CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211192Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 211192
Review #1

Drug Name/Dosage Form	**TIBSOVO (ivosidenib) tablets, 250 mg**
Strength	250 mg
Route of Administration	Oral
Rx/OTC Dispensed	R_x
Applicant	Agios Pharmaceuticals
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	21-Dec-17	All
Amendment (SD 0006)	30-Jan-18	DP
Amendment (SD 0014)	22-Mar-18	DS
Amendment (SD 0017)	30-Mar-18	DP
Amendment (SD 0023)	01-May-18	DS
Amendment (SD 0025)	10-May-18	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Rohit Tiwari	Charles Jewel
Drug Product	Amit Mitra	Anamitro Banerjee
Process	Ying Zhang	Rakhi Shah
Microbiology	n/a	n/a
Facility	Ying Zhang	Zhihao Peter Qiu
Biopharmaceutics	Joan Zhao	Banu Zolnik
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	Amit Mitra	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	119341	Ivosidenib development

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 211192 for TIBSOVO (ivosidenib) tablets, 250 mg. As part of this action, OPQ grants a (b) (4) month re-test period for the drug substance (b) (4) and a 24-month drug product expiration period when stored at stored 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]. There are no outstanding issues and no post-approval quality agreements to be conveyed to the applicant.

II. Summary of Quality Assessments

A. Product Overview

NDA 211192 was submitted for TIBSOVO (ivosidenib) tablets, 250 mg in accordance with section 505(b)(1) of the Food, Drug and Cosmetic Act. Ivosidenib is a once daily, orally bioavailable, small-molecule, isocitrate dehydrogenase-1 inhibitor indicated for the treatment of adult patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test. Ivosidenib is an NME which was originally investigated under IND 119341 and was granted orphan designation for the treatment of AML.

Ivosidenib is a small chiral molecule with two stereogenic centers. It is manufactured (b) (4) As the drug substance is a BCS Class 2 compound with low aqueous solubility, (b) (4) The drug product, TIBSOVO (ivosidenib) tablets, 250 mg, is presented as a 250-mg, immediate-release solid oral dosage form containing the (b) (4) micro-crystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide, and magnesium stearate. It is a blue, oval tablet debossed with "IVO" on one side and "250" on the other.

The recommended dosing regimen for TIBSOVO (ivosidenib) tablets is 500 mg orally once daily until disease progression or unacceptable toxicity.

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, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 211192 and grants a (b) (4) month re-test period for the drug substance and a **24**-month expiration period for the drug product when stored at USP controlled room temperature in the proposed commercial packaging.

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test.
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	500 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

Ivosidenib is a small chiral molecule with two stereogenic centers. It is a white to light yellow, non-hygroscopic crystalline solid that is practically insoluble in aqueous solutions across a physiological relevant pH range (b) (4) Ivosidenib has excellent permeability across *Caco-2* cells and has therefore been classified as a BCS Class 2 compound.

(b) (4)

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