

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209606Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

**NDA 209606
Review #1**

Drug Name/Dosage Form	Enasidenib Mesylate tablets
Strength	50 and 100 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Celgene Corp.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	12/30/16	All
Amendment (SD 0005)	02/03/17	Process
Amendment (SD 0012)	03/15/17	DP
Amendment (SD 0013)	03/30/17	DP, Process
Amendment (SD 0018)	04/20/17	Process
Amendment (SD 0022)	05/02/17	DP
Amendment (SD 0026)	05/11/17	DP, Process
Amendment (SD 0028)	05/18/17	DP
Amendment (SD 0030)	05/23/17	DP
Amendment (SD 0031)	05/30/17	DP
Amendment (SD 0032)	05/31/17	DP
Amendment (SD 0032)	05/30/17	Process

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Rohit Tiwari	Benjamin Stevens
Drug Product	Nina Ni	Anamitro Banerjee
Process	David Anderson	Ying Zhang
Microbiology	n/a	n/a
Facility	Zhong Li	Zhihao Peter Qiu
Biopharmaceutics	Banu Zolnik	Okponanabofa Eradiri
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a
Environmental	Nina Ni	Anamitro Banerjee

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type IV		(b) (4)	Adequate	1/26/17	n/a
	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	117631	Development of Enasidenib

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of the NDA 209606 for IDHIFA™ (enasidenib) tablets 50 and 100 mg with the following Post-Approval Commitment:

The applicant has committed to a Post Marketing Commitment (PMC) to provide a revised control strategy for mitigating risks related to (b) (4)

As part of this action, OPQ grants a (b) (4)-month re-test period for the drug substance when stored (b) (4) and an 18-month drug product expiration period when stored at USP controlled room temperature conditions [i.e. 20°C - 25°C (68°F - 77°F)] with excursions permitted between 15°C - 30°C (59°F - 86°F).

II. Summary of Quality Assessments

A. Product Overview

NDA 209606 was submitted as a 505(b)(1) NDA under the Federal Food, Drug and Cosmetic Act by the Celgene Corporation. The drug product, IDHIFA™ (enasidenib) tablets, 50 and 100 mg, is a first-in-class, selective, targeted inhibitor of the mutant isocitrate dehydrogenase-2 (IDH2) enzyme indicated for the treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an IDH2 mutation. The active, enasidenib mesylate is a new molecular entity (NME) which received orphan designation. Enasidenib mesylate was originally investigated under IND 117631.

The dosing regimen for IDHIFA™ (enasidenib) Tablets consists of 100 mg once daily until disease progression or until unacceptable toxicity. Dose adjustments for toxicities are outlined and include interruption of administration until toxicity resolves then resuming at 50 mg daily increasing to 100 mg daily if the patient continues to tolerate therapy.

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 209606 and grants a (b) (4)-month re-test period for the drug substance and an 18-month drug product expiration period when stored under controlled room temperature in the commercial packaging with the aforementioned PMC.

Proposed Indication(s) including Intended Patient Population	Treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an IDH2 mutation
Duration of Treatment	Chronic (minimum of 6 months)

Maximum Daily Dose	100 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

The drug substance, enasidenib mesylate, is a white to off-white non-hygroscopic powder. The drug substance is an achiral molecule that exhibits polymorphic behavior. Multiple crystalline forms for the mesylate salt (15) and for the free base (11) were identified and characterized. Polymorph control was discussed prior to NDA submission (July 2016 Type B meeting) and during the review cycle (see Drug Product review pages 19-21). Ultimately it was concluded that (b)(4) was the most (b)(4) form and was chosen for development.

Enasidenib mesylate drug substance is a NME that is synthesized by (b)(4)

There were fourteen potentially genotoxic impurities identified. Of the fourteen, thirteen were AMES negative and Derek inactive and one impurity was confirmed genotoxic ((b)(4)). The use of (b)(4) has the potential to form (b)(4) which are genotoxic. The applicant addresses that concern by including specification and acceptance criteria for (b)(4) in the drug product release specifications.

The drug substance is stored in (b)(4). The applicant provided 12 months of long term and 6 months accelerated stability data for the drug substance packaged in the aforementioned container closure system and proposed a (b)(4) month re-test date for the drug substance. The stability data was acceptable and demonstrated no noteworthy trends. Accordingly, the proposed (b)(4)-month re-test date for the drug substance stored at (b)(4) in the proposed container closure can be granted.

