CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216993Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA OPQ Review and Evaluation

NDA 216993
Review # XX

OPQ RECOMMENDATION: APPROVAL

Drug Substance Retest Period: [redacted] (b) (4) are the proposed retest period and storage conditions.
FDA Assessment: Retest date of [redacted] (b) (4) may be granted when stored at the proposed storage conditions

Drug Product Expiration Dating Period: 60 months at Controlled Room Temperature 20°–25°C (68°–77° F) are the proposed shelf life and storage conditions.
FDA Assessment: An expiration dating period of 60 months may be granted when stored at the proposed storage conditions.

[Applicant will complete this section.]

Drug Name/Dosage Form	Quizartinib Tablets
Strength	17.7 mg and 26.5 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Indication	VANFLYTA is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and as continuation monotherapy following consolidation, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) who are FMS like tyrosine kinase 3-internal tandem duplication (FLT3-ITD) positive, as detected by an FDA approved test.
Applicant	Daiichi Sankyo Inc.
US agent, if applicable	N/A

[FDA will complete these sections.]

Submit Date(s)	August 24, 2022
Received Date(s)	August 24, 2022
PDUFA Goal Date	April 24, 2023

FDA assessment is indicated in colored fonts

Division/Office	Division of Hematology Malignancies 1/Office of Oncologic Diseases
Review Completion Date	January 20, 2023
Established Name	Quizartinib
(Proposed) Trade Name	VANFLYTA
Pharmacologic Class	Quizartinib is a class III receptor tyrosine kinase (RTK) inhibitor exhibiting highly potent and selective inhibition of feline McDonough sarcoma (FMS)-like tyrosine kinase 3 (FLT3).
Recommendation on Regulatory Action	Approval

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA #0001	*08/24/2022*	*All: API, DP, OPMA, Biopharm*
Amendment #0010	*11/17/2022*	*API*
Amendment #0013	*11/22/2022*	*DP*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Raymond Frankewich	Haripada Sarker
Drug Product	Xiao Hong Chen	Sherita McLamore
Manufacturing	Huiquan Wu	Zhaoyang Mung
Biopharmaceutics	Min Kang	Kevin Wei
Regulatory Business Process Manager	Dahlia Walters	
Application Technical Lead	Xiao Hong Chen	
ORA Lead		
Environmental	Xiao Hong Chen	Sherita McLamore

ORBIS Partner Agency Quality Review Team (To be redacted for FOIA)

Agency	PRIMARY REVIEWER	SECONDARY REVIEWER
HC Canada		
HSA Singapore		
TGA Australia		
Swissmedic Switzerland		

RELATED/SUPPORTING DOCUMENTS

DMFs:

[Applicant will complete]				[FDA will complete]	
DMF #	**Type**	**Holder**	**Item Referenced**	**Status**	**Comments**
(b) (4)	III		(b) (4)	Adequate	Adequate information provided in NDA. No DMF review is necessary.
	III			Adequate	Adequate information provided in NDA. No DMF review is necessary.

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

[Applicant will complete this section.]

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	074552	Investigational New Drug Application for AC220 (Quizartinib)

CONSULTS

[FDA will complete this section.]

N/A

TABLE OF CONTENTS

Evaluation of the Quality Information

DIFFERENCES IN M3 MODULE IN SUBMISSIONS TO DIFFERENT AGENCIES

Stand-alone US NDA submission. Does not apply.

1. EXECUTIVE SUMMARY

[FDA ATL will complete this section.]

NDA 216993 was submitted as a 505(b)(1) NDA under the Federal Food, Drug and Cosmetic Act for VANFLYTA® (quizartinib) tablets, 17.7 mg and 26.5 mg by Daiichi Sankyo, Inc. Quizartinib is an orally bioavailable small molecule second-generation Class III receptor tyrosine kinase (RTK) inhibitor exhibiting highly potent and selective inhibition of Feline McDonough Sarcoma-like tyrosine kinase 3 (FLT3). Quizartinib is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and as continuation monotherapy following consolidation, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML). Quizartinib is an NME that was granted Fast Track Designation (03/30/2022) and Orphan Designation (3/18/2009) for the aforementioned indication and the Rolling Review Request was granted on 4/12/2022.

