

**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)} ^{(b) (4)}. As the drug substance is a BCS Class 2 compound with low aqueous solubility, ^{(b) (4)} ^{(b) (4)}.

^{(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)

Ivosidenib Tablets:

The drug product, TIBSOVO (ivosidenib) tablets, 250 mg, is presented as a 250-mg, immediate-release solid oral dosage form containing the (b) (4) microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide, and magnesium stearate. (b) (4)

The drug product is a blue, oval tablet debossed with “IVO” on one side and “250” on the other. The drug product formulation contains no novel excipient. All excipients are compendial and commonly used in solid oral dosage forms and demonstrate good compatibility with the drug substance.

The QTPP was defined and the CQAs were identified. CQAs for the drug product include description, identification, assay, degradation products, uniformity of dosage units, (b) (4) solid form and dissolution.

The drug product is manufactured by (b) (4) at a commercial batch size (b) (4) Kg which corresponds to (b) (4) tablets. The drug product is packaged in 90 and 175 cc square, HDPE bottles (14 and 60 count, respectively) with a 1.0 gram (b) (4) desiccant canister and a 38 mm (b) (4) closure with an induction seal.

The drug product specifications are consistent with ICH Q6A and are based on batch analyses as well as stability data. Of note the acceptance criterion for (b) (4) was NMT (b) (4)%. This limit was proposed based on batch analyses and stability data. Results from the open dish study (b) (4) (b) (4)%. Accordingly the proposed (b) (4)% acceptance criteria was adequately justified. The originally proposed drug product specification did not include tests or acceptance criteria for microbial limits or elemental impurities. In the January 30, 2018 amendment the applicant provided a

risk-based assessment of potential sources of elemental impurities. This assessment was based on ICH Q3D. The results demonstrated that the total elemental impurity level from all sources in the drug product is expected to be consistently less than (b) (4)% of the permitted daily exposure (PDE). Accordingly, no additional controls are required. The microbial attributes of the drug product were tested on stability for up to 18 months and no significant trends were observed. Additionally, the drug product was (b) (4). The results of (b) (4) were well below the accepted limit of (b) (4). The drug product specifications provide adequate controls to ensure the quality of the drug product throughout the product expiry.

The proposed specification and acceptance criteria for the drug product, together with controls for impurities in the drug substance are adequate to ensure that the critical quality attributes of this product are well controlled.

In support of the proposed 24 month expiry, the applicant provided up to 12 months of stability data for three pilot scale batches of the drug product (batches WNSB, WNSC and WNSD). The batches were manufactured according to the commercial process and packaged in 90-cc 14 count and 175-cc 60-count HDPE bottles. The samples were stored under the long-term (30°C/65% RH) and accelerated (40°C/75% RH) conditions. The samples were stored in the 60- and 14-count bottles. The samples in the 60-count bottles were film-coated and debossed. The samples in the 14-count bottles were film-coated and non-debossed. Additional supportive studies were performed (b) (4) for up to 12 months) and in an open dish to help assess the impact of temperature and humidity on the relevant critical quality attributes of the drug product (b) (4).

The applicant also completed a bulk hold study, photostability, and forced degradation studies for the drug product. The stability studies were executed in accordance with the ICH 1A and Q1B. No significant changes were observed in description, assay, or degradation products under any storage condition. (b) (4)

The available stability data shows consistency over time and support the proposed expiry. Based on the 12 months of stability data included in this application, Agios proposed and the FDA accepts the expiration dating period of **24 months** for the drug product when stored at stored at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

The application is recommended for approval from a drug product perspective.

Process

(b) (4)

(b) (4)

Biopharmaceutics

The acceptability of the proposed dissolution method and acceptance criterion for the routine QC testing of the proposed drug product at batch release and on stability was assessed. The dissolution method included a USP Apparatus II (Paddle) at 50 rpm in 900 mL of 50mM phosphate buffer, pH 6.8 with 0.6% SDS. The proposed dissolution acceptance criterion is $Q = \frac{(b)}{(4)}\%$ in 30 minute. The applicant used in vitro comparative dissolution profiles to bridge the clinical and commercial drug product. The calculated f_2 values ranged from 63 to 81 which demonstrate that the dissolution profiles are similar.