Drug Product

The drug product, IDHIFA™ (enasidenib) tablets, is presented as 50 and 100 mg yellow film coated tablets containing 60 and 120 mg of the drug substance (enasidenib mesylate), respectively. The 50 and 100 mg tablets are debossed with either “50” or “100” on one side and “ENA” on the other. The drug product composition includes: the active, colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose acetate succinate, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sodium lauryl sulfate, sodium starch glycolate, talc, and titanium dioxide. The 50 and 100 mg tablets are dose proportional and are manufactured from (b)(4) at a commercial batch size of (b)(4) Kg. The (b)(4) Kg batch size translates to (b)(4) of the 50 mg tablets and

(b) (4) of the 100 mg tablets. The drug product will be packaged in 30-count, square, white HDPE bottles with a push down and turn (b) (4) closure, a liner and desiccant.

Eighteen months of long term and 6 months of accelerated stability data were included for six commercial scale batches (3 batches of each strength) of the drug product manufactured at the proposed commercial manufacturing site and packaged in the proposed commercial container closure system. The data was acceptable and within the prescribed acceptance criteria with no notable trends or excursions. The proposed drug product specification together with the PMC and the controls for impurities in the drug substance are adequate to ensure that the critical quality attributes of this product are well controlled. The available stability data supports the proposed ***18-month expiry for the drug product when stored under USP controlled room temperature.***

Process

(b) (4)

Biopharmaceutics

This application included data from the PK, bioavailability and food effect studies in healthy volunteers. Results of the aforementioned studies will be reviewed by the Office of Clinical Pharmacology (OCP). The Applicant conducted a Phase 1 PK study with the 50 and 100 mg strengths of enasidenib, therefore, no Biowaiver was requested.

The proposed dissolution method for the drug product is USP Apparatus 2 (paddle) at 75 rpm for $Q = \frac{(b)}{(4)}\%$ in 30. This method is acceptable and the NDA is recommended for approval from the Biopharmaceutics perspective.

Facilities

This NDA included the following seven sites :

-
-
-
-
-
-
-

(b) (4)

Adequate descriptions were provided for all sites. Following a review of the application, inspectional documents, and pre-approval inspection results, there are no significant, outstanding manufacturing or facility risks that prevent the approval of this application. The Overall Manufacturing Inspection Recommendation is approval.

Environmental Assessment

Approval of this NDA will increase the use of the active moiety, enasidenib mesylate. However, the applicant included a claim for categorical exclusion from conducting an environmental impact statement (EIS) or environmental assessment (EA) under 21 Code of Federal Regulations (CFR) Sections 25.31(b) on the basis that estimated concentration of the active moiety into the aquatic environment is less than 1 part per billion (ppb).

The claim of categorical exclusion from an environmental assessment is valid since the estimated increase usage of the active moiety is well below the allowable EIC of 1 part per billion (ppb).

The request for categorical exclusion is granted.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment

Included drug product section of this IQA.



Sherita
McLamore

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{For NDA Only}

I. Package Insert

1. Highlights of Prescribing Information

IDHIFA™ (enasidenib) tablets, for oral use
Initial U.S. Approval: 201X

Tablets: 50 mg or 100 mg (3)

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Provided
Dosage form, route of administration	Provided
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Provided

2. Section 2 Dosage and Administration

Do not split or crush IDHIFA tablets. Administer IDHIFA tablets orally about the same time each day.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Provided

3. Section 3 Dosage Forms and Strengths

IDHIFA is available in the following tablet strengths:

- 50 mg tablet: Pale yellow to yellow oval-shaped film-coated tablet debossed “ENA” on one side and “50” on the other side.
- 100 mg tablet: Pale yellow to yellow capsule-shaped film-coated tablet debossed “ENA” on one side and “100” on the other side.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Provided
Strengths: in metric system	Provided
Active moiety expression of strength with equivalence statement (if applicable)	Provided
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Provided

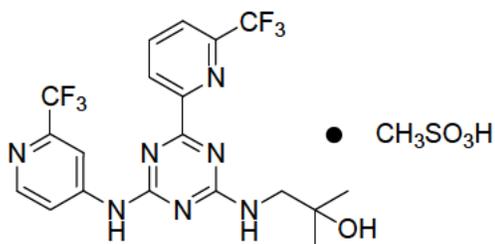
4. Section 11 Description

IDHIFA (enasidenib) is an inhibitor of isocitrate dehydrogenase-2 (IDH2) enzyme. Enasidenib is available as the mesylate salt with the chemical name: 2-methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{{2-(trifluoromethyl)pyridin-4-yl}amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate.