Quizartinib is a small achiral BCS class 4 molecule that is manufactured (b) (4) . The drug product, Vanflyta (quizartinib) Tablets is an immediate release solid oral dosage that is presented in two strengths (17.7 and 26.5 mg). The two strengths are manufactured (b) (4) are differentiated by tablet size, color and debossing information. The 17.7 mg dosage form is presented as an 8.9 mm, white round, filmcoated tablet with DSC511 debossed on one side. The 26.6 mg dosage form is presented as a 10.2 mm, yellow, round, film-coated tablet with DSC512 debossed on one side.

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety and efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 216993 and grants a shelf life of 60 months for the drug product when stored in HDPE bottles at 20ºC to 25ºC (68ºF to 77ºF), excursions permitted to 15ºC to 30ºC (59ºF to 86ºF) (See USP Controlled Room Temperature).

Life Cycle Considerations:
N/A

2. APPLICATION BACKGROUND

Studies for quizartinib are being conducted under US IND 074552, which was submitted to FDA on 27 Sep 2006 by Ambit BioSciences Corporation (Ambit) and transferred to Daiichi Sankyo Inc. on 15 Sep 2015. A summary of key interactions with FDA is included in Table 1.

Table 1 - Summary of US Regulatory Background

Date	Type of Meeting	Communication
07 Jul 2015	Type B EOP2	Discussion of the design and endpoints for Study AC220-A-U302 in newly diagnosed *FLT3*-ITD (+) AML.
26 Oct 2015	Type C	Discussion of patient reported outcome measures and instruments for Study AC220-A-U302.
18 May 2021	Type C	Agreement reached regarding the content and format of the planned NDA submission in newly diagnosed *FLT3*-ITD (+) AML, the timing of the primary analysis, and the hierarchical testing order for secondary endpoints. FDA reiterated the request to revise the definition of EFS using the 42-day window for ITF assessment and to adjust the statistical hierarchy
24 Mar 2022	Type B Pre-NDA	Agreement reached that results from AC220-A-U302 support NDA submission and on the contents of the NDA.

3. SUMMARY OF CMC SPECIFIC PRESUBMISSION AGREEMENTS

The Applicant's Position:

Table 2 - Key CMC Specific Pre-submission Agreements

Date	Type of Meeting (CMC)	Key Aspects/Outcomes of the Meeting
30 Jul 2009	Type C	Agreement reached on designated GMP starting materials, drug substance specifications, and proposed stability protocol for the drug substance.
18 Oct 2011	Type C	Agreement reached on control strategy for process impurities and stability program for the drug substance and on approach to be taken for genotoxic impurities.
14 Oct 2015	Type C	Agreement reached on control strategy for mutagenic and elemental impurities, testing protocol and drug substance commercial specifications, drug substance stability protocol and testing requirements, stability data requirements to support (b) (4) shelf life, requirements for development of the (b) (4) requirements for dissolution method development, and stability protocol for the drug product.
11 Apr 2018	Type B Pre-NDA	Agreement reached on developmental tests and acceptance criteria for drug substance and control strategy for the (b) (4)
22 May 2018	FDA Advice Letter	FDA acceptance of proposed dissolution method for commercial quizartinib tablets noting that the dissolution method acceptance criteria will be a review issue.
24 Mar 2022	Type B Pre-NDA	Agreement reached on the content of a complete application, including Module 3 (Quality) and that a separate CMC pre-NDA meeting is not required

The FDA's Assessment: ***Consistent with FDA's records***

4. ENVIRONMENTAL ASSESSMENT

The Applicant's Position:

The estimated EIC for quizartinib, based on the predicted peak usage is below the threshold of 1 ppb and, therefore, quizartinib is considered to be of low risk to the aquatic environment during this period and may be excluded from the requirement to conduct an environmental risk assessment. Since the potential introduction concentration is far less than 1 ppb, the product qualifies for the Tier 0 approach and categorical exclusion from preparation of an environmental assessment (see Module 1.12.14).

The FDA's Assessment: ***Adequate***

The applicant has submitted a claim of categorical exclusion. The categorical exclusion cited at 21CFR 25.31(b) is appropriate for the estimated amount of drug to be produced for direct use. A statement of no extraordinary circumstances has been submitted. The claim of categorical exclusion is acceptable.

