

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210496Orig1s000

PRODUCT QUALITY REVIEW(S)

ADDENDUM TO THE LABELING REVIEW

I. Package Insert

1. *Section 16 How Supplied/Storage and Handling*

BRAFTOVI (encorafenib) is supplied as 50 and 75 mg hard gelatin capsules.

50 mg: stylized "A" on orange cap and "LGX 50mg" on beige body, available in cartons (NDC 70255-020-01) containing two bottles of 60 capsules each (NDC 70255-020- (b) (4))

75 mg: stylized "A" on beige cap and "LGX 75mg" on white body, available in cartons (NDC 70255-025-01) containing two bottles of 90 capsules each (NDC 70255-025-02). Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Do not use if safety seal under cap is broken or missing. Dispense in original bottle. Do not remove desiccant. Protect from moisture. Keep container tightly closed.

2. *Section 17 Patient Counseling Information*

Storage

BRAFTOVI is moisture sensitive. Advise patients to store BRAFTOVI in the original bottle with desiccant and to keep the cap of the bottle tightly closed. Do not remove the desiccants from the bottle .

Reviewer's Assessment of Package Insert: *Adequate.*

- Given the drug product stability information provided in the stability section of the NDA and the manufacturing process development section, higher temperature (40°C) and/or higher humidity conditions may have an undesired effect on the product quality.
- Based on the anecdotal evidence that patients could remove the medication from the original containers and fill them in the pill dispensers for a weekly supply, BRAFTOVI could be exposed to high temperature or humidity conditions. Therefore it was recommended in the T-con on 4/25/2018 that Array could add the label "Protect from Moisture" and "Do not remove the desiccant from the bottle" on the bottle and cartons so that patients would be alerted of the fact that it may be desirable to keep BRAFTOVI in the original container closure with the desiccant at all times. To keep consistency with the bottles and cartons, this reviewer discussed

the possibility of addition of these two labels in the prescription insert with Stacy Shord and she agreed with the recommendation.