Or

2-Propanol, 2-methyl-1-[[4-[6-(trifluoromethyl)-2-pyridinyl]-6-[[2-(trifluoromethyl)-4-pyridinyl]amino]-1,3,5-triazin-2-yl]amino]-, methanesulfonate (1:1).

The chemical structure is:



The empirical formula is $C_{19}H_{17}F_6N_7O \cdot CH_3SO_3H$ ($C_{20}H_{21}F_6N_7O_4S$), and the molecular weight is 569.48 g/mol. Enasidenib is practically insoluble (solubility ≤ 74 mcg/mL) in aqueous solutions across physiological pH range (pH 1.2 and 7.4).

IDHIFA (enasidenib) is available as a 50 mg tablet (equivalent to 60 mg enasidenib mesylate) and a 100 mg tablet (equivalent to 120 mg enasidenib mesylate) for oral administration. Each tablet contains inactive ingredients of colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose acetate succinate, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sodium lauryl sulfate, sodium starch glycolate, talc, and titanium dioxide.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Provided
Dosage form and route of administration	Provided
Active moiety expression of strength with equivalence statement (if applicable)	Provided
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Provided
Statement of being sterile (if applicable)	NA
Pharmacological/ therapeutic class	Provided
Chemical name, structural formula, molecular weight	Provided
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	Provided

5. Section 16 How Supplied/Storage and Handling

16.1 How Supplied

50 mg tablet: Pale yellow to yellow oval-shaped film-coated tablet debossed “ENA” on one side and “50” on the other side.

- (b) (4) revised to
- Bottles of 30 with a desiccant canister (NDC 59572-705-30)

100 mg tablet: Pale yellow to yellow capsule-shaped film-coated tablet debossed “ENA” on one side and “100” on the other side.

- (b) (4) revised to
- Bottles of 30 with a desiccant canister (NDC 59572-710-30)

16.2 Storage

Store at 20°C - 25°C (68°F - 77°F); excursions permitted between 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature]. Keep the bottle tightly closed. Store in the original bottle (with a desiccant canister) to protect from moisture.

(b) (4)

Manufactured for and marketed by:
Celgene Corporation
Summit, NJ 07901

Licensed from:
Agius Pharmaceuticals
Cambridge, MA 02139

Trademarks are the property of their respective owners.

IDHIFA™ is a trademark of Celgene Corporation.

Pat. www.celgene.com/therapies

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IDHPI.001/PPI.001 XX/17

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Provided
Available units (e.g., bottles of 100 tablets)	Provided
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided
Special handling (e.g., protect from light)	Provided
Storage conditions	Provided
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Provided

Reviewer's Assessment of Package Insert: Adequate with comment.

See assessment above.

II. Labels:

Container and Carton Labels

Container Label:



Carton Label:

The product is not packaged in carton. So there is no carton label provided.

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Provided	NA
Dosage strength (21CFR 201.10(d)(1); 21 CFR 201.100(b)(4))	Provided	NA
Route of administration (21 CFR 201.100(b)(3)), not required for oral	Not required for oral tablets	NA
Net contents* (21 CFR 201.51(a))	Provided	NA
“Rx only” displayed prominently on the main panel (21 CFR 201.100(b)(1))	Provided	NA
The list of inactive ingredients, 21CFR 201.10(a), if not oral dosage form; and quantitative ingredient information, if parenteral injection. 21CFR 201.100(b)(5)(iii)**, only required for carton label	Not required for oral tablets	NA
NDC number (21 CFR 207.35(b)(3)(i))	Provided	NA
Lot number and expiration date (21 CFR 201.17)	Provided	NA
Storage conditions	Provided, need to revise	NA
Bar code (21CFR 201.25)***	Provided	NA
Sterility Information (if applicable)	NA	NA
See packaging insert for dosage information (21 CFR 201.55), only required for carton label	Provided	NA
Name of manufacturer/distributor	Provided	NA
And others, if space is available	Add “Swallow whole, do not chew or split tablets”	NA

*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.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

***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 of Labels: *Adequate with comment.*

The following comment on the container label needs to be conveyed to the applicant:

- The storage condition listed in the container needs to be revised to: Store at 20°C - 25°C (68°F - 77°F); excursions permitted between 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature]. Keep the bottle tightly closed.

