CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216196Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 216196 PYRUKYND® (mitapivat) Tablets

Integrated Quality Review

Recommendation: Approval

Drug Name/Dosage Form	PYRUKYND® (mitapivat) tablets, for oral use
Strength	5 mg, 20 mg, 50 mg tablets
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Agios Pharmaceuticals, Inc.
Submission(s) Reviewed	Original NDA 216196, and all submitted CMC amendments

Quality Review Team

Discipline	Reviewer/Secondary	Branch/division
Drug Substance	Daniel Jansen/ Suong Tran	OPQ/ONDP/DNDAPI/NDB3
Drug Product, Labeling, and Environmental Assessment	Theodore Carver/ Mohan Sapru	OPQ/ONDP/DNDPIII/NDPB5
Process/ Facility	Liya Tang/ Feiyan Jin	OPQ/OPMA/DPMAIII/PMB7
Biopharmaceutics	Rebecca Moody/ Poonam Delvadia	OPQ/ONDP/DB/BB3
Regulatory Business Process Manager	Grafton Adams	OPQ/OPRO/DRBPMI/RBPMB2
Application Technical Lead	Theodore Carver	OPQ/ONDP/DNDPIII/NDPB5

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)		adequate	Information in NDA adequate for review; last reviewed 2/2/16	LOA dated 3/19/21
	III			adequate	Information in NDA adequate for review; last reviewed 8/13/20	LOA dated 4/8/21

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	119825	Mitapivat (AG-348)

2. CONSULTS: None

Executive Summary

1. Recommendations and Conclusions on Approvability

The Office of Pharmaceutical Quality Review team has assessed NDA 216196 for PYRUKYND® (mitapivat) tablets, for oral use with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports to have. As such, OPQ recommends approval of this NDA from a quality perspective.

2. Background Summary

The applicant, Agios Pharmaceuticals, Inc., submitted the 505(b)(1) NDA for PYRUKYND® (mitapivat) tablets seeking marketing approval for the proposed indication of treatment of adult patients with pyruvate kinase deficiency. Mitapivat is a new molecular entity and has been granted orphan drug designation. The application includes data from two Phase 3 studies to support approval, as well as other supportive studies. The proposed commercial formulations for mitapivat are 5mg, 20mg, and 50mg, round or oblong, blue, film-coated, immediate-release tablets for oral administration.

3. Summary of Quality Assessments

3.1 Drug Substance (Mitapivat)

The drug substance, mitapivat (AG-348), is a synthetic small molecule that is (b) (4). The structure and properties are well-characterized. The starting materials are appropriate justified per ICH Q11. The manufacturing and controls, including (b) (4) were reviewed for the drug substance and found to be adequate and capable of yielding a drug substance of consistent and well-defined quality. The drug substance specification includes appropriate tests and acceptance criteria to ensure the quality of the drug substance for use in manufacturing the drug product. (b) (4) is the only specified impurity with acceptance criteria of NMT (b) (4)%. Potential process-related impurities include (b) (4), a known genotoxic impurity, and (b) (4), which are controlled with appropriate limits per ICH M7 and ICH Q3C. Stability data support a retest of (b) (4) months for the mitapivat drug substance when stored (b) (4) at or below (b) (4).

3.2 Drug product (Mitapivat tablets)

A) Product Design and Specification: The mitapivat tablets are manufactured as an immediate release formulation in three strengths, 5 mg, 20 mg, and 50 mg, (b) (4) . Each strength is distinguished by size, imprint, and shape. The drug product is packaged in clear blister strips containing seven tablets per blister card, and all contact components comply with food additive regulations. The excipients are all USP/NF grade or comprised of USP/NF grade components. Impurities in the drug product are controlled as unspecified impurities in the drug product with limits that comply with recommendations in the ICH Q3B guideline. Risk assessments for elemental impurities and (b) (4) impurities are provided in the NDA. In response to information requests regarding control of potential (b) (4) impurities, the Applicant provided additional information to address this risk. The drug product specifications for all strengths include appropriate tests and acceptance criteria with respect to the identity, purity, assay, quality, and stability of the drug product.

