | |



| | | | |
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|-----------------|-----------------------------------|-------------------|-----------------|
| | <i>Drug Substance</i> | Sam Bain | Donna Christner |
| | <i>Drug Product/ Labeling</i> | Xin Feng | Craig M. Bertha |
| | <i>Manufacturing</i> | Pratibha Bhat | Chengjiu Hu |
| | <i>Biopharmaceutics</i> | Leah Falade | Tapash Ghosh |
| | <i>Microbiology</i> | N/A | |
| | <i>Other (specify):</i> | N/A | |
| | <i>RBPM</i> | Anika Lalmansingh | |
| | <i>ATL</i> | Craig M. Bertha | |
| Consults | N/A | | |

2. Final Overall Recommendation: Adequate

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

All CMC deficiencies have been resolved,¹ thus the application is recommended for approval.

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

Recommendation by Subdiscipline:

Drug Substance - **Adequate**
Drug Product - **Adequate**
Quality Labeling - **Pending¹**
Manufacturing - **Adequate**

¹ The labeling review decision is pending for this IQA due to ongoing negotiations with the applicant. There are only minor labeling deficiencies from the CMC perspective and we expect the applicant will accept our recommendations. Refer to the CMC sections of the final approved labeling.



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Biopharmaceutics - Adequate
Microbiology - N/A

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: N/A

Application Technical Lead Name and Date:
Craig M. Bertha, 12/14/2022



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Final Risk Assessment for Leniolisib Tablets

| DP CQA | Factors that may impact the CQA | O ² | S ^{1,3} | D ¹ | Initial RA FMECA RPN # | Comment & considerations for risk assessment | Final RA | Comments/Lifecycle considerations |
|------------|---------------------------------|----------------|------------------|----------------|------------------------|----------------------------------------------|----------|-----------------------------------|
| Appearance | (b) (4) | 3 | 3 | 2 | 18 | (b) (4) | | |
| ID | | 3 | 3 | 4 | 36 | | 1x3x4=12 | (b) (4) |

² O = Probability of Occurrence; S = Severity of Effect; D = Detectability

³ Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs (thus a median value of “3” will be used throughout)



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Final Risk Assessment for Leniolisib Tablets

| | | | | | | | |
|-------------------------------------------------------|---------|---|---|---|----|---------|--|
| Assay | (b) (4) | 2 | 3 | 1 | 6 | (b) (4) | |
| Degradation Products /Purity | | 2 | 3 | 1 | 6 | | |
| Dissolution | | 2 | 3 | 3 | 18 | | |
| Uniformity of Dosage Units (content uniformity or CU) | | 2 | 3 | 4 | 24 | | |



| | |
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Final Risk Assessment for Leniolisib Tablets

| | | | | | | | |
|------------------|---------|--|--|--|--|---------|--|
| | (b) (4) | | | | | (b) (4) | |
| Microbial limits | | | | | | | |

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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](#)

1.0 PRESCRIBING INFORMATION



(b) (4)

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

| Item | Items 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 | | |
| Established name(s) ¹ | Adequate | |
| Route(s) of administration | Adequate | "for oral use" included |
| Dosage Forms and Strengths Heading in Highlights | | |
| Summary of the dosage form(s) and strength(s) in metric system | Adequate | |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored". | N/A | |

¹ Established name = [Drug] [Route of Administration] [Dosage Form]

| | | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>For injectable drug products for parental 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.</p> | <p>N/A</p> | |
| <p>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).</p> | <p>Inadequate</p> | <p>The drug product contains leniolisib phosphate. The label should clearly state whether the strength is based on the active moiety leniolisib or active ingredient (leniolisib phosphate).</p> |

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)



(b) (4)

| <p>Item</p> | <p>Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")</p> | <p>Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)</p> |
|-----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| <p>DOSAGE AND ADMINISTRATION section</p> | | |
| <p>Special instructions for product preparation (e.g., reconstitution and resulting</p> | <p>N/A</p> | |