List of Deficiencies:

The following comment needs to be conveyed to the applicant regarding the container label:

- The storage condition listed in the container needs to be revised to: Store at 20°C - 25°C (68°F - 77°F); excursions permitted between 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature]. Keep the bottle tightly closed.

Overall Assessment and Recommendation: Approval pending on the update on the container label.

See evaluation above.

Primary Labeling Reviewer Name and Date: Nina Ni, Ph.D., 05/31/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Anamitro Banerjee, Ph.D., May 31, 2017



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Banerjee

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BIOPHARMACEUTICS

Product Background:

NDA: 209606-ORIG-1

Drug Product Name / Strength: Idhifa® (enasidenib) tablet, 50 mg and 100 mg

Route of Administration: Oral

Applicant Name: Celgene Corporation

Review Summary:

Enasidenib is a targeted inhibitor of the mutant isocitrate dehydrogenase-2 enzyme indicated for the treatment of patients with relapsed or refractory acute myeloid leukemia with an IDH2 mutation.

Enasidenib tablet is to be administered orally once daily.

The clinical development of the proposed drug product included 8 clinical studies. Four Phase 1-3 studies were conducted. The approval of the application is based on Study AG221-C-001. Three studies assessed the PK, bioavailability and food effect in healthy volunteers.

The final regulatory dissolution method and acceptance criterion are shown below.

USP Apparatus/RPM	Medium	Volume	Acceptance Criteria
USP II (paddle), 75 rpm	0.6% SDS in 0.1 N HCL	900 mL	Q = ^(b) / ₍₄₎ % in 30 minutes

Discriminating power of the dissolution method was not demonstrated for critical process and manufacturing parameters.

The Applicant conducted a Phase 1 PK study (AG-221-CP-001) with both proposed strengths of enasidenib (50 mg, 100 mg). Therefore, there is no need for a Biowaiver request. The aforementioned PK study is being evaluated by the OCP Reviewer.

The clinical development program for the proposed product included mainly Formulation 2 and Formulation 3. The differences between the Formulation 2 and Formulation 3 are deemed

minor by the Drug Product Reviewer. In addition, the Applicant used both formulations in the clinical safety and efficacy study. The comparative dissolution profiles between F2 formulation and F3 formulation for the 50 mg and 100 mg strengths, respectively, indicated that the minor formulation change did not impact dissolution.

Some minor manufacturing changes i.e. debossing were implemented for the commercial to-be-marketed drug product. In support of this change, dissolution profile comparisons between Formulation 3 and the To-be-Marketed (TBM) drug product were submitted. Dissolution profiles between formulation 3 and the TBM drug product are overlapping indicating that debossing did not impact dissolution.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 209606 for Idhifa® (enasidenib) tablet, 50 mg and 100 mg is recommended for **APPROVAL**.

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Composition Information:

Enasidenib tablets are prepared from (b) (4). Note that the Applicant is seeking approval for only 50 mg and 100 mg strengths (Table 1).

Table 1. Composition of Enasidenib Tablets (Formulation 3)

Component	Quality Reference	Function	Strength (label claim) ¹		Content (%)
			50 mg	100 mg	
CC-90007 mesylate drug substance	Module 3.2.S.4.1 Specifications	Active ingredient	60	120	(b) (4)
Microcrystalline cellulose	NF/Ph. Eur.	(b) (4)	(b) (4)		(b) (4)
Hydroxypropyl cellulose	NF/Ph. Eur.				
Sodium lauryl sulfate	NF/Ph. Eur.				
Sodium starch glycolate	NF/Ph. Eur.				
Hypromellose acetate succinate	NF				
Colloidal silicone dioxide	NF/Ph. Eur.				
Magnesium stearate	NF/Ph. Eur.				
	(b) (4)				
Total			249.6	499.2	(b) (4)

Reference: ELN 8353

List Submissions being reviewed (table):

Original dated 12/30/2016

BCS Designation

Reviewer's Assessment:

Solubility:

Enasidenib has low aqueous solubility. The solubility data in aqueous media in the pH range of 1.2-7.5 is shown in Table 2. The solubility in various biologically relevant media is shown in Table 3. The Applicant stated that enasidenib exhibits a high permeability across Caco-2 cells (17.9×10^{-6} cm/s). Therefore, it may be classified as a BCS Class II compound.