B) Drug Product Manufacturing: The drug product manufacturing process was reviewed and found to be adequate. (b) (4)

C) Biopharmaceutics Aspects: The biopharmaceutics review concluded that the biopharmaceutics information provided, the proposed in vitro release test method, and the acceptance criterion are adequate to support approval of this NDA. Mitapivat behaves as a highly soluble drug substance at pH $\leq$ 5.5 for all strengths. Although the dissolution method has limited discriminating capability with respect to changes in quality attributes, the risk is sufficiently mitigated by the data provided, including stability and manufacturing data. See the review below for additional information including the approved dissolution method and acceptance criterion.

D) Container Closure System: The CMC information for the container-closure components was reviewed and found to be adequate. Mitapivat tablets are packaged in (b) (4) blister film material, with aluminum lid stock comprised of (b) (4) . The blister film layer is made of clear plastic, which is supported by the photostability of the drug product. All product contact materials comply with food additive regulations. Each tablet

strength is packaged in blister cards containing seven tablets.

4. **Assessment of Manufacturing Facilities:** The Office of Product Manufacturing Assessment has recommended an overall approval for all the currently listed manufacturing facilities for this NDA. There are two drug substance manufacturing facilities, (b) (4) and (b) (4), which were approved based on previous history. The drug product manufacturing and release testing facility, (b) (4) was approved based on previous history. All other testing facilities for the drug substance and drug product were found acceptable based on inspection history and district recommendation. Therefore, all facilities have been reviewed and found acceptable based on firm's capability and inspection outcomes. See the facilities table on page 2 of the manufacturing integrated assessment for a summary of all facility assessments.

5. **Environmental Assessment**: Information for the environmental assessment was reviewed by Dr. James Laurenson from the environmental assessment team and Dr. Carver, the drug product reviewer. The Applicant submitted a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase in use but result in an expected introduction concentration (EIC) of < 1 ppb. The Applicant provided additional data to address potential reproduction and development risks, which were reviewed in the supporting IND 119825. FDA concludes that extraordinary circumstances are not indicated, in accordance with 21 CFR 25.15, and that this application qualifies for the categorical exclusion from an EA as defined in 21 CFR 21.31(b).

6. **Expiration Dating and Storage Conditions**: The supporting stability studies, which included both long-term and accelerated stability data, were reviewed as part of the drug product review and were found to be adequate. The long-term storage condition for the drug product is 20 to 25ºC (USP controlled room temperature) with excursions allowed to 15 to 30ºC. The submission includes 24 months of long-term stability data for three lots of each strength manufactured at commercial scale/primary packaging and 12 months of stability data for an additional three lots of each tablet strength, (b) (4). Based on the Applicant's statistical analysis of the data provided and the observed trending in assay, (b) (4), and dissolution, a shelf life of 36 months is granted for the drug product stored at 20 to 25ºC.

7. **Quality Labeling**: The container and carton label were reviewed as part of the drug product review. The dosage form description, strength, established name, NDC #, Lot #/Expiry, and storage conditions are adequately described in the carton and container label, which meets relevant regulatory requirements for labeling. Comments regarding the draft USPI were conveyed to the Applicant and will be finalized as part of the labeling.

8. **List of CMC Deficiencies:** None

OVERALL ASSESSMENT AND SIGNATURES:

At present, there are no outstanding deficiencies related to the drug substance, drug product, biopharmaceutics, manufacturing, and environmental assessment sections of this NDA. The OPQ overall recommendation for NDA 216196 is *approval.*

Theodore Carver, Ph.D. 12/15/21
Senior Pharmaceutical Quality Assessor
Application Technical Lead

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FDA U.S. FOOD & DRUG ADMINISTRATION

CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

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]	Inadequate **PYRUKYND® (mitapivat), for oral use**	Dosage form omitted. Change to **PYRUKYND® (mitapivat) tablets, for oral use**
Route(s) of administration	Adequate	For oral use
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate Tablets: 5 mg, 20 mg and 50 mg (3)	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	Adequate	Not scored.
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	
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	Adequate	The active ingredient is a salt, but strength is expressed in terms of the active moiety, not the salt.