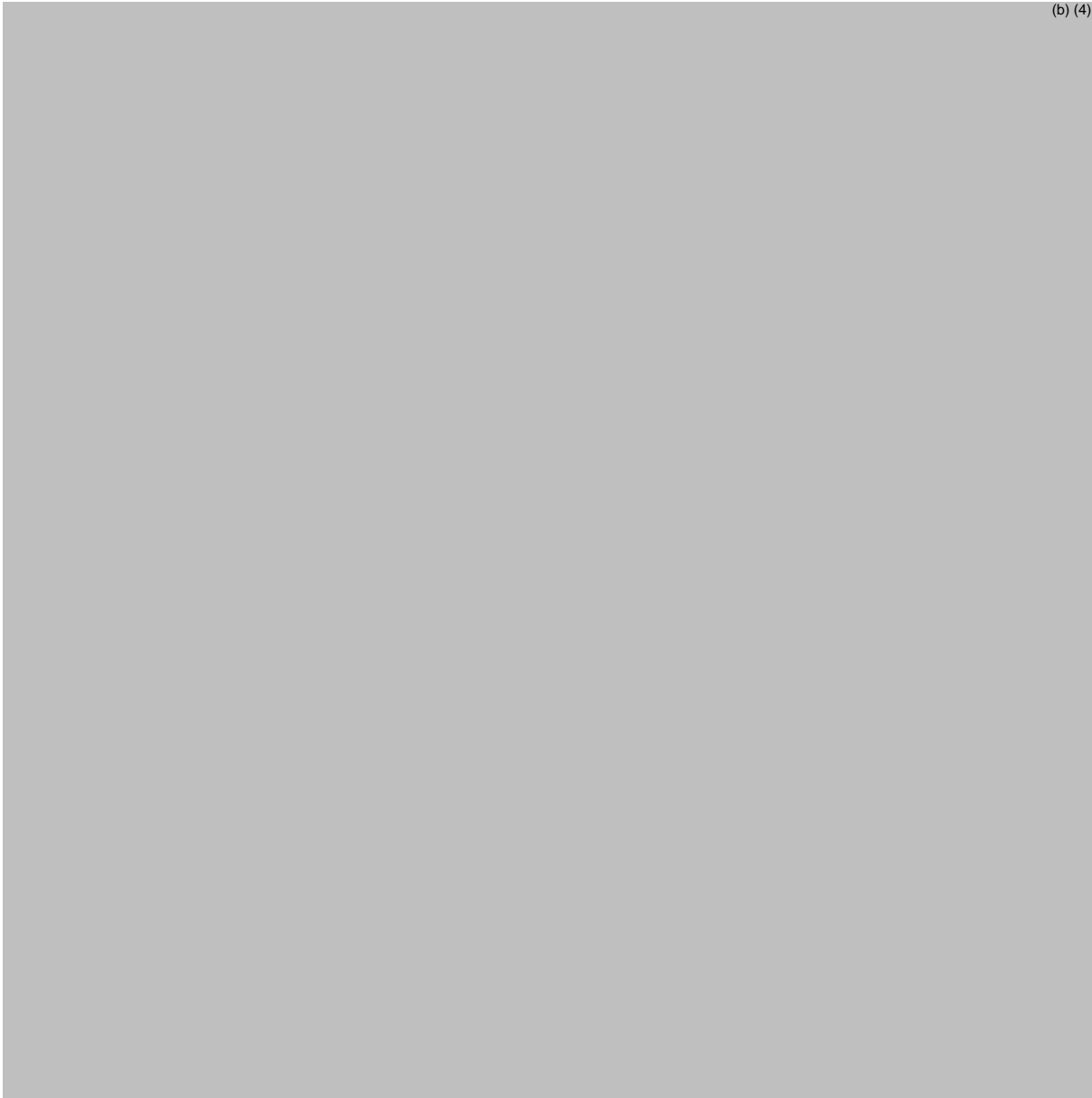
| | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|--|
| <p>concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)</p> | | |
| <p>Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)</p> | <p>N/A</p> | |
| <p>For parenteral products: include statement: <i>“Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit”</i></p> | <p>N/A</p> | |
| <p>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 11).</p> | <p>N/A</p> | |
| <p>For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug</p> | <p>N/A</p> | |
| <p>For hazardous products, include the statement <i>“DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.^x”</i> with x numerical citation to <i>“OSHA Hazardous Drugs”</i>.</p> | <p>N/A</p> | |

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)



(b) (4)

| Item | Items 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 | |
| Strength(s) in metric system | Adequate | |
| 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 (Tablets: 10 mg of drug-x hydrochloride). | Inadequate | The drug product contains leniolisib phosphate. The label should clearly state whether the strength is based on the active moiety leniolosib or active ingredient (leniolisib phosphate). Please apply USP Salt Policy per FDA guidance (e.g. Each tablet contains 85 ^(b) ₍₄₎ mg Leniolisib phosphate salt to provide 70 mg of leniolosib as the free base). |
| 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 | |
| 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 parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package. | N/A | |