Both the proposed dissolution method and acceptance criterion were deemed acceptable for batch release and stability testing. The f_2 values were sufficiently similar to substantiate the bridge; therefore, the bridging between the clinical batches (non-debossed) and the proposed commercial drug product (debossed) is acceptable. This application is recommended for approval from a biopharmaceutics perspective.

Facilities

There were 7 facilities included in this application:

(b) (4)

DRUG SUBSTANCE:

Drug substance, Ivosidenib, is manufactured by (b) (4)

(b) (4) This site was responsible for drug substance manufacture,

packaging and quality control testing. Based on the initial risk assessment, this site was considered high risk by virtue of the drug substance being designated as a new molecule entity (NME), high potent drug with orphan drug designation. The manufacturing process (b) (4) The site was last inspected on (b) (4) with profile code (b) (4) covered. Accordingly a PAI was not requested and the site was recommended for approval for the aforementioned operations based on the information provided in the submission and satisfactory compliance history.

(b) (4) is responsible for elemental impurity testing for the drug substance. This site was most recently tested in (b) (4) The inspection did not issue any 483 observations and CTL profile is acceptable. Since there is no application specific concern identified, this site is considered acceptable for to perform the aforementioned operations based on the information provided in the submission and satisfactory compliance history.

(b) (4) is responsible for testing of primary stability batches of ivosidenib drug substance, (b) (4) and Ivosidenib Tablets, 250 mg, stability testing of annual commitment batches of ivosidenib drug substance, (b) (4) and Ivosidenib Tablets, 250 mg, and Quality control testing of Ivosidenib Tablets, 250 mg (b) (4) Based on the initial risk assessment, this site was considered to have a medium risk. This facility was last inspected in (b) (4) for a PAI only and no 483 was issued. Based on the inspection history, this site was recommended for approval for the aforementioned operations based on the information provided in the submission and satisfactory compliance history.

(b) (4)

Drug product, TIBSOVO (ivosidenib) tablets, is manufactured, quality control, release and stability tested by (b) (4)

(b) (4)

(b) (4) was included in this NDA as the site to preform primary packaging for the drug product. The drug product is packaged into white HDPE bottles with (b) (4) desiccant. The bottles are closed with (b) (4) closure with an induction heat seal liner. The facility was last inspected in (b) (4) with the focus on PAI of a combination product. The facility is considered acceptable and is recommended for approval based on the inspection history.

(b) (4) was included in this NDA as the site to preform secondary packaging for the drug product. No additional evaluation will be performed.

Environmental Assessment

The approval of this application will increase the use of Ivosidenib; however, the estimated concentration of the substance at the point of entry into the aquatic environment is (b) (4) ppb ((b) (4) ppb). The applicant provided a claim for categorical exclusion and a statement of no extraordinary circumstances under 21 Code of Federal Regulations (CFR) Sections 25.31(b). The categorical exclusion cited is appropriate based on the estimated amount of drug to be produced for direct use. The claim of categorical exclusion is therefore acceptable and should be granted.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment (see Attachment)

Appended at the end of the drug product review.



Sherita
McLamore

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LABELING

{For NDA only}

R Regional Information (NDA (b) (4))

1.14 Labeling

1. Package Insert: Is being conducted with the labeling review. ***
(a) “Highlights” Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Tibsovo Established Name: ivosidenib tablets	Satisfactory
Dosage form, route of administration	tablets, oral	Satisfactory
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Tablets: 250 mg	Satisfactory

Reviewer’s Assessment: The highlight is satisfactory with respect to proprietary and established name, dosage form and strengths.