Table 2. Solubility of enasidenib at various pH range

pH	Prep	pH (measured)	Solubility (µg/mL)
1.2	0.1N HCl	1.25	74
2	0.01N HCl	2.3	11
3	50 mM PO ₄	3	5
4.5	50 mM acetate	4.6	3
6.8	50 mM PO ₄	6.8	4
7.5	50 mM PO ₄	7.4	3

Reference: ELN 8353

Table 3. Solubility of enasidenib in various physiologically relevant media

Solution	Solubility ($\mu\text{g/mL}$)
Water	1
Simulated Gastric Fluid (SGF)	9.5
Fasted State Simulated Intestinal Fluid (FaSSIF)	< 0.77
Fed State Simulated Intestinal Fluid (FeSSIF)	170
Reference: ELN 8353	

(b) (4)

Permeability:

The Applicant stated that enasidenib has a high permeability (17.9×10^{-6} cm/s) across Caco-2 cells. Based on this information, enasidenib is likely to be a BCS Class 2 drug.

Dissolution Method and Acceptance Criteria

USP Apparatus/RPM	Medium	Volume	Acceptance Criteria
USP II (paddle), 75 rpm	0.6% SDS in 0.1 N HCL	900 mL	Q = ^(b) ₍₄₎ % in 30 minutes

Reviewer's Assessment:**Dissolution Method Development**

(b) (4)

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Figure 4. % CC-9007 Released at Various Paddle Speeds

(b) (4)

Discriminatory ability of the dissolution method:

The Applicant evaluated the discriminating ability of the dissolution method for the selected process variables ((b) (4)) and formulation variables ((b) (4) amount, API particle size). The flow diagram below shows the process of

enasidenib tablets; the highlighted input and processes were evaluated for the discriminating ability of

Figure 7. Process Flow Diagram for Commercial FCTs (Formulation 3, Commercial Formulation)

(b) (4)



Figure 5. Process flow diagram for commercial enasidenib tablet production

1) The Effect of Process Variables

(b) (4)

2) Effect of (b) (4) Variations on Dissolution

The Applicant evaluated the discriminating ability of the dissolution method for (b) (4) content. The target tablets have (b) (4)

2) Effect of API particle size on Dissolution

Three different API particle size ranges were used in the manufacture of the tablets which were subjected to dissolution testing (Table 5). Dissolution profiles of tablets with micronized, target, and large API are shown in Figure 7.

Table 6. Enasidenib tablets manufactured with different API particle size

Table 11. CC-90007 API Particle Sizes Tested

API Type	Lot	Dv (10) (µm)	Dv (50) (µm)	Dv (90) (µm) ^{(b) (4)}
Micronized	150029-micronized			
Typical	150029			
Large	404-14-05-75			
Reference: ELN 8353				