Section 11 (DESCRIPTION)

(b) (4)

| Item | Items 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) | Inadequate | |
| Dosage form(s) and route(s) of administration | Adequate | |
| 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)" | Inadequate | The drug product contains leniolisib phosphate. The label should clearly state whether the strength is based on the active moiety leniolisib or active ingredient (leniolisib phosphate). Please apply USP Salt Policy per FDA guidance (e.g. Each tablet contains 85 ^{(b) (4)} mg Leniolisib phosphate salt to provide 70 mg of leniolisib as the free base). |
| List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names. | Adequate | |
| 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. | N/A | |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol | N/A | |
| Sterility statement (if applicable) | N/A | |
| Pharmacological/Therapeutic class | Adequate | |
| Chemical name, structural formula, molecular weight | Adequate | |
| If radioactive, statement of important nuclear characteristics. | N/A | |
| Other important chemical or physical properties (such as pKa or pH) | Adequate | |

Section 11 (DESCRIPTION) Continued

| Item | Items 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 oral prescription drug products, include gluten statement (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") | Adequate | |
| 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 | |

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)



(b) (4)

| Item | Items 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) | Adequate | Tablets |
| Strength(s) in metric system | Adequate | 70 mg |
| Available units (e.g., bottles of 100 tablets) | Adequate | 60 tablets in one bottle |
| Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) | Inadequate | Revision added "JOENJA is available in 70 mg tablet: yellow, oval-shaped, biconvex, bevelled edge film-coated tablet debossed with "70" on one side and "LNB" on the other side. It is supplied in bottles with a child-resistant cap of 60 tablets (NDC 71274-170-60)." |
| 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 parental 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. | N/A | |
| 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." | Inadequate | Please provide reason why "Store and dispense in original container." (e.g., to protect from light or moisture, to maintain stability, etc.). |

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

| Item | Items 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) |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. | 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]. Do not refrigerate. |
| 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: <i>“Not made with natural rubber latex. Avoid statements such as “latex-free.”</i> | Adequate | No terms like “latex-free” or other latex related terms were used |
| Include information about child-resistant packaging | Inadequate | Revision added “It is supplied in bottles with a child-resistant cap of 60 tablets (NDC 71274-170-60).” |

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)

| Item | Items 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) |
|---------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Manufacturing Information After Section 17 | | |
| Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer | Inadequate | Please add location of the business (street address, city, state, and zip code) of the manufacturer. |

2.0 PATIENT LABELING

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

17 PATIENT COUNSELING INFORMATION



(b) (4)



| Item | Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| Established name ² | Adequate | |
| Special preparation instructions (if applicable) | N/A | |
| Storage and handling information (if applicable) | N/A | |
| 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 differs from the dosage form. | N/A | |
| Active ingredient(s) (if applicable) | N/A | |
| Alphabetical listing of inactive ingredients (if applicable) | N/A | |
| Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer | Inadequate | Please add location of the business (street address, city, state, and zip code) of the manufacturer. |

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

² Established name = [Drug] [Route of Administration] [Dosage Form]

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

| Item | Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”) | Assessor’s Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| Established name ³ , (font size and prominence) | Adequate | |
| Strength(s) in metric system | Adequate | 70 mg |
| Route(s) of administration | Adequate | (b) (4) |
| If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP . | Adequate | |
| Net contents (e.g., tablet count, volume of liquid) | Adequate | 60 tablets |
| “Rx only” displayed on the principal display | Adequate | Rx only displayed |
| NDC | Adequate | NDC provided |
| Lot number and expiration date | Adequate | |
| Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD). | Adequate | |
| For injectable drug products for parental 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. | N/A | |
| For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. | N/A | |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol | N/A | |
| Linear Bar code | Adequate | |

³ Established name = [Drug] [Route of Administration] [Dosage Form]

| Item | Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| Name of manufacturer/distributor /packer | Adequate | |
| If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient. | N/A | |
| No text on Ferrule and Cap overseal, unless a cautionary statement is required. | Adequate | |
| If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. | N/A | |
| 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. | N/A | |
| And others, if space is available. | N/A | |

Assessment of Carton and Container Labeling: Adequate

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

The labeling information is in general adequate from CMC perspective. Some minor editorial change will be made during the team labeling review.