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

ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

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 AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate **2 DOSAGE AND ADMINISTRATION** PYRUKYND is taken (b) (4) with or without food (b) (4) swallowed whole. Do not split, crush, chew, or dissolve the tablets.	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	

Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).		
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	

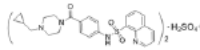
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

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 • 5 mg tablets: round, blue, film-coated, (b) (4) tablets with "M5" printed on one side. • 20 mg tablets: round, blue, film-coated, (b) (4) tablets with "M20" printed on one side. • 50 mg tablets: oblong, blue, film-coated, (b) (4) tablets with "M50" printed on one side.	
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).	Adequate	Strength is based on the active moiety, not the salt.
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	Inadequate	The highlighted text above, "(b) (4) tablets" needs to be deleted from the description of the dosage form.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Adequate	Not scored.
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)

APPEARS THIS WAY ON ORIGINAL

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 The chemical name (b) (4) is 8-Quinolinesulfonamide, N-[4-[[4-(cyclopropylmethyl)-1-piperazinyl]carbonyl]phenyl]-, sulfate, hydrate (2:1:3).	Change to "The active ingredient of PYRUKYND is mitapivat, a pyruvate kinase activator, present as mitapivat sulfate. The chemical name of mitapivat sulfate is 8-quinolinesulfonamide, N-[4-[[4-(cyclopropylmethyl)-1-piperazinyl]carbonyl]phenyl]-, sulfate, hydrate (2:1:3).
Dosage form(s) and route(s) of administration	Inadequate PYRUKYND is available as 5 mg, 20 mg, and 50 mg (b) (4) tablets for oral administration.	Delete highlighted descriptive terms: PYRUKYND is available as 5 mg, 20 mg, and 50 mg tablets for oral administration.
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 Each (b) (4) tablet contains (b) (4) 5 mg, 20 mg, or 50 mg mitapivat free-base (as the sulfate hydrate salt) and the following inactive ingredients: croscarmellose sodium, mannitol, microcrystalline cellulose, and sodium stearyl fumarate.	Revise as follows: Each (b) (4) tablet contains (b) (4)-5 mg, 20 mg, or 50 mg of mitapivat free-base, provided as 5.85, 23.4, or 58.5 mg of the the sulfate hydrate salt, respectively, and the following inactive ingredients: croscarmellose sodium, mannitol, microcrystalline cellulose, and sodium stearyl fumarate. The tablet film coating contains the (b) (4) inactive ingredients: FD&C Blue No. 2, hypromellose, lactose monohydrate, titanium dioxide, and triacetin. The tablets are imprinted with black ink containing ammonium hydroxide, ferrosoferric oxide, isopropyl alcohol, n-butyl alcohol, propylene glycol, and shellac glaze.
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Inadequate	See revised text above.
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	Inadequate	Therapeutic class not provided. See highlighted text above with class from highlights. To be confirmed with pharmacology reviewers.
Chemical name, structural formula, molecular weight	Inadequate  The molecular formula is (C24H26N4SO3)2 • H2SO4 • 3H2O and the (b) (4) 053.23 (b) (4)	See revised text for name above. Structure, formula, MW align with 3.2.S.
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Inadequate	Add physical description of drug substance in text above: "Mitapivat sulfate is a white to off-white (b) (4) and is slightly soluble in water."

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)	Choose an item.	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	Inadequate	See revised text. "(b) (4) " removed.
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)

APPEARS THIS WAY ON ORIGINAL

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 (b) (4)	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	

Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not scored; may not be split
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."	Adequate Store at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F) *[see USP Controlled Room Temperature]*. Store the blister (b) (4) in the original carton until use.	

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	See above.
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*	N/A	

with natural rubber latex. Avoid statements such as "latex-free."		
Include information about child-resistant packaging	N/A	

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.

See recommendations regarding the patient information section below.

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	Adequate	Name and location of manufacturer/distributor were provided.