5. FACILITIES

[Applicant will complete this section.]
Drug substance manufacturing, packaging and testing facilities are listed below:

---------- [Applicant to fill] ----------			[FDA to fill]
Site/address	**FEI/DUNS**	**Responsibility**	**Recommendation**
(b) (4)		Drug substance manufacturing, packaging and testing	Approval

Drug product manufacturing, packaging and testing facilities are listed below:

---------- [Applicant to fill] ----------			[FDA to fill]
Site/address	**FEI/DUNS**	**Responsibility**	**Recommendation**
(b) (4)		Drug product (b) (4)	Approval
		Quizartinib tablets 17.7 mg and 26.5 mg are manufactured, tested in-process, for release and on stability, and bulk packaging	Approval
		Primary packaging of quizartinib tablets 17.7 mg and 26.5 mg	Approval
		Primary packaging of quizartinib tablets 17.7 mg and 26.5 mg	Approval
		Drug Product testing (b) (4)	Approval

(b) (4)

The FDA's Assessment: *Adequate*

[FDA will complete this section.]

There are six manufacturing and analytical testing facilities referenced in this NDA for commercial manufacturing. They are all approved based on previous inspection histories and acceptable profile codes. The essential facility information (name, address, responsibilities, FEI#), facility profile code(s), and FDA facility assessment recommendations are summarized below:

- (b) (4)

  Facility was approved based on previous inspection history and acceptable profile codes.

- (b) (4)

  approved based on previous inspection history and acceptable profile code.

- Daiichi Sankyo Europe GmbH. Bulk packaging of quizartinib tablets 17.7 mg and 26.5 mg. FEI#3003282622. Profile code: TCM. Facility was approved based on previous inspection history and acceptable profile code.

- (b) (4)

In summary, OMIR is completed with facilities approval. Facilities are adequate.

(b) (4)

[redacted]

8. BIOPHARMACEUTICS - *Adequate*

a. BCS Classification

Applicant to fill:	FDA assessment (FDA to fill):
BCS Classification: BCS IV	Acceptable

Information to support the BCS Class I designation request, if applicable.

b. Dissolution Test

USP Apparatus	Paddle Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
2	50 rpm	900 mL	37°C	0.1M hydrochloric acid	Q = (b) (4)% at 30 minutes

Biopharmaceutics Figure 1: Dissolution Profiles as a function of:

(b) (4)

(b) (4)

[redacted]

	Applicant to fill:	FDA assessment:
The dissolution method is discriminating for:		
i) Particle size distribution (PSD) Link[1]:	Not applicable	Not applicable Page#:
ii) Polymorph/solid state form Link[1]: Module 3.2.P.2.2	Discriminating	Not agree Page#: 42
iii) Formulation variations Link[1]: Module 3.2.P.2.2	Discriminating	Agree Page#: 41
iv) Manufacturing process variations Link[1]: Module 3.2.P.2.2	Discriminating	Agree Page#: 44, 46
v) Other (specify): Link[1]:	Choose an item.	Choose an item. Page#:

[1]The applicant to provide link to the appropriate section in the submission. FDA reviewer may update the link as needed.

FDA assessment (FDA to fill):

Dissolution Method – **ADEQUATE**

During the IND stage, the Division of Biopharmaceutics has determined that the proposed QC dissolution method is acceptable for routine QC of the proposed drug product because 1) the selected dissolution method parameters are adequately justified and 2) the proposed dissolution method is discriminative against the (1) ratio of the API to the HP-β-CD (b) (4) (2) tablet hardness level and (3) film coating level. Note, however, that the proposed QC dissolution method has limited ability (b) (4) in the drug product. Thus, the Applicant has (b) (4) in the Finished Drug Product's QC Specifications for batch release and stability testing. See Biopharmaceutics Review of IND 74552, SDN-396 finalized in DARRTS on 5/18/2018.

Dissolution Acceptance Criteria – **ADEQUATE**;

For routine QC of both strengths of the proposed drug product at batch release and during stability testing, a dissolution acceptance criterion is "Q = (b) (4) % at 30 min" is proposed in the current submission. Based on the submitted dissolution data and information such as (1) the dissolution profile data of the pivotal Phase 3 (AC220-007) clinical trial lots measured over the reported duration of clinical trial use, i.e., approximately 36 months from time of manufacture, as shown in Figure 1, and (2) concerns regarding (b) (4) the proposed dissolution acceptance criterion is considered acceptable.