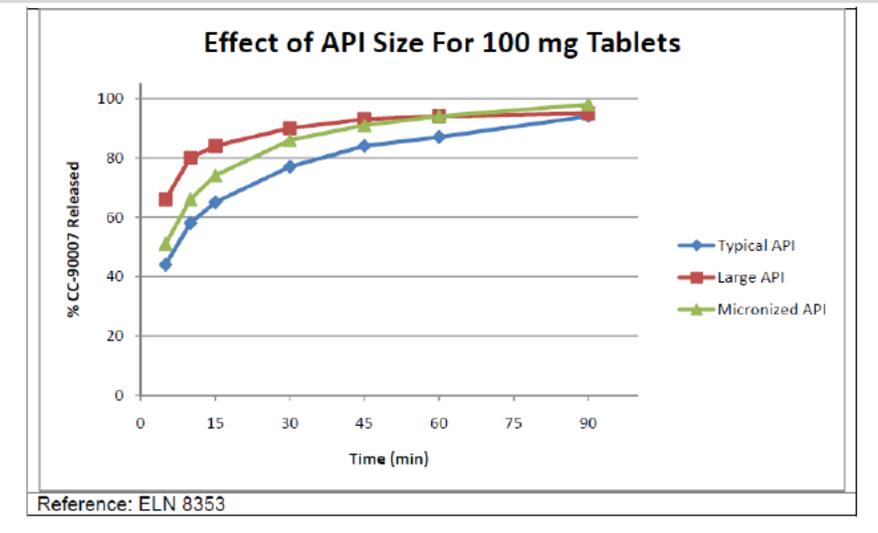


Figure 7. The effect of particle size on dissolution of 100 mg enasidenib tablets

It was found that tablets with larger API particle size exhibited faster dissolution than tablets with smaller particle size. This is an unusual phenomenon since tablets with micronized API are expected to exhibit faster dissolution due to increased surface area. The Applicant asserts that ^{(b) (4)} differences between the tablets contributed to this behavior; however this rationale is not fully supported by the data. It is this Reviewer’s opinion that the dissolution method is not discriminatory for changes in API particle size, and the particle size range should be included in the specifications. During the review cycle, the Drug Product Reviewer sent IR comments to the Applicant regarding the need for an API particle size specification; an upper D90 limit of ^{(b) (4)} µm was set for the API (for further details refer to the Drug Product Review).

3) Effect of Dissolution

(b) (4) Content on

Tablets were prepared with high ((b) (4) %), target ((b) (4) %) and low ((b) (4) %) (b) (4) content. Dissolution profiles of tablets prepared with (b) (4) are shown in Figure 8. It appears that dissolution is not discriminatory for variations in (b) (4) content. Similar to levels of the (b) (4) the changes in the (b) (4) content did not impact dissolution (data not shown).



Figure 7. The effect of (b) (4) on dissolution of 100 mg enasidenib tablets

In conclusion, the dissolution method is discriminating for changes in (b) (4) levels that are greater than (b) (4) % relative to the target formulation. The method is not discriminating for (b) (4) (b) (4), API particle size, (b) (4) and (b) (4) levels. Overall, the dissolution method is not discriminating for critical process and manufacturing parameters.

Dissolution method acceptance criteria

Reviewer's Assessment:

The Applicant's proposed acceptance criteria of $Q = (b) (4) \%$ in 30 min is acceptable.

Bridging of Formulations**Reviewer's Assessment:**

The clinical development program for the proposed product included mainly Formulation 2 and Formulation 3 (refer to the schematic overview below). The Applicant conducted Study AG22-C-001, a Phase 1/2 dose escalation study, with all the formulations (Formulation 1a, Formulation 1b, Formulation 2 and Formulation 3). Parts 1 and 2 expansion phases of Study AG221-C-001, which is the basis for approval, were conducted with Formulation 2 and Formulation 3. The Applicant conducted the food effect study (AG221-C-002) with Formulation 2 and the single dose PK (AG221-CP-001) and ADME-BA (AG221-CP-002) studies with Formulation 3. The differences between Formulation 2 and Formulation 3 are deemed minor by the Drug Product Reviewer. The PK studies are being evaluated by the OCP Reviewer. The comparative dissolution profiles between F2 formulation and F3 formulation for 50 mg and 100 mg tablets are shown in Figures 8 a-b. The similarity values between the F2 vs F3 formulations for 50 mg and 100 mg strengths are 56 and 82, respectively, indicating that the minor formulation change did not impact dissolution.

Some minor manufacturing changes i.e. debossing were implemented for Formulation 3, and for the commercial to-be-marketed drug product. In support of this change, dissolution profile comparisons between Formulation 3 and the To-be-Marketed (TBM) drug product were submitted (Figure 9 a-b). Dissolution profiles between Formulation 3 and the TBM drug product are overlapping indicating that debossing did not impact dissolution.