Primary Labeling Assessor Name and Date: Xin Feng, 12-Dec-2022

Secondary Assessor Name and Date (and Secondary Summary, as needed): Craig Bertha, 12-Dec-2022



Xin
Feng

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CHAPTER VI: BIOPHARMACEUTICS

| | |
|-----------------------------------------------------|---------------------------------------------------------------------------------------|
| NDA Number | NDA-217759-ORIG-1 |
| Assessment Cycle Number | 1 |
| Drug Product Name/ Strength | Leniolisib Phosphate Tablets/70 mg |
| Route of Administration | Oral |
| Applicant Name | Pharming Technologies B.V. |
| Therapeutic Classification/ OND Division | Miscellaneous Respiratory/Division of Pulmonology, Allergy, and Critical Care (DPACC) |
| RLD/RS Number | N/A |
| Proposed Indication | For the treatment of Activated PI3Kδ Syndrome (APDS) |
| Primary Reviewer | Leah W. Falade, Ph.D. |
| Secondary Reviewer | Tapash Ghosh, Ph.D. |

Assessment Recommendation: Adequate

Assessment Summary:

The Applicant is seeking approval for its Leniolisib Phosphate Tablets, 70 mg following the 505(b)(1) regulatory pathways. The proposed product is indicated for treatment of activated phosphoinositide 3-kinase-delta (PI3K-δ) syndrome (APDS) in adolescent and adult patients.

The clinical package in support of this NDA includes 3 Phase 2/3 pivotal clinical studies. These studies will be assessed by the Office of Clinical Pharmacology.

The Biopharmaceutics review focuses on the evaluation and acceptability of:

1. Dissolution method and acceptance criterion:

The Applicant's dissolution method (USP Apparatus 1 (basket) at 100 rpm, with 900 mL of pH 4.0 acetate buffer/37°C) is adequately justified and considered acceptable for batch release and stability testing. Data was provided to support the discriminating ability of the method by altering the target formulation by changing the excipients (b) (4)

The drug substance has low solubility and is classified as a BCS Class 2 drug. The Applicant's proposed acceptance criterion is acceptable.

2. Bridging of formulations:

During the drug product development, 2 different formulations were manufactured at 2 different facilities. For early Phase 1 studies, a hard gelatin capsule formulation (HGC) was manufactured at Novartis in Switzerland. A film-coated tablet (FCT) formulation was manufactured

at Skyepharma in France for Phase 2/3 studies. The FCT formulation manufactured at Skyepharma is the to-be-marketed (TBM) formulation at the proposed manufacturing site. The dissolution behaviors of the HGC and FCT formulations are not the same. Bioequivalence studies were performed to bridge the two formulations and manufacturing sites. The BE studies will be assessed by the Office of Clinical Pharmacology. Therefore, from a Biopharmaceutics perspective, formulation bridging is not applicable.

Recommendation

From a Biopharmaceutics perspective, NDA-217759-ORIG-1 for the proposed Leniolisib Phosphate Tablets, 70 mg is recommended for **approval**.

FDA-Approved Dissolution Method and Acceptance Criterion for batch release and stability testing for Leniolisib Phosphate Tablets:

| Apparatus | Speed | Medium/Temperature | Volume | Dissolution Acceptance Criterion |
|------------|---------|----------------------------------|--------|----------------------------------|
| 1 (basket) | 100 rpm | pH 4.0 Acetate Buffer/37.0±0.5°C | 900 mL | Q ^{(b) (4)} % in 45 min |

List Submissions being assessed:

| Document(s) Assessed | Date Received |
|--------------------------------|---------------|
| Original (Seq 0001) | 07/29/2022 |
| Quality IR Response (Seq 0010) | 10/05/2022 |
| Quality IR Response (Seq 0027) | 12/02/2022 |

Highlight Key Issues from Last Cycle and Their Resolution: This is the first review cycle.

Concise Description of Outstanding Issues: None

B.1 BCS DESIGNATION

Assessment: The Applicant did not submit a BCS Designation request.

Solubility: The solubility of the drug substance is pH-dependent with the highest solubility accruing in acidic pH medium (0.1 N HCl, pH 1.0). The pH solubility profile is presented below.

Table 1. Equilibrium Solubility of Leniolisib Phosphate

| Buffer (pH) | Solubility (mg/mL) |
|---------------------------|--------------------|
| 0.1 M HCl (pH 1.0) | 8.88 |
| Citrate buffer (pH 4.2) | 0.70 |
| Citrate buffer (pH 5.2) | 0.09 |
| Phosphate buffer (pH 6.2) | 0.04 |
| Phosphate buffer (pH 6.8) | 0.04 |

Source: 3.2.S.1.3 General Properties.