2.0 PATIENT LABELING

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

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 **PATIENT INFORMATION** **PYRUKYND [pye roo' kind]** **(mitapivat)** **tablets, for oral use**	
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Inadequate	Add the below section for storage: How should I store PYRUKYND? • Store PYRUKYND at room temperature between 68°F to 77°F (20°C to 25°C). Store the blister (b) (4) in the original carton until use. Keep PYRUKYND and all medicines out of the reach of children
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)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Inadequate	**Revise to include all inactive ingredients:** **What are the ingredients in PYRUKYND?** **Active ingredient:** mitapivat **Inactive ingredients:** croscarmellose sodium, mannitol, microcrystalline cellulose, and sodium stearyl fumarate. The film coating contains: FD&C Blue No. 2, hypromellose, lactose monohydrate, titanium dioxide, and triacetin. The (b) (4) ink contains: ammonium hydroxide, ferrosoferric oxide, isopropyl alcohol, n-butyl alcohol, propylene glycol, and shellac glaze.
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate **Manufactured for and Distributed by:** Agios Pharmaceuticals, Inc. Cambridge, MA 02139	

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

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

(Copy/paste or refer to a representative example of a proposed container)

Example blister monthly pack labeling, 20 and 50 mg:

Example of taper pack labeling, 5 mg:

3 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	
Route(s) of administration	Adequate	"(b) (4)" displayed on carton labels;
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Inadequate	Equivalency statement needs to be added to carton label
Net contents (e.g., tablet count, volume of liquid)	Adequate	Tablet count displayed on the carton labels
"Rx only" displayed on the principal display	Inadequate	Rx only is displayed on the carton but not the blister cards.
NDC	Adequate	
Lot number and expiration date	Adequate	Provided for each blister
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	Provided on blister card/carton

[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	Provided on carton.
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.	N/A	
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: ***Pending revisions to be incorporated by the Applicant.***

ITEMS FOR ADDITIONAL ASSESSMENT

Deficiencies have been conveyed to Applicant in draft labeling.

Overall Assessment and Recommendation:

The labeling will be adequate after the Applicant incorporates the recommended changes.

Primary Labeling Assessor Name and Date: Theodore Carver, 12/8/21

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Mohan Sapru, 12/8/21

Theodore Carver

Digitally signed by Theodore Carver
Date: 12/08/2021 05:56:14PM
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Mohan Sapru

Digitally signed by Mohan Sapru
Date: 12/08/2021 06:58:53PM
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CHAPTER VI: BIOPHARMACEUTICS

For more details about the items in this template, please see Chapter VI (Biopharmaceutics) of the NDA IQA Guide

Product Information	NME; Mitapivat sulfate film-coated immediate-release tablets for oral administration
NDA Number	216196
Assessment Cycle Number	1
Drug Product Name/ Strength	Mitapivat IR Tablet, 5 mg, 20 mg, and 50 mg
Route of Administration	Oral
Applicant Name	Agio Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	Division of Non-Malignant Hematology (DNH)
RLD/RS Number	N/A
Proposed Indication	Treatment of adult patients with pyruvate kinase deficiency (PK deficiency)

Assessment Recommendation: **Adequate**

Assessment Summary:

On 6/17/2021, Agio Pharmaceuticals, Inc., the Applicant, submitted an NDA under 505(b)(1) seeking marketing approval for PYRUKYND (mitapivat) Tablet, 5 mg, 20 mg, and 50 mg, indicated for the treatment of adult patients with pyruvate kinase deficiency (PK deficiency). Mitapivat is formulated as a film-coated immediate-release tablet for oral administration. The initial dose is 5 mg twice daily taken with or without food. The maximum recommended dose is 50 mg twice daily.

The Biopharmaceutics assessment is focused on the evaluation and acceptability of the proposed quality control dissolution method and acceptance criterion.

The approved dissolution method and acceptance criterion for quality control (finished drug product batch release and stability testing) are:

Method Conditions/ Acceptance Criterion	Mitapivat Tablets (5, 20, and 50 mg)
Medium	100 mM sodium phosphate, pH 6.8, with 0.05% w/w SLS
Volume/Temp	900 mL; 37°C
Apparatus	II
Speed	70 rpm
Acceptance Criterion	NLT (b)(4)% (Q) in 15 min

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
0001 (1) Original Submission	June 17, 2021

Highlight Key Issues from Last Cycle and Their Resolution: N/A

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

B.1 BCS DESIGNATION

Assessment: No BCS Designation was requested.

Solubility: Mitapivat was developed as a sulfate hydrate salt. The salt form has high kinetic solubility across the physiologically relevant pH range, while the thermodynamically stable free base exhibits pH dependent equilibrium solubility. Mitapivat free base demonstrates relatively high solubility at pH ranges from 1.0 – 5.5 and low solubility at pH ranges from 5.5 – 8.0 (see Table 1).