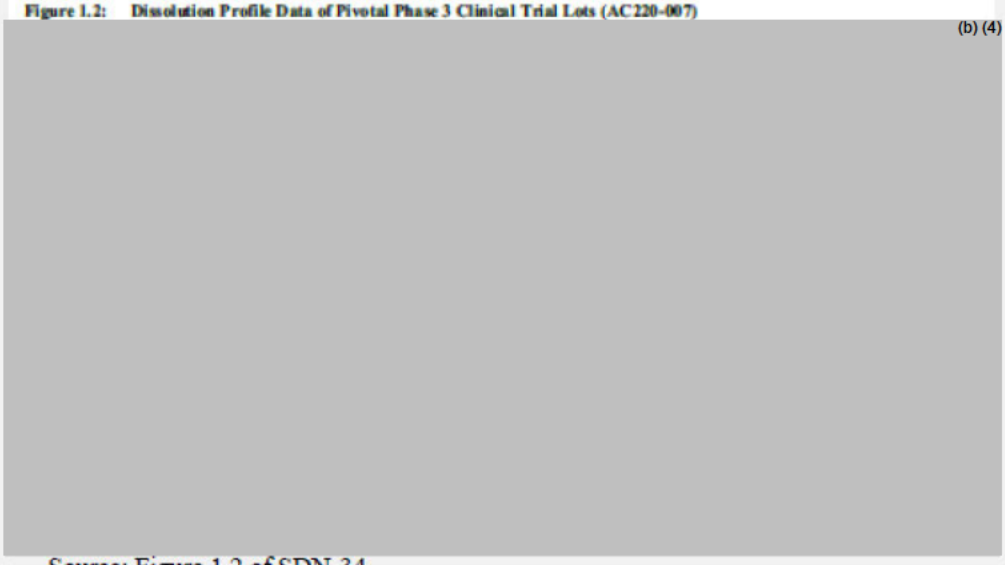
Dissolution on Stability

Dissolution data at 30 min (b) (4) were provided for the Phase 3 pivotal clinical batches and registration batches of quizartinib tablets 17.7 mg and 26.5 mg packaged in HDPE bottles (b) (4) The applicant noted (b) (4) the ones in bottles, suggesting the dissolution method's stability indicating potential when using 30 min as the dissolution specification time point. The Applicant also noted (b) (4) than those in bottles. Thus, given the foregoing observations, a dissolution specification time point of 30 min (b) (4) is selected for a better stability indicating stability. It's noted that the dissolution profile of drug product packaged in HDPE Bottles (i.e., clinical trial lots and some of the registration batches) showed greater stability than the remainder of the registration batches (b) (4) during 36 months of long-term storage.

Figure 1. Mean Dissolution Profiles of Phase 3 Pivotal Clinical Batches and Registration Batches for Quizartinib Tablets 20 mg and 30 mg, at release and after storage of 24 months

Figure 1.2: Dissolution Profile Data of Pivotal Phase 3 Clinical Trial Lots (AC220-007)

(b) (4)



Source: Figure 1.2 of SDN-34

c. Bridging Throughout Drug Product Development (Formulation, Process, or Site Change)

Link: Module 3.2.P.2.2 Page#: 28

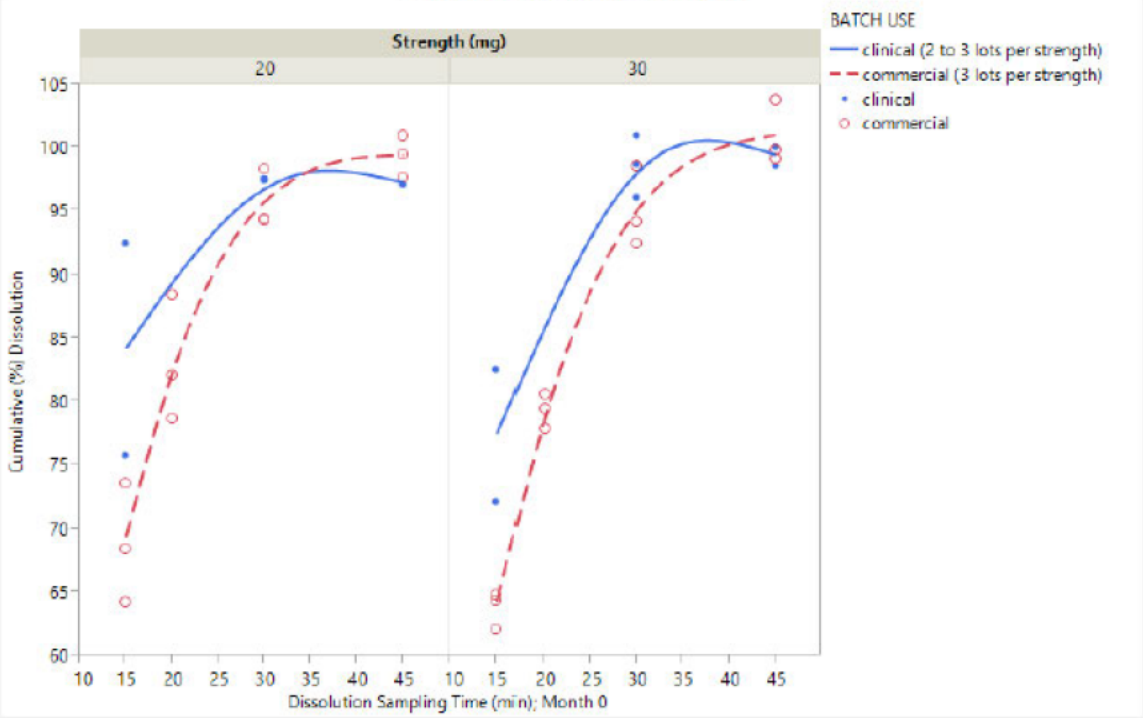
Drug Product	Formulation	Manufacturing Process	Clinical Studies	Notes
Drug Substance in Bottle (50, 350 mg)	None: drug substance only	N/A	CP0001	Initial IND
Quizartinib Oral Powder for Reconstitution (OPR) (60, 90, 135, 200 mg)	Quizartinib HPβCD	(b) (4)	AC220-002 AC220-006 AC220-008 AC220-012 AC220-014	Formulation of API/ HPβCD (b) (4)