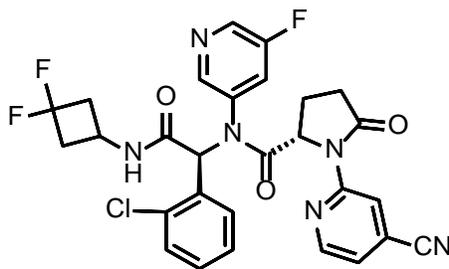
(b) "Full Prescribing Information" Section**# 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))**

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Tablets	Satisfactory
Strengths: in metric system	250 mg	Satisfactory
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Blue oval-shaped film-coated tablet debossed "IVO" on one side and "250" on the other side.	Satisfactory

Reviewer's Assessment: This section may be modified according to PLR, if needed.

#11: Description (21CFR 201.57(c)(12))

TIBSOVO (ivosidenib) is an inhibitor of isocitrate dehydrogenase-1 (IDH1) enzyme. The chemical name is (2S)-N-((1S)-1-(2-chlorophenyl)-2-[(3,3-difluorocyclobutyl)-amino]-2-oxoethyl)-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide. The chemical structure is:



The molecular formula is $C_{28}H_{22}ClF_3N_6O_3$ and the molecular weight is 583.0 g/mol. Ivosidenib is practically insoluble in aqueous solutions between pH 1.2 and 7.4.

TIBSOVO (ivosidenib) is available as a film-coated 250 mg tablet for oral administration. Each tablet contains **the following** inactive ingredients: ^(b)₍₄₎-colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablet coating includes FD&C blue #2, hypromellose, lactose monohydrate, titanium dioxide, and triacetin.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Proprietary name: TIBSOVO Established name: ivosidenib tablets	Satisfactory
Dosage form and route of administration	Tablets, Oral	Satisfactory
Active moiety expression of strength with equivalence statement for salt (if applicable)	"TIBSOVO (ivosidenib) is available as a film-coated 250 mg tablet ---".	Satisfactory
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	See the text above under description section	Satisfactory for oral dosage form
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	inhibitor of isocitrate dehydrogenase-1 (IDH1) enzyme	Satisfactory
Chemical name, structural formula, molecular weight	Yes	Satisfactory
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Yes	Satisfactory

Reviewer's Assessment: The applicant could not determine the pKa. Since the drug is practically insoluble within physiological pH, there is no need to provide pH of solution information. The minor edits (highlighted in yellow and strikeouts) of the "Description Section" was included in the PI.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

250 mg tablet: Blue oval-shaped film-coated tablet debossed "IVO" on one side and "250" on the other side.

- 60-count bottles of 250 mg tablets with a desiccant canister (NDC 71334-100-01)

Handling and Disposal

Storage: 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].

Reviewer’s Assessment: It was decided in the labeling meeting that no special handling of this oncology drug is needed.

Item	Information Provided in NDA	Reviewer’s Assessment
Strength of dosage form	250 mg tablets	Satisfactory
Available units (e.g., bottles of 100 tablets)	60 tablets	Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	250 mg tablet: Blue oval-shaped film-coated tablet debossed “IVO” on one side and “250” on the other side.	Satisfactory
Special handling (e.g., protect from light, do not freeze)	None	Satisfactory
Storage 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].	Satisfactory

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer’s Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured for and marketed by: Agios Pharmaceuticals, Inc. Cambridge, MA 02139	Satisfactory

Immediate Container Label

250 mg tablets

**Reviewer's Assessment:**

The applicant provided the following required items: Established name, dose strength, prescription only, lot #, bar code, and expiration date. DMEPA may have additional comments.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence) (21 CFR 201.10(g)(2))	Proprietary name: Tibsovo Established name: ivosidenib tablets	Satisfactory
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Correct strength was included.	Satisfactory
Net contents (21 CFR 201.51(a))	60 tablets	Satisfactory
Lot number per 21 CFR 201.18	None	Satisfactory
Expiration date per 21 CFR 201.17	None	Satisfactory
“Rx only” statement per 21 CFR 201.100(b)(1)	None	Satisfactory
Storage (not required)	None	Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	None	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	None	Satisfactory
Name of manufacturer/distributor	None	Satisfactory
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

**Not required for Physician’s samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Reviewer’s Assessment: Satisfactory

Carton Labeling: None included.