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Schematic Overview of Clinical Development –

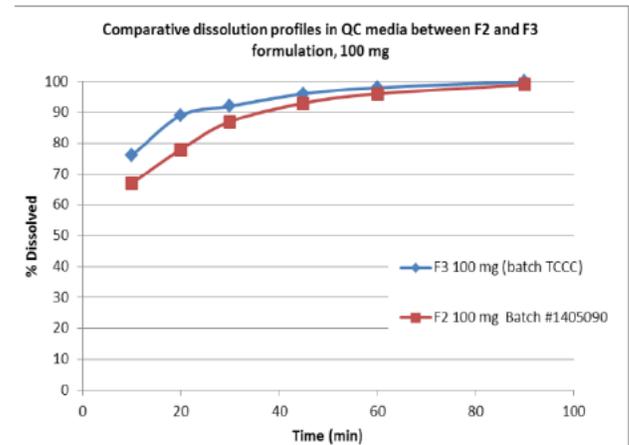
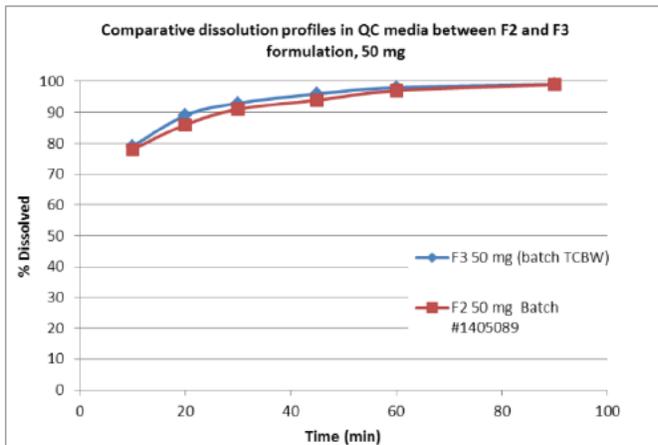
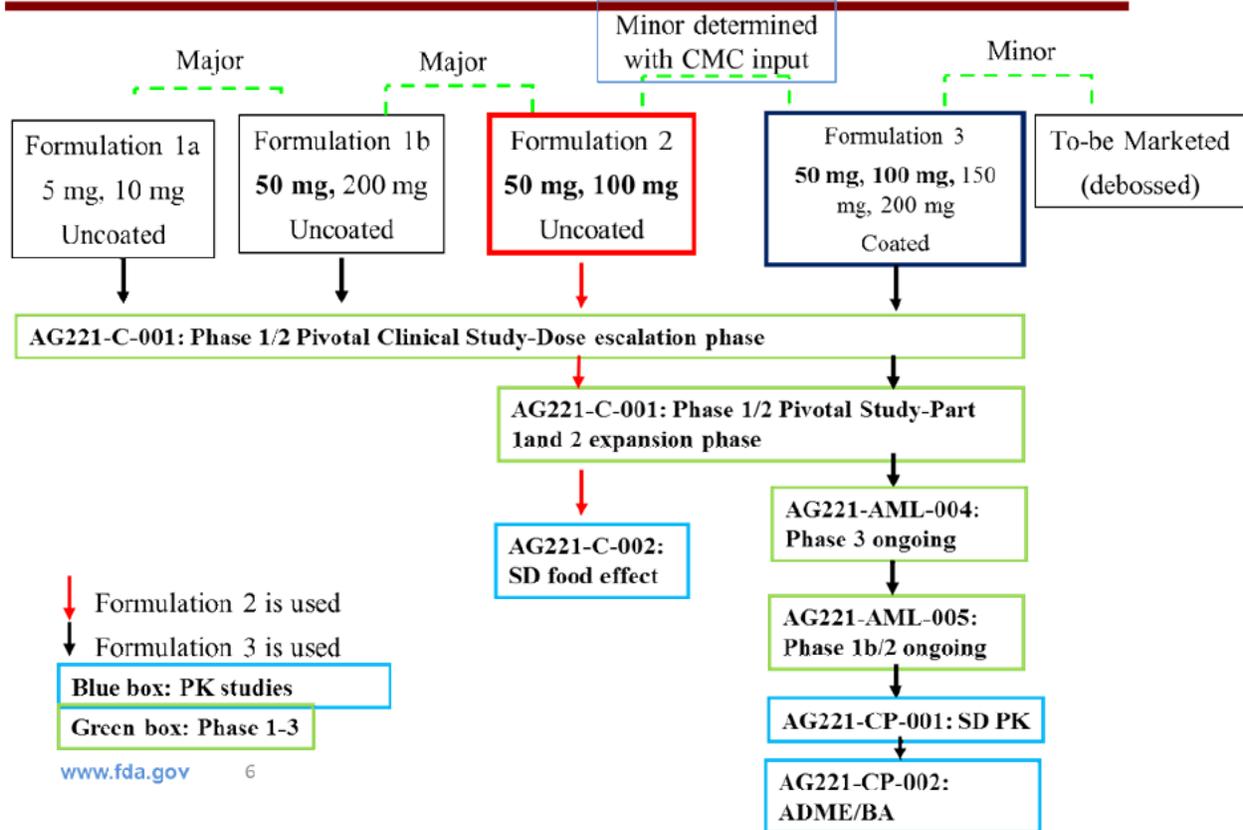
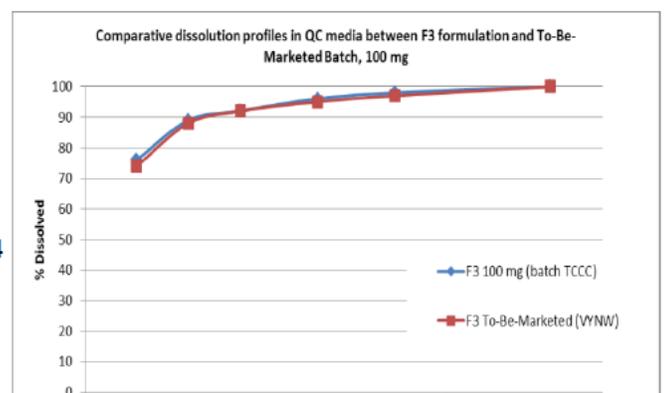