			2689 CL 0005 2689 CL-0011 2689-CL-2004	
Quizartinib Fil-coated Tablets (20 mg and 30 mg, FCF)	Quizartinib HPβCD Microcrystalline Cellulose, Magnesium Stearate Film coating mixture	(b) (4)	AC220-007 (QuANTUM-R) AC220-A-U302 (QuANTUM-First) AC220-014 AC220-015 AC220-016 AC220-018 AC220-019 2689-CL-0011 2689-CL-2004 AC220-A-J101 AC220-A-J201 AC220-A-J102 AC220-A-A103 AC220-A-U104 AC220-A-U105 AC220-A-U106 AC220-A-U107	To be marketed formulation. Formulation and method of manufacture (b) (4) unchanged from Phase 2 to Phase 3. Registration Stability Studies conducted on this formulation. Study AC220-014: the relative bioavailability of the 30 mg FCF tablet formulation to the OPR formulation was determined. Dose proportionality was also assessed from 30 mg to 90 mg using the FCF 30 mg tablet. (b) (4) so separate PK studies were not performed with the 20 mg tablet. Both strengths used in studies AC220-A-U301 and AC220-007

The FDA's Assessment: ***Adequate***

Unlike the proposed to-be-marketed tablets which are debossed with either "DSC 511" or "DSC 512", the clinical trial tablets were unmarked. Figure 3 shows that the mean dissolution profiles of the pivotal clinical trial lots and that tablet batches exhibiting the final commercial image are comparable; the Reviewer's calculated profile similarity factors were >50 for both 17.7 mg and 26.5 mg strengths.

Figure 3
Mean Dissolution Profiles of the Phase 3 Pivotal Clinical Trial Batches versus the Final Commercial Image Tablets



Note that [(b) (4)] (the proposed commercial drug product manufacturer) also manufactured the pivotal clinical trial lots and the stability lots, at the same or similar

[(b) (4)] (the proposed commercial drug product manufacturer) also manufactured the pivotal clinical trial lots and the stability lots, at the same or similar batch scale/size. Additionally, the proposed commercial API [(b) (4)] supplier, [(b) (4)] manufactured the API [(b) (4)] used for the registration stability, pivotal clinical/relative BA, and validation batches, using the proposed commercial process and similar scale [(b) (4)] See Tables 1.1 and 1.2 of 3.2.P.5.4 for details.

Therefore, no addition data/information to support the bridging between the pivotal clinical, registration and commercial batches is needed.

In vivo BA/BE studies were conducted to support the bridging of the earlier clinical trial formulations/dosage forms (e.g., [(b) (4)] in Bottle used in Phase 2 clinical trials) to the final proposed formulation/tablet dosage form evaluated in the pivotal Phase 3 clinical trial. These relative BA studies (including AC220-014 which used a 26.5 mg tablet manufactured by [(b) (4)] instead of [(b) (4)]) will be reviewed by OCP. The review of the provided in vivo BA/BE data is deferred to the Office of Clinical Pharmacology (OCP).

d. Biowaiver Request

The Applicant's Position:

The NDA does not contain a biowaiver request

Link: N/A Page#: N/A

Quizartinib is a BCS Class IV compound and therefore a biowaiver is not applicable. In addition, a biowaiver is not required because both quizartinib 17.7 mg and 26.5 mg tablet strengths were used in the pivotal clinical trial (AC220-A-U302).