Table 1. Equilibrium Solubility of Mitapivat Sulfate in Physiological Aqueous Buffer Solutions at 37°C and pH 1-8

Aqueous Solutions	Buffer Concentration	pH	Mitapivat Equilibrium Solubility (mg/mL)[1]	BCS Solubility[2]
Water (n=2)	NA	NA[3]	2.09	High
HCl (n=2)	0.1 N	1.1	9.72	High
Phosphate Buffer (n=2)	50 mM	2.8	3.20	High
Acetate Buffer (n=2)	50 mM	4.8	2.23	High
Acetate Buffer (n=4)	100 mM	5.5	0.34	High
Phosphate-Citrate Buffer (n=4)	100 mM	6.0	0.12	Low
Phosphate Buffer (n=4)	100 mM	6.5	0.04	Low
Phosphate Buffer (n=4)	100 mM	6.8	0.03	Low
Phosphate Buffer (n=2)	50 mM	7.5[3]	0.03	Low
Phosphate Buffer (n=2)	50 mM	8.0[3]	0.02	Low

[1] 24-hours equilibrium solubility data presented. Reported values are the average of replicate preparations. Mitapivat concentration expressed on a free base basis

[2] High solubility is defined as ≥ 0.20 mg/mL and low solubility is defined as < 0.20 mg/mL for mitapivat; calculated as outlined in the BCS classification guidance

[3] pH drift lower at 24 hrs (end of study)

Permeability: Mitapivat showed good permeability in the Caco-2 cell assay with apparent permeability in the apical-to-basal direction of > 18.2 x 10^{-6} cm/s. The human ADME study (Study AG348-C-009) also indicated good permeability with the fraction absorbed (f_a) x fraction escaping gut metabolism (f_g) calculated at > 0.8. The absolute bioavailability of mitapivat after a single dose ranged from 65.3% to 86.3% for individual subjects.

Dissolution: See below.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: *Adequate*

The Applicant proposed the following dissolution method for the proposed Mitapivat Tablets.

Method Conditions/ Acceptance Criterion	Mitapivat Tablets (5, 20, and 50 mg)
Medium	100 mM sodium phosphate, pH 6.8, with 0.05% w/w SLS
Volume/Temp	900 mL; 37°C
Apparatus	II
Speed	70 rpm
Acceptance Criterion	NLT (b) (4)% (Q) in 15 min

The Applicant provided details of their dissolution method development in the Pharmaceutical Development (Module 3.2.P.2). It is noted that the Applicant provided their full dissolution method development in an IND amendment for review prior to NDA submission.[1] The Applicant was requested to evaluate lower agitation speeds and determine the method's discriminating capability with respect to (b) (4). The details provided below are a summary of the Applicant's dissolution method development.

(b) (4)

[redacted]

[1] IND 119825 Seq 0150 CMC Amendment: Mitapivat sulfate, AG-348. Dissolution Method Development. April 21, 2020

[1] CDER Informatics Platform--IND 119825 IND Amendment Biopharmaceutics Review

[1] IND 119825 Seq 0189 Type B Pre-NDA CMC Meeting Briefing Document. Page 85 of 112. January 6, 2021