Figure 8. Comparative dissolution profiles between F2 vs. F3 formulation in QC media (a) Left panel-50 mg, (b) Right panel-100 mg (Plotted by the Reviewer)

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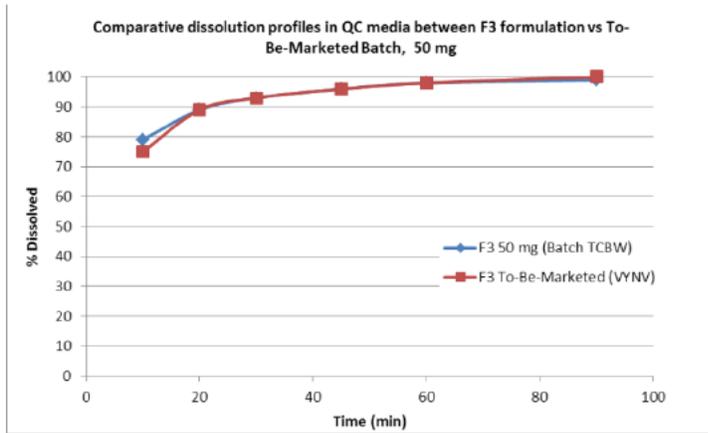


Figure 9. Comparative dissolution profiles between F3 formulation vs. To-Be-Marketed Formulation in QC media (a) Left panel-50 mg, (b) Right panel-100 mg (Plotted by the Reviewer)

Biowaiver Request

Reviewer’s Assessment:

The Applicant conducted Phase 1 PK study (AG-221-CP-001) with 50 mg, 100 mg strengths. Therefore, there is no need for a Biowaiver request. This study is being evaluated by OCP reviewer.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 209606 for Idhifa® (enasidenib) tablet, 50 mg and 100 mg is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date:

6/1/2017

Banu S. Zolnik, PhD

Secondary Reviewer Name and Date

6/1/2017

Okpo Eradiri, PhD



Banu
Zolnik

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA 209606 (IDHIFA™ tablets), Celgene Corporation

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay, Stability	<ul style="list-style-type: none"> • Formulation • Container closure • Process parameters • Scale/equipments • Site 	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place.
Physical stability (solid state)	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	M	Assessed during Development and controlled via specs.	Acceptable	PMC to provide a revised control strategy for mitigating risks related to (b) (4)
Content Uniformity	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place.
Microbial Limits	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place
Dissolution – BCS Class I & III	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place



Sherita
McLamore

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