The FDA's Assessment: ***Not Applicable***

Both 20 mg and 30 mg (salt) strengths of the final proposed commercial formulation/ tablet dosage form were evaluated for PK, PD, efficacy and safety in the pivotal Phase 3 clinical trial (AC220-007). In addition, the 30 mg (salt) strength of the final proposed commercial tablet was evaluated for PK, PD, and/or efficacy/safety in other clinical pharmacology studies (e.g., food-effect study AC220-019, dose escalation study A220-A-J101, PK in hepatic impairment AC220-016, DDI with ketoconazole/ fluconazole AC220-015, DDI with lansoprazole AC220-018). Because both propose strengths of were evaluated in the pivotal clinical study, a biowaiver request is not warranted.

e. Data to Support IVIVC and/or PBBM Modeling, If Applicable.

Link: N/A Page#: N/A

Not applicable

The FDA's Assessment: ***Not Applicable***

9. LABELING

[FDA will complete this section.]

USPI
Highlights: ***Adequate***
In the #1 of the highlight section, it contains the following information: "Tablets: 17.7 mg or 26.5 mg".

Section 2 (if relevant): ***Adequate***
The tablet will be taken orally. No additional product quality related information is provided here.

Section 3 Dosage Forms and Strengths: ***Adequate***
In this section, it contains the following information:

Tablets:

- *17.7 mg quizartinib* (b) (4) *, white, round, film-coated, debossed with "DSC511"*
- *26.5 mg quizartinib* (b) (4) *yellow, round, film-coated , debossed with "DSC512"*

Section 11 Description: ***Adequate***
If the following excipients used in the drug product, include warning/declaration in the USPI:

- FD&C Yellow No.5 or No.6, as a color additive (21 CFR 201.20) is not used.
- Phenylalanine, as a component of aspartame (21 CFR 201.21) is not used.
- Sulfites (21 CFR 201.22) is not used.

Section 11 contains all the required drug substance and drug product information.

Section 16 How Supplied/Storage and Handling: ***Adequate***
Section 16 contains all the required information such as storage conditions, packaging presentation, NDC number for each strength and product presentation.

Manufacturer Information (Name and Address): Choose an item.
The name and the location of the manufacturer are provided. However, no street address is provided. The comment of adding the street address will be conveyed during OND labeling review meeting.

Carton/Container Label ***Adequate***
(Add notes as necessary)

Final Risk Assessments

[FDA will complete this section.]
To the Review Team: *Keep the appropriate Table; delete the rest*

SOLID ORAL

Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	Low	(b) (4)	Low	
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	
Content Uniformity	• Formulation • Container closure • Raw material • Process Parameters • Scale/equipment • Site	Medium		Low	
(b) (4)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	Low		Low	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	
Dissolution – BCS Class II & IV	• Formulation • Container Closure • Raw materials • Process parameters • Scale/equipment • Site	High		Medium	The proposed QC dissolution method has limited ability to (b) (4) is included in the Drug Product's QC Specifications for batch release and stability testing.

Recommendation Page

[FDA will complete this section.]

Drug Substance: Approval

Primary Reviewer: Raymond P. Frankewich Date: January 20, 2023
Secondary Reviewer: Haripada Sarker Date: January 28, 2023

Drug Product: Approval

Primary Reviewer: Xiao Hong Chen Date: January 3, 2023
Secondary Reviewer: Sherita McLamore Date: January 7, 2023

Manufacturing: Approval

Primary Reviewer: Huiquan Wu Date: November 17, 2022
Secondary Reviewer: Zhaoyang Meng Date: December 2, 2022

Biopharmaceutics: Approval

Primary Reviewer: Min Kang Date: January 12, 2023
Secondary Reviewer: Kevin Wei Date: January 13, 2023

Application Technical Lead: Approval

Xiao Hong Chen Date: February 2, 2023

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

XIAOHONG CHEN
02/02/2023 04:17:31 PM

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HUIQUAN WU
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ZHAOYANG MENG
02/03/2023 09:42:54 AM

MIN K KANG
02/03/2023 10:50:52 AM

LINYI WEI
02/03/2023 10:52:26 AM