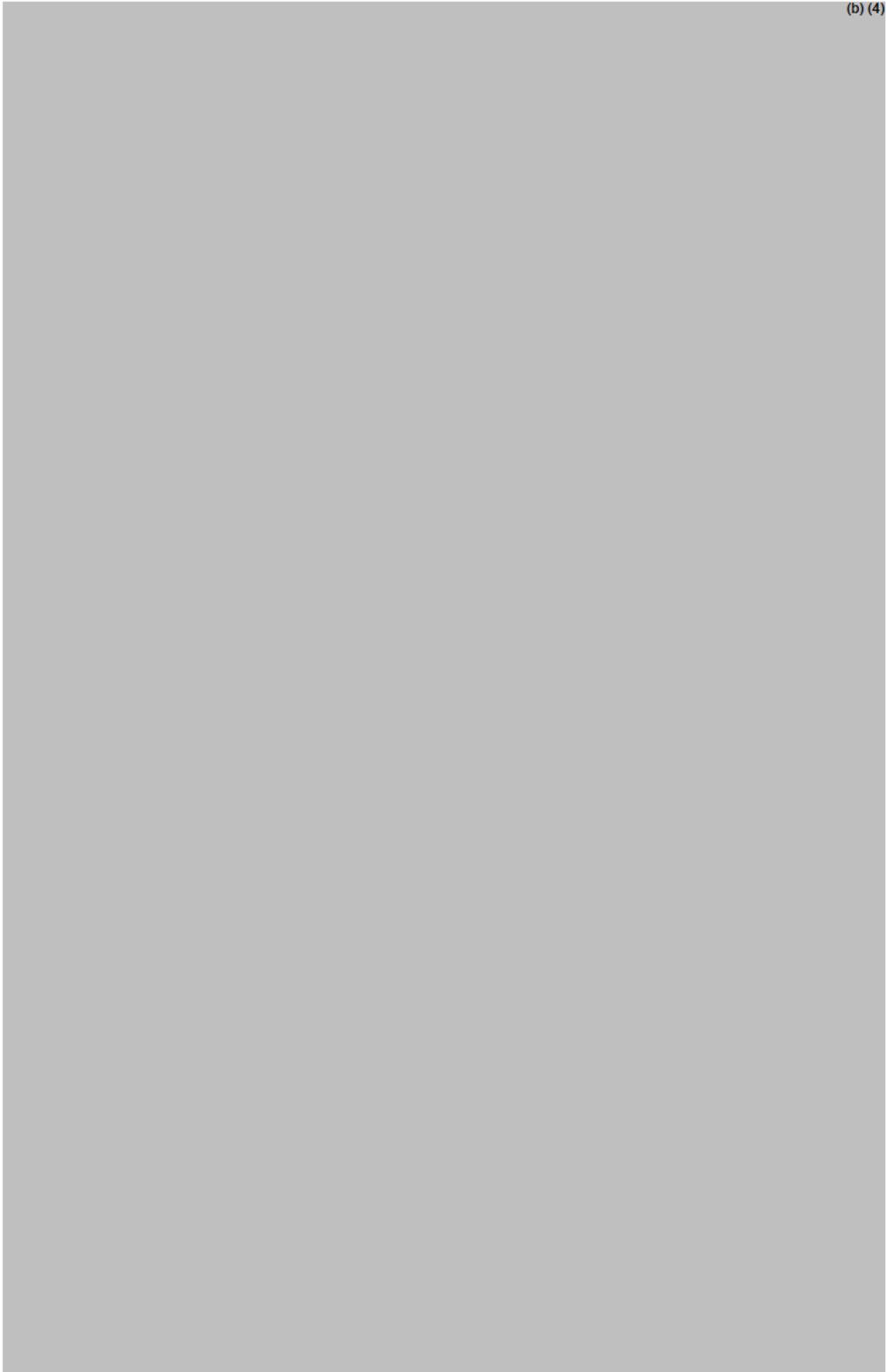
- Dr. Ann Marie Trentacosti additionally pointed out that for moisture sensitive drug products, it is not uncommon to add the label “keep the cap of the bottle tightly closed” to alert patients about the sensitivity of the drug product further. Therefore, this label was added in the Section 17 of the prescription insert. Similar language has been added in the MedGuide.

II. Labels:

1. *Container and Carton Labels*



2. Carton Label



(b) (4)



Reviewer's Assessment of Labels: *Adequate*

- As per the discussion in the T-con on 4/25/2018, Array updated their container and carton labels to include "Protect from Moisture" and "Do not remove desiccant". Based on additional recommendation by Dr. Ann Marie Trentacosti, Array added "Keep container tightly closed" label on both containers and cartons.
- This reviewer additionally notes here that DMEPA recommended Array to develop unit dose packaging systems (blister packs) to aid in the hospital pharmacy settings.

List of Deficiencies:***Overall Assessment and Recommendation:***

Approval.

Primary Labeling Reviewer Name and Date: Rohit V. Tiwari, Ph.D. 5/29/2018

Secondary Reviewer Name and Date: Anamitro Banerjee, Ph.D. 5/29/2018



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Tiwari

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Recommendation: APPROVAL

NDA 210496

Review #1

Drug Name/Dosage Form	encorafenib(BRAFTOVI)(LGX818)Capsule
Strength	50 mg, 75 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Array BioPharma Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	06/30/2017	All Disciplines
Quality Amendment	12/05/2017	Drug Substance, Biopharm, Process
Quality Amendment	12/11/2017	Office of Testing and Research
Quality Amendment	01/05/2018	Drug Substance, Drug Product
Quality Amendment	01/09/2018	Drug Substance
Quality Amendment	01/16/2018	Process