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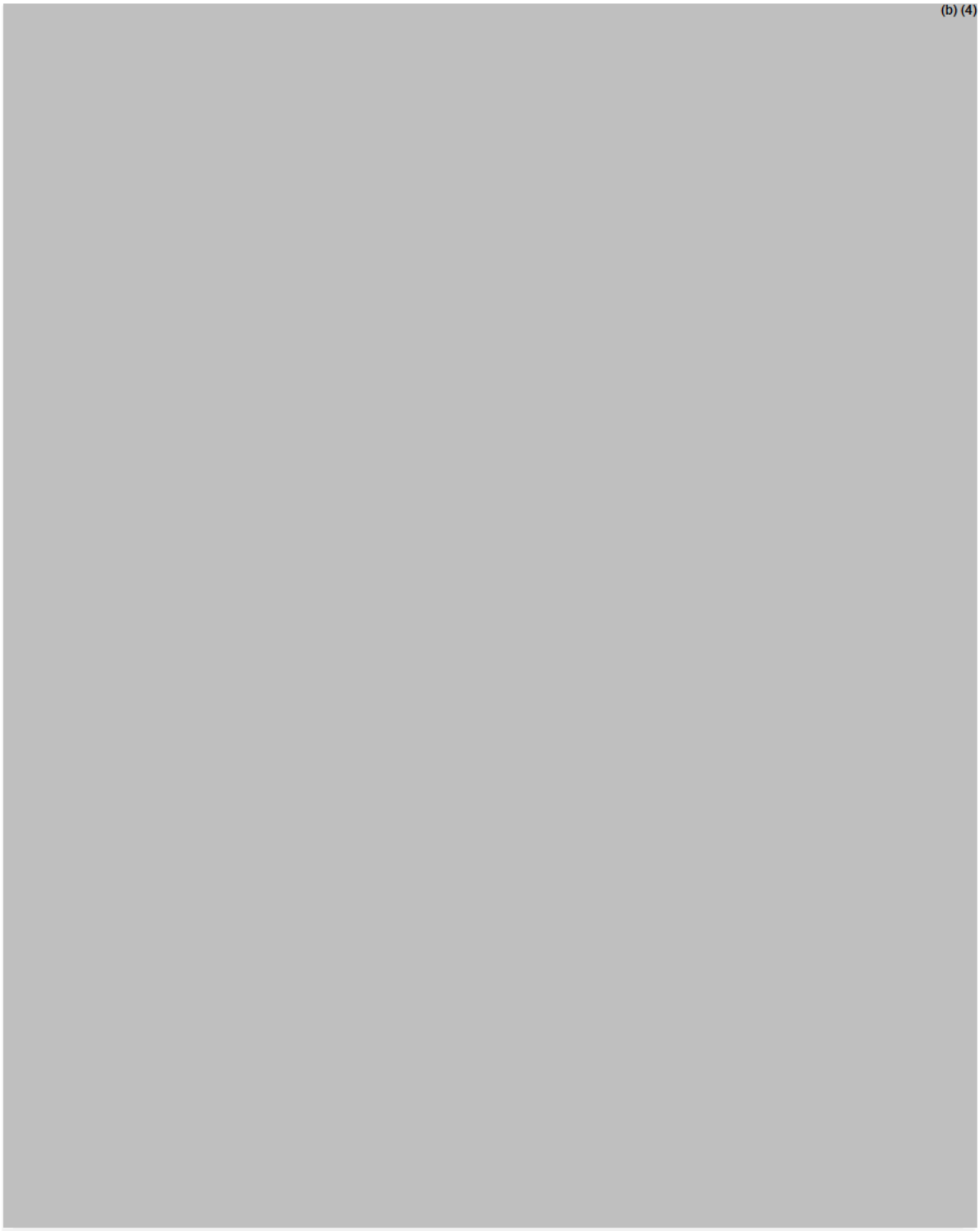
(b) (4)



Discriminating Ability of the Method: The summary of the method's discriminating ability is provided in Table 3.

Table 3. Studies evaluating discriminating ability of the dissolution method

Parameter(s)	Tablet Strengths (mg)	Study Range	Results	
			f_2 Discriminating	ANOVA Sensitive
(b) (4)	5	(b) (4)	Yes	
	50		Yes	
	5		Yes	
	50		Yes	
	5		No	No
	50		No	No
API Particle Size [D90]	5	(b) (4) µm	No	No
	50	(b) (4) µm	No	Yes
(b) (4)	5	(b) (4)	No	Yes
	50		Yes	Yes
	5		No	Yes
	50		No	Yes

[1] (b) (4)

The Applicant noted that the proposed method was discriminating against changes to (b) (4) and (b) (4). The discriminating ability was more pronounced for tablets with low (b) (4) and high (b) (4). However, the range for the variables tested was outside of meaningful changes (i.e., ± 20%). The method is not discriminating against changes to (b) (4), DS particle size, (b) (4). The Applicant argued that, in cases where the method was not discriminating towards changes in parameters, it was *sensitive* via ANOVA method (i.e., changes in percent dissolved at 15 minutes were statistically significant).

Dissolution Acceptance Criterion: The proposed dissolution acceptance criterion is "NLT (b) (4)% (Q) in 15 minutes," which is acceptable based on the submitted data.