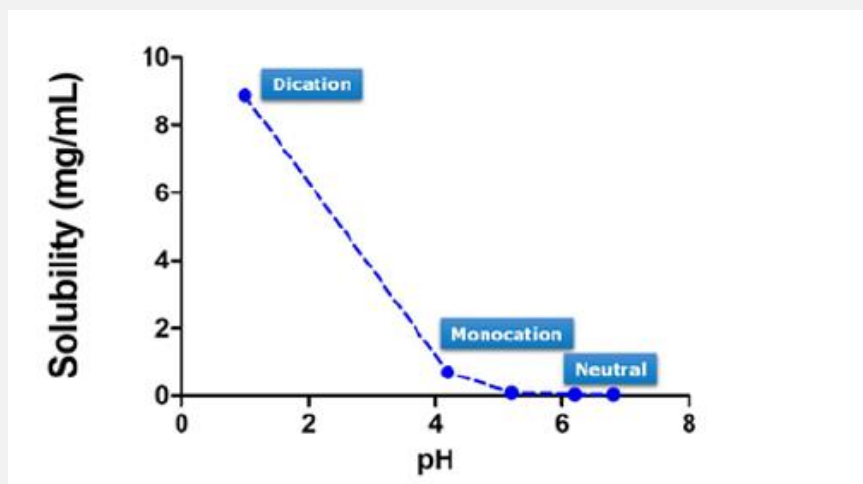


Figure 1. pH-Dependent Solubility Profile of Leniolisib Phosphate

Permeability: An in-vitro study in Caco-2 cells was submitted (<\\CDSESUB1\EVSPROD\nda217759\0001\m4\42-stud-rep\422-pk\4222-absorp\1400727\1400727-pre-clinical-study-report.pdf>) showing that the permeability of the drug substance is high and human intestinal absorption is expected to be >90%. The drug substance can be classified as BCS Class 2 based on the low solubility and high permeability.

Dissolution: See next section for dissolution data.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERION

Assessment: Adequate

In response to an Information Request (IR), the Applicant noted that there was no formal method development provided. However, the following data was provided to justify the selection of the dissolution method.

(b) (4)



Discriminating Ability

The Applicant referred to the dissolution data during product development to provide justification of the discriminating ability of the dissolution method. (b) (4)



the different tablet formulations have different dissolution profiles using the proposed dissolution method. Therefore, the dissolution method is discriminating to changes in (b) (4) amount and location (b) (4). The Applicant also performed an in vivo bioequivalence study on the capsules manufactured by Novartis vs. the film-coated tablets manufactured by Skyepharma. Although the two formulations were found to be bioequivalent, then in vitro dissolution profiles are not similar. Therefore, the in vitro method is not discriminatory towards bioequivalence.

Acceptance Criterion

The Applicant proposes $Q = \frac{(b)}{(4)}\%$ in 45 min as the acceptance criterion for release and stability testing. The Applicant provided dissolution data on 6 clinical batches, which includes the capsule formulation. The capsule formulation has a different dissolution profile than the to-be-marketed (TBM) film-coated tablet formulation. Therefore, this Reviewer only considers the tablet formulations used in the clinical studies for setting the acceptance criterion. Lot #101006227 was manufactured at Novartis, which is not the manufacturing site for the TBM product. Therefore, the first 3 lots are considered below which were all manufactured at Skyepharma, which is the manufacturing site for the TBM product. The dissolution data and profiles are provided below.

Table 2. Dissolution Data for Clinical Batches, n=12

| Lot/Time (min) | 0 | 10 | 15 | 20 | 30 | 45 | 60 | 75 |
|---------------------------|----------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| PV2100040 | 0 | (b) (4) | | | | | | |
| PV2100059 | 0 | (b) (4) | | | | | | |
| PVV2100080 | 0 | (b) (4) | | | | | | |
| 1010016227 | 0 | (b) (4) | | | | | | |
| Mean | 0 | 64.8 | 74.6 | 79.8 | 85.2 | 89.4 | 92.0 | 95.6 |
| Standard Deviation | 0 | 6.0 | 6.3 | 6.4 | 6.1 | 5.5 | 4.8 | 3.5 |
| %CV | 0 | 9.2 | 8.4 | 8.1 | 7.2 | 6.2 | 5.2 | 3.7 |
| Min | 0 | (b) (4) | | | | | | |
| Max | 0 | (b) (4) | | | | | | |

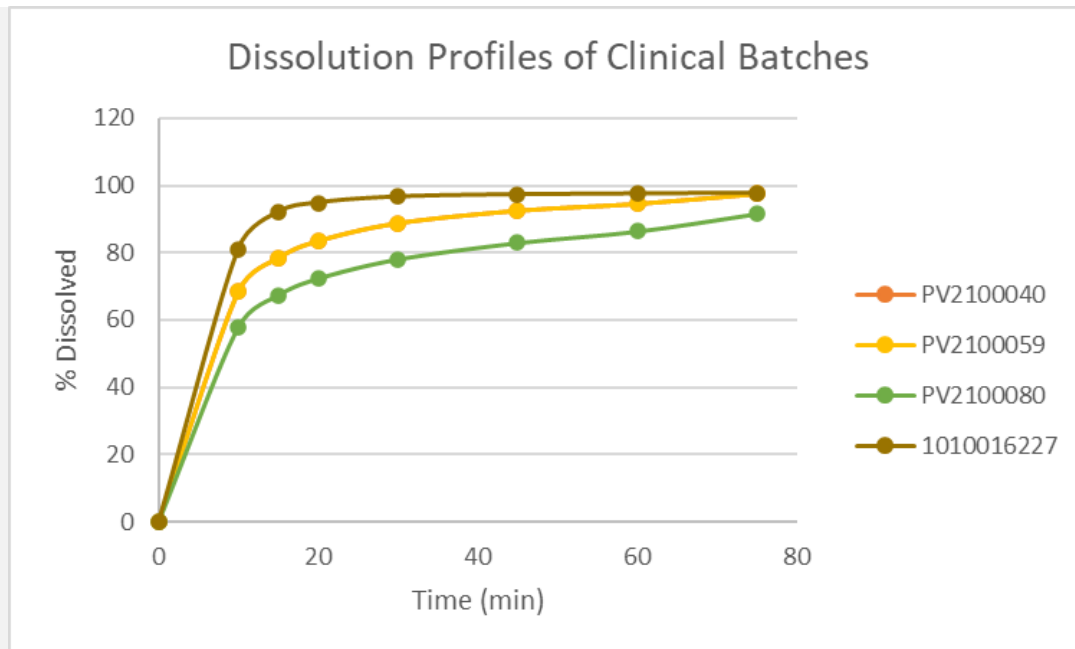


Figure 5. Dissolution Profiles of Clinical Batches, n=12

The Applicant was asked to explain why lot PV100080 dissolved slower than the other 2 clinical batches manufactured at the same facility. In the response dated 12/02/2022 (Seq 0027), the Applicant did not address the slower release, but clarified that the stability batches met the proposed acceptance criterion of “Q= (b) (4)% in 45 min” at Stage 1 and Stage 2 testing. For immediate release drug products with high solubility, “Q= (b) (4)% in (b) (4) min” is recommended. However, this drug substance has low solubility. The Applicant’s proposed acceptance criterion is acceptable due to the following:

1. The drug substance has low solubility and is classified as a BCS Class 2 drug.
2. The stability data meet the proposed acceptance criterion at Stage 1 and Stage 2 testing.
3. The drug is >90% released in 60 min which should not have a clinical effect on absorption because the median T_{max} is 1 and 4 hours under fasting and fed conditions, respectively.

The following dissolution method and acceptance criterion are approved for QC dissolution testing for release and stability:

| Apparatus | Speed | Medium/Temperature | Volume | Dissolution Acceptance Criterion |
|------------|---------|----------------------------------|--------|----------------------------------|
| 1 (basket) | 100 rpm | pH 4.0 Acetate Buffer/37.0±0.5°C | 900 mL | Q= (b) (4)% in 45 min |

B.3 BRIDGING OF FORMULATIONS

Assessment: Adequate

The early phase clinical studies used a hard gelatin capsule formulation. (b) (4)

A pivotal Phase 2/3 bioequivalence (BE) study was performed to bridge the HGC and FCT formulations. The HGC product was manufactured at Novartis in Switzerland and the intended commercial product was manufactured at Skyepharma in France. The adequacy of the BE study will be assessed by the Office of Clinical Pharmacology. Formulation bridging is therefore not applicable from a Biopharmaceutics perspective.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date: Leah W. Falade, Ph.D.. 12/06/2022

Secondary Assessor Name and Date: Tapash Ghosh, Ph.D.. 12/06/2022



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