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	BRANCH/DIVISION
Drug Substance	Rohit Tiwari/Benjamin Stevens	OPQ/ONDP/DNDAPI/B1
Drug Product	Rohit Tiwari/ Anamitro Banerjee	OPQ/ONDP/DNDAPI/B1 and OPQ/ONDP/DNDP1/B2
Process	Diane Goll/Ying Zhang	OPQ/OPF
Microbiology Facility	Aditi Thakur/Christina Capacci-Daniel	
Biopharmaceutics	Joan (Zhuojun) Zhao/Okpo Eradiri	OPQ/ONDP/DB/BB1
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO/B1
Application Technical Lead	Rohit Tiwari	OPQ/ONDP/DNDAPI/B1
Laboratory (OTR)	Alicia Hoover/Laura Pogue	OPQ/OTR/DPA
ORA Lead	Caryn McNab	
Environmental	Rohit Tiwari	OPQ/ONDP/DNDAPI/B1

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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)				Not reviewed	N/A	Information is provided in the submission.
				Not reviewed	N/A	Information is provided in the submission.
				Not reviewed	N/A	Information is provided in the submission.
				Not reviewed	N/A	Information is provided in the submission.
				Not reviewed	N/A	Information is provided in the submission.
				Not reviewed	N/A	Information is provided in the submission.
				Not reviewed	N/A	Information is provided in the submission.
				Not reviewed	N/A	Information is provided in the submission.
				Not reviewed	N/A	Information is provided in the submission.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
(b) (4)		
(b) (4)		
(b) (4)		
IND	113850	Encorafenib – capsule – Unresectable/metastatic melanoma
(b) (4)		
NDA	210498	Binimetinib
PMA	P120014-S008	ThxID BRAF Assay Kit – Submitted to CDRH

2. CONSULTS
N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA is recommended for APPROVAL from the CMC point of view. No outstanding CMC deficiencies were identified at this time.

II. Summary of Quality Assessments

A. Product Overview

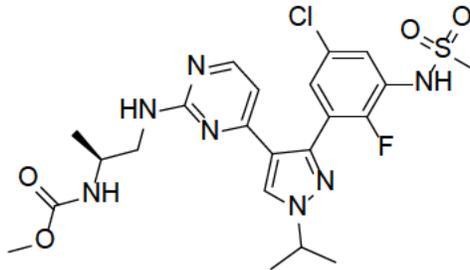
NDA 210496 was submitted as a 505(b)(1) NDA under the Federal Food, Drug and Cosmetic Act by Array Biopharma Inc. BRAFTOVI™ (Encorafenib) is being developed as a therapeutic agent to be administered orally in combination with MEKTOVI™ (Binimetinib, NDA 210498 currently under review) for the treatment of patients with *BRAF* V600 E or K mutation-positive unresectable or metastatic melanoma as detected by an FDA-approved test. The proposed recommended dose is 450 mg QD when administered in combination with binimetinib 45 mg BID.

Based on the information provided in this application, OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately

Proposed Indication(s) including Intended Patient Population	Indicated in combination with binimetinib for the treatment of patients with unresectable or metastatic melanoma
Duration of Treatment	Continue treatment until disease progression or occurrence of unacceptable toxicity
Maximum Daily Dose	450 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

1. Chemical Name or IUPAC Name/Structure: Methyl N-((2*S*)-1-[(4-{3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-(propan-2-yl)-1*H*-pyrazol-4-yl}pyrimidin-2-yl)amino]propan-2-yl} carbamate



Drug Substance

The drug substance, encorafenib is white to almost white powder. It has only one chiral center, exhibits only one stable crystalline polymorph, (b) (4) and is non-hygroscopic. Encorafenib drug substance has very low aqueous solubility that slightly improves under acidic pH of (b) (4). Encorafenib is an NME and the manufacturing process of encorafenib is (b) (4)

(b) (4)

The information provided for the control of critical steps and intermediate for the manufacture of encorafenib seems adequate to meet its specifications. The (b) (4) (b) (4) specified and unspecified impurities in the drug substance are controlled as per ICH Q3A limits. The (b) (4) is controlled as per ICHQ3A (R2) qualification threshold. The specified impurity, (b) (4). The in silico method indicated no structural alerts for this impurity. The LOQ of HPLC for this impurity is < (b) (4) % and the commercial batches have (b) (4) % of this impurity. The unspecified impurities are controlled in the encorafenib drug substance as per ICHQ3A(R2) identification threshold.