Reviewer's Assessment:

List of Deficiencies: None

Primary Labeling Reviewer Name and Date:

Secondary Reviewer Name and Date (and Secondary Summary, as needed):



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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: 211192-ORIG-1 [505(b)(1)]

Drug Product Name / Strength: TIBSOVO (ivosidenib) tablets, 250 mg

Route of Administration: Oral

Applicant Name: Agios Pharmaceuticals Inc. (Agios)

Review Summary:

TIBSOVO (ivosidenib) tablets 250 mg, an isocitrate dehydrogenase-1 inhibitor, is proposed for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an IDH1 mutation as detected by an FDA-approved test.

The Biopharmaceutics review is focused on the evaluation of the adequacy of the overall information/data supporting the proposed dissolution method and acceptance criterion, as well as formulation bridging in the drug product development.

In Vitro Dissolution Method and Acceptance Criterion:

The Applicant's proposed dissolution method was reviewed in IND 119341, in which a (b) (4) SDS (b) (4) % was recommended¹. In the current submission, the Applicant provided an additional data to justify the amount of surfactant in the proposed dissolution medium. Based on the provided data, the following dissolution method and acceptance criterion are acceptable for release and stability:

USP Apparatus	Rotation Speed	Medium	Volume	Cumulative % of Drug Dissolved (Label Claim)
USP II (Paddle)	50 RPM	50 mM Phosphate Buffer pH 6.8 with 0.6% SDS	900 mL	Q (b) (4) % in 30 minutes

Formulation Bridging:

The Applicant provided adequate dissolution data to support the bridging between the clinical batches (non-debossed) and the proposed commercial drug product (debossed).

RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 211192 for TIBSOVO (ivosidenib) tablets, 250 mg, is recommended for **APPROVAL**.

¹ DARRTS: IND 119341 REV-QUALBIOPHARM-21 (Primary Review), final date 09/15/2017

SIGNATURES***Primary Biopharmaceutics Reviewer Name and Date:***

Zhuojun Zhao, PhD
Division of Biopharmaceutics
Office of New Drug Products, OPQ

05/22/2018

Secondary Biopharmaceutics Reviewer Name and Date:

Banu Zolnik, PhD
Division of Biopharmaceutics
Office of New Drug Products, OPQ

5/29/2018

BIOPHARMACEUTICS ASSESSMENT

List of Submissions being reviewed:

Submissions Reviewed	Document Date
Original Submission	12/21/2017

I. Background:

The Applicant's dissolution method development report was reviewed in IND 119341¹. The proposed dissolution conditions, including the apparatus, rotation speed and volume of the dissolution medium, were found acceptable. However, additional data were requested in Type B CMC Teleconference Meeting dated September 18, 2017² to justify the amount of surfactant used in the proposed dissolution medium (50 mM Phosphate buffer, pH 6.8 containing 0.6% SDS).

II. Current Submission

a. Dissolution Method



(b) (4)

² DARRTS: IND 119341 COR-MEET-03 (Meeting Minutes), final date 10/2/2017

(b) (4)



(b) (4)

Reviewer’s Comment:

Based on the provided information, the proposed dissolution method medium, i.e. 50 mM Phosphate Buffer, pH 6.8 containing 0.6% SDS is adequately justified. Therefore, the proposed dissolution method is acceptable for the QC dissolution testing of the proposed drug product.

The proposed dissolution method could discriminate variation in (b) (4)

b. Dissolution Acceptance Criterion:

The Applicant proposed a dissolution acceptance criterion of $Q = \text{span style="background-color: grey; color: grey;">(b) (4) % in 30 minutes based on dissolution profile data from the primary registration and supporting stability batches and release data for representative clinical batches⁴.$

Figure 2. Pooled Release and Stability Results for Ivosidenib Tablets, 250 mg



⁴ <\\cdsesub1\evsprod\nda211192\0001\m3\32-body-data\32r-reg-info\32r4-dissol-data\dissol-res.pdf>

Figure 3. Individual Dissolution Results for Release and Stability (t=30 minutes)



Reviewer’s Comment:

The proposed dissolution acceptance criterion is acceptable.

c. Bridging of Formulations:

Two tablet presentations have been used during clinical development: (1) uncoated tablets (50, 200, and 250 mg) and (2) film-coated blue non-debossed tablets (250 mg). The difference between the film-coated clinical presentation and the proposed commercial product is the addition of a debossed product identifier. The overview of tablet presentation used in each clinical studies is shown in [Appendix 1](#). The composition of the Ivosidenib Tablets, 50 mg, 200 mg, and 250 mg used in clinical studies is shown below:

Table 1: Composition of Ivosidenib Tablets, 50 mg, 200 mg, and 250 mg

Component	Function	Amount per Tablet Core by Strength (Label Claim)				Tablet Core Composition (Weight %)
		Uncoated			Coated	
		50 mg	200 mg	250 mg	250 mg	
Ivosidenib	(b) (4) Active	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Microcrystalline cellulose						(b) (4)
Croscarmellose sodium						
Sodium lauryl sulfate						
Colloidal silicon dioxide						
Magnesium stearate						(b) (4)

The proposed commercial product, Ivosidenib Tablets, 250 mg is the same color and composition as the film-coated Ivosidenib Tablets, 250 mg in Table 1. The only difference between the clinical product and the proposed commercial product is the addition of a debossed product identifier. The intended commercial product is an oval, blue, film-coated tablet, debossed with “IVO” on one side of the tablet and “250” on the opposite side.

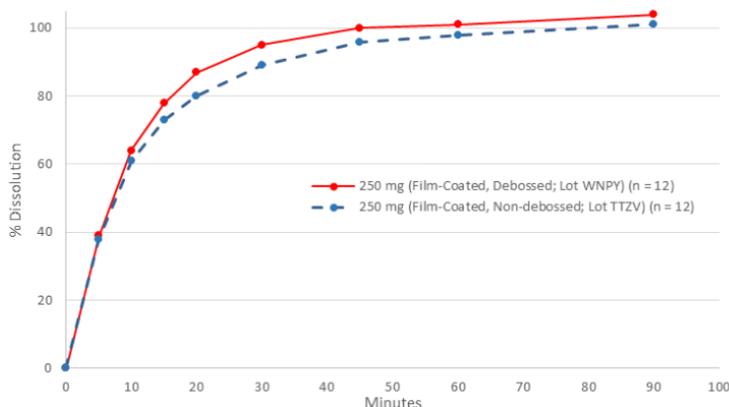
The Applicant provided dissolution data and f_2 values to support the comparability between the non-debossed clinical tablets (uncoated (lot: TTZS) and film-coated (WDGF)) and debossed film-coated registration batch (Lot: WNPY). The registration batches (primary stability batches) were manufactured using production scale equipment according to the commercial process at the commercial site.

Table 2: Summary of Comparative Dissolution Results

Reference Lot(s)	Test Lot	f_2 Result ²
Ivosidenib Tablet, 50 mg, uncoated, non-debossed (Lot TWMP) + Ivosidenib Tablet, 200 mg, uncoated, non-debossed (Lot TWMS)	Ivosidenib Tablet, 250 mg, uncoated, non-debossed (Lot TTZS)	81.5
Ivosidenib Tablet, 250 mg, uncoated, non-debossed (Lot TTZS)	Ivosidenib Tablet, 250 mg, film-coated, non-debossed (Lot TTZV)	73.3
Ivosidenib Tablet, 250 mg, film-coated, non-debossed (Lot TTZV)	Ivosidenib Tablet, 250 mg, film-coated, debossed (Lot WNPY)	66.4
Ivosidenib Tablet, 250 mg, uncoated, non-debossed (Lot WDFG) [Clinical Lot ¹]	Ivosidenib Tablet, 250 mg, film-coated, debossed (Lot WNPY)	63.8
Ivosidenib Tablet, 50 mg, uncoated, non-debossed (Lot TWMP) + Ivosidenib Tablet, 200 mg, uncoated, non-debossed (Lot TWMS)	Ivosidenib Tablet, 250 mg, film-coated, debossed (Lot WNPY)	66.0

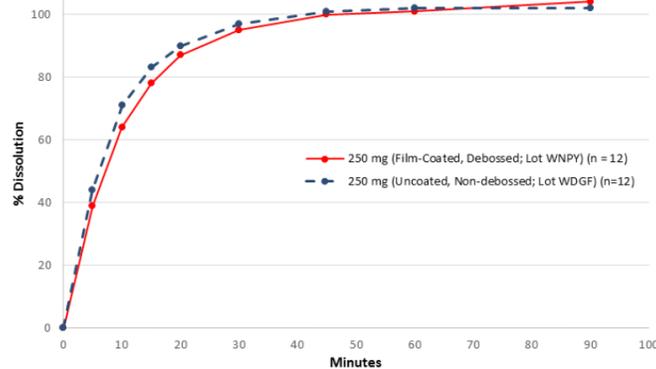
¹Used in clinical studies AG120-C-001 and AG120-C-002

Figure 4. Dissolution Profiles for Ivosidenib Tablets, 250 mg: Film-Coated, Non-debossed (Clinical Lot TTZV⁵) Versus Commercial Presentation Film-Coated, Debossed (Lot WNPY)



⁵ Used in clinical study AG120-C-004 (food effect) and AG120-C-007 (clinical DDI study with itraconazole)

Figure 5. Comparative Dissolution Profiles for Ivosidenib Tablets, 250 mg (Uncoated, Non-debossed; Lot WDFG) Versus Commercial Presentation (Ivosidenib Tablets, 250 mg, Film-Coated, Debossed; Lot WNPY)



As shown above, the addition of debossing does not have any detectable impact on the drug product's dissolution profiles. Therefore, the dissolution data support the bridge between the clinical batches and the commercial presentation.

d. Biowaiver Request:

The Applicant is seeking approval for only one dosage strength (250 mg) and thus biowaiver request is not applicable for the application.

R Regional Information

Comparability Protocols: N/A

Lifecycle Management Considerations: N/A

APPENDIX I: Overview of Tablet Presentation Used in Clinical Studies

Study	Brief Description	Dosage Strength/Tablet Presentation
Ivosidenib safety, PK, PD, and clinical activity (Primary clinical study, CSR AG120-C-001)	Dose escalation: Subjects with advanced hematologic malignancies Dose: Single and multiple oral doses at daily dose from 100 to 1,200 mg	50 and 200 mg Uncoated tablets
	Expansion: Dose: Single and multiple oral doses at 500 mg QD	50, 200, 250 mg Uncoated tablets
Ivosidenib safety, PK (AG120-C-002 NDA Safety/PK Report)	Dose escalation: Subjects with advanced solid tumors Dose: Single and multiple oral doses at daily doses from 100 to 1,200 mg	50 and 200 mg Uncoated tablets
	Expansion: Dose: Single and multiple oral doses at 500 mg QD	50, 200, 250 mg Uncoated tablets
Food effect (CSR AG120-C-004)	Healthy Subjects Dose: Part 1: Single oral dose of 500 mg ivosidenib Part 2: Single oral dose of 1,000 mg ivosidenib	250 mg Blue film-coated tablet
PK in Japanese relative to Caucasians (CSR AG120-C-006)	Healthy males Dose: Single oral dose of 250, 500, and 1,000 mg ivosidenib	250 mg Blue film-coated tablet
Clinical DDI study with itraconazole (CSR AG120-C-007)	Healthy Subjects Dose: Single oral dose of 250 mg ivosidenib; itraconazole 200 mg QD for 18 days	250 mg Blue film-coated tablet



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