Reviewer's Assessment: Mitapivat behaves as a highly soluble drug substance in pH ≤ 5.5 (with the 5 mg and 20 mg having high solubility across the full physiological pH range). While the method has limited discriminating capability, it is adequate for the quality control of the proposed drug product as the Applicant has mitigated risks (i.e., specifications for DS particle size, controls for process parameters, etc.). Further, the Applicant submitted stability data collected using a qualified XRPD method that supports the stability (b) (4).[2] Overall, from a biopharmaceutics perspective, the potential risk is mitigated.

The dissolution profile of pivotal clinical trial and registration batches support the proposed dissolution acceptance criterion of NLT (b) (4)% (Q) in 15 min.[3]

[2] Communication with Drug Product reviewer, Dr. Theodore Carver

[3] NDA 216196 Module 3.2.P.8.1 Dissolution Data for Clinical and Registration Batches (Page 7 of 29). Individual dissolution data provided in Module 3.2.R

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

Assessment: *Adequate*

The proposed Mitapivat tablets are an immediate release dosage form with rapid disintegration (< (b) (4) minutes) and absorption (T_{max}= 0.75 hours). The proposed AC of "NLT (b) (4) % (Q) in 15 minutes" is therefore adequate with respect to clinical performance of the drug product.

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: *Adequate*

The Applicant tested the robustness of the intended commercial formulation by varying the amount of (b) (4) . The Applicant used a bracketing approach, testing the 5 mg and 50 mg tablets, (b) (4) . The Applicant found that (b) (4) , tablet strength (5 mg-50 mg), and (b) (4) had a statistically significant effect on dissolution. However, all aberrant batches met the proposed commercial specifications (e.g., (b) (4) uniformity, dissolution, assay, degradation products, (b) (4), and XRPD) and thus, demonstrate the robustness of the formulation's manufacturability. The Applicant also found the risk of variance in (b) (4) to be low as it did not influence dissolution in the range studied (i.e., (b) (4) %).

Further, the Applicant tested the effect of different mitapivat suppliers, drug substance particle size, and (b) (4) on the drug product quality attributes. The proposed commercial specification for particle size is D_{90} < (b) (4) µm. Drug products were manufactured with the proposed process parameter ranges for commercial manufacturing, aside from varying the (b) (4), using drug substance batches from two different API suppliers that had varying particle sizes (D_{90}= (b) (4) µm). While the tablet strength, (b) (4) , and DS D_{90} impacted disintegration time, the (b) (4) tablet disintegration times were within the specification limit (< (b) (4) min). No meaningful impact was seen on dissolution for the 5 mg tablet strengths, but slightly slower dissolution was seen for the 50 mg tablet, which can be explained by tablet geometry and longer disintegration times. All 50 mg tablet strengths passed S2 testing at the proposed commercial specification (NLT (b) (4) % (Q) in 15 minutes).

B.5 B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

Pivotal phase 3 clinical and registration batches are representative of the to-be-marketed formulation and manufacturing process aside from a cosmetic imprinting step (b) (4) The Applicant provided multi-pH comparative dissolution testing that demonstrated similarity for plain-faced and imprinted tablets. Comparative dissolution testing was also provided for mitapivat tablets manufactured using both drug substance

suppliers ((b) (4) and (b) (4)). All tablets had greater than 85% dissolved in 15 minutes.[45]

B. 13 BIOWAIVER REQUEST

Assessment: *N/A*

Pharmacokinetics is characterized for all three strengths in the pivotal phase 3 study (AG348-C-006). After a single dose, AUC and C_{max} increase in a dose-proportional manner across tested doses of 30 to 2,500 mg. After multiple dosing, mitapivat exposure was dose-proportional up to 60 mg BID with less than dose-proportional increases in exposure at higher doses.

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:
Rebecca Moody, Ph.D.

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Poonam Delvadia, Ph.D.

[4] NDA 216196 Module 3.2.P.2 Comparative Dissolution Study between tablets with different API source (page 48 of 116).
[5] NDA 216196 Module 2.7.1 Comparative Dissolution Study between nonprinted and imprinted tablets (Page 18 of 72).

Poonam Delvadia

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Rebecca Moody

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Date: 10/15/2021 09:44:42AM
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Theodore Carver

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