Encorafenib drug substance is packaged in (b) (4)

(b) (4)

(b) (4)

(b) (4) The stability data was acceptable and no undesirable trends were observed. The (b) (4) (b) (4) for encorafenib is (b) (4) RH, and the retest period is (b) (4) months.

Drug Product

Encorafenib drug product is an immediate release hard gelatin capsule for oral administration. Capsules are provided in two dosage strengths of 50 mg and 75 mg. The

50 mg capsule is size 0 with a (b) (4) orange opaque cap and flesh opaque body, printed with a stylized “A” on the cap and “LGX 50 mg” on the body. The 75 mg capsule is size 00 with a flesh colored opaque cap and white opaque body, printed with a stylized “A” on the cap and “LGX 75 mg” on the body.

The encorafenib capsule drug product formulations for both strengths include the following compendial excipients: copovidone, poloxamer 188, microcrystalline cellulose, succinic acid, crospovidone, colloidal silicon dioxide, and magnesium stearate. The levels of the excipients in the proposed drug product formulation are below the IIG database for the oral administration. The clinical trial formulation was same as the proposed formulation. Therefore, the levels of excipients in the proposed drug products are acceptable.

The primary commercial container closure systems consist of HDPE, (b) (4) bottles with (b) (4) cap, and 2 g desiccant soft packet. Bottle sizes are 325 cc (for 90 count 75 mg capsules) and 175 cc (for 60 count 50 mg capsules).

The drug product is labeled for storage at USP controlled room temperature. The provided stability data summarized above supports the above storage conditions in the working range of 20°C to 25°C with short term excursions down to 15°C and up to 30°C. The applicant proposed the initial shelf life of 15 months is acceptable based on the data provided in the application.

Process

The manufacturing process is composed of (b) (4)

A (b) (4) is used for production of both 50 mg and 75 mg strength encorafenib capsules. The batch formulae for a production scale batches of 50 mg strength capsules ((b) (4) capsule theoretical batch size) and 75 mg strength capsules ((b) (4) capsule theoretical batch size) is provided above.

Biopharmaceutics

Based on the provided dissolution data, the following dissolution method and the acceptance criterion are acceptable:

Method	USP II (Paddle) with a stainless steel cage sinker in 900 mL pH 4.5 Ammonium Acetate Buffer at 100 RPM
Acceptance Criterion	NLT (b) (4) % (Q) in 45minutes

No formulation bridging is needed, as the formulation of the proposed commercial BRAFTOVI Capsules, 50 mg is the same as the clinical batch. And the Applicant's biowaiver request of the proposed, Encorafenib Capsule, 75 mg is granted based on 21 CFR 320.22(b).

Facilities

This NDA included the following 10 sites:

- [REDACTED] (b) (4)
- Novartis Pharma (b) (4)

Adequate descriptions were provided for all sites. The Overall Manufacturing Inspection Recommendation is approval.

Environmental Assessment

The applicant has submitted a claim of categorical exclusion and the required statement of no extraordinary circumstances for encorafenib. The categorical exclusion cited at 21 CFR 25.31(b) is appropriate for the estimated amount of drug to be produced for direct use. Because this application contains a new molecular entity, James Laurenson from the CDER Environmental Team screened the categorical exclusion and noted that based on data from the applicant, the substance does not appear to be subject to FDA's 2016 guidance, *Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity*. The claim of categorical exclusion is acceptable.

C. Special Product Quality Labeling Recommendations

The labeling is reviewed and is acceptable from CMC perspective.

D. Final Risk Assessment (See Below)

Initial Risk Identification			Review Assessment		
Product 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 • Raw materials • Process parameters • Scale/equipment • Site 	L	Assessed during Development and Controlled via specification	Acceptable	Controls are in place
Physical stability (solid state)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	M	Assessed during Development and Controlled via specification	Acceptable	Controls are in place
Content Uniformity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	M	Assessed during Development and Controlled via specification	Acceptable	Controls are in place
Palatability	<ul style="list-style-type: none"> • Formulation • Excipient change • Process parameters • Scale/equipment • Site 	M	Assessed during Development and Controlled via specification	Acceptable	Controls are in place
Microbial Limits	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	L	Assessed during Development and Controlled via specification	Acceptable	Controls are in place
Dissolution – BCS class II & IV	<ul style="list-style-type: none"> • Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipments • Site 	M	Assessed during Development and Controlled via specification	Acceptable	Controls are in place



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Tiwari

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Post-Approval Stability Protocol and Commitment

Reviewer's Assessment:

R Regional Information

Environmental Analysis

Reviewer's Assessment: The applicant has submitted a claim of categorical exclusion and the required statement of no extraordinary circumstances for encorafenib. The categorical exclusion cited at 21 CFR 25.31(b) is appropriate for the estimated amount of drug to be produced for direct use. Because this application contains a new molecular entity, James Laursen from the CDER Environmental Team screened the categorical exclusion and noted that based on data from the applicant, the substance does not appear to be subject to FDA's 2016 guidance, *Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity*. **The claim of categorical exclusion is acceptable.**

Methods Verification Package

Reviewer's Assessment: The method verification package to assess the dissolution method in the specification for the drug product was requested on 9/29/2017. The final report was issued on 1/8/2018. The Division of Pharmaceutical Analysis (DPA) concluded that the dissolution test

method was able to discriminate

(b) (4)

(b) (4) for 50 mg Encorafenib capsules.

Comparability Protocols

Reviewer's Assessment:

Post-Approval Commitments

Reviewer's Assessment:

Lifecycle Management Considerations

Reviewer's Assessment:

List of Deficiencies

Primary Drug Product Reviewer Name and Date: Rohit V. Tiwari, Ph.D., February 9, 2018.

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Anamitro Banerjee, Ph.D., February 12, 2018



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LABELING

{For NDA Only}

I. Package Insert

1. Highlights of Prescribing Information

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

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

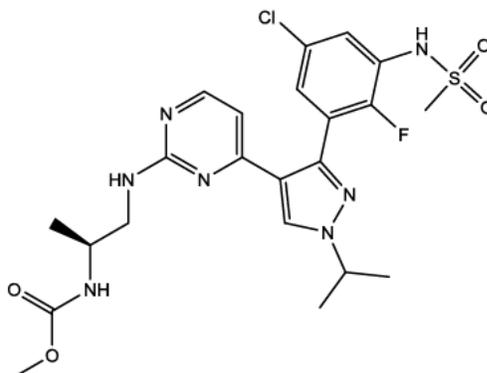
3. Section 3 Dosage Forms and Strengths

- 50 mg capsules: Orange/beige hard gelatin capsules with a stylized “A” printed on the cap and “LGX 50mg” printed on the body
- 75 mg capsules: Beige/white colored hard gelatin capsules with a stylized “A” printed on the cap and “LGX 75mg” printed on the body

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)	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Provided

4. Section 11 Description

- Encorafenib is a protein kinase inhibitor. The chemical name is methyl *N*-{(2*S*)-1-[(4-{3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-(propan-2-yl)-1*H*-pyrazol-4-yl}pyrimidin-2-yl)amino]propan-2-yl}carbamate. It has the molecular formula $C_{22}H_{27}ClFN_7O_4S$ and a molecular mass of 540.0. Encorafenib has the following chemical structure:



- Encorafenib is a white to almost white powder. It is slightly soluble in aqueous media at pH 1, very slightly soluble at pH 2, and insoluble at pH 3 and above.
- BRAFTOVI (encorafenib) capsules are available in 50 mg and 75 mg dosage strengths. The 50 mg strength capsules are size 0 orange/beige colored hard gelatin capsules with a stylized “A” printed on the cap and “LGX 50mg” printed on the body. The 75 mg strength capsules are size 00 beige/white colored hard gelatin capsules with a stylized “A” printed on the cap and “LGX 75mg” printed on the body. Each 50 mg strength capsule contains 50 mg encorafenib. Each 75 mg strength capsule contains 75 mg encorafenib.
- The inactive ingredients of BRAFTOVI are: **Capsule Fill:** copovidone, poloxamer 188, microcrystalline cellulose, succinic acid, crospovidone, colloidal silicon dioxide, magnesium stearate (vegetable origin). **Capsule Shell:** gelatin,

titanium dioxide, iron oxide red, iron oxide yellow, ferrosferric oxide, monogramming ink (pharmaceutical glaze, ferrosferric oxide, (b) (4) (b) (4) propylene glycol, (b) (4)).

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	Dosage form provided, route of administration not provided.
Active moiety expression of strength with equivalence statement (if applicable)	NA
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>)	NA
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

BRAFTOVI (encorafenib) is supplied as 50 and 75 mg capsules.

50 mg: Orange/beige colored hard gelatin capsules with a stylized “A” printed on the cap and “LGX 50mg” printed on the body, available in cartons containing two bottles of 60 capsules (NDC 72055-020 (b) (4))

75 mg: Beige/white colored hard gelatin capsules with a stylized “A” printed on the cap and “LGX 75mg” printed on the body, available in cartons containing two bottles of 90 capsules (NDC 72055- (b) (4))

Storage and Stability: Store at room temperature 20°C–25°C (68°F–77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

Distributed by:

Array BioPharma Inc.
 3200 Walnut Street
 Boulder, CO 80301

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)	NA
Storage conditions	Provided
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Provided

Reviewer’s Assessment of Package Insert: *Adequate with the following comment*

- The route of administration is not provided in this section. It is recommended that the route of administration may be included in Section 11.

II. Labels:

1. Container and Carton Labels

(b) (4)

2. Carton Label

(b) (4)



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	Provided
Dosage strength	Provided	Provided
Net contents	Provided	Provided
“Rx only” displayed prominently on the main panel	Provided	Provided
NDC number (21 CFR 207.35(b)(3)(i))	Provided	Provided
Lot number and expiration date (21 CFR 201.17)	Provided	NOT Provided
Storage conditions	Provided	Provided
Bar code (21CFR 201.25)	Provided	Provided
Name of manufacturer/distributor	Provided	Provided
And others, if space is available	Do not use if safety seal under cap is broken or missing. Dispense in original bottle.	Do not use if safety seal under cap is broken or missing. Dispense in original bottle.

Reviewer’s Assessment of Labels: *Inadequate*

➤ The encorafenib carton labels do not show expiration date or lot number.

List of Deficiencies:

The route of administration is not provided in this section. It is recommended that the route of administration may be included in Section 11.

The encorafenib carton labels do not show expiration date and lot numbers. This deficiency has been conveyed to the applicant.

Overall Assessment and Recommendation:

Approval pending on the update of the carton label.

Primary Labeling Reviewer Name and Date: Rohit V. Tiwari, Ph.D. 2/14/2018

Secondary Reviewer Name and Date: Anamitro Banerjee, Ph.D. 2/14/2018



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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: 210496-ORIG-1 (505(b)(1))

Drug Product Name / Strength: Encorafenib (BRAFTOVI) IR Capsules (hard gelatin), 50 and 75 mg

Route of Administration: Oral

Applicant Name: Array BioPharma Inc.

Review Summary:

BRAFTOVI (encorafenib) Capsules, 50 and 75 mg are indicated, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-Approved test. A reference is made to NDA (b) (4) (binimetinib tablets, 15 mg), which was submitted in parallel to the Division of Oncology Products 2 (DOP2).

The drug substance encorafenib, is a selective, reversible small molecule RAF kinase inhibitor which suppresses the RAF/MEK/ERK pathway in tumor cells expressing several mutated forms of BRAF kinase (V600E, D and K). The drug substance has one chiral center and only one stable crystalline anhydrous form, (b) (4) has been identified.

Encorafenib exhibits pH dependent solubility. BRAFTOVI is formulated using conventional/compendial excipients and manufactured (b) (4)

(b) (4)

Based on the provided dissolution data, the following dissolution method and the acceptance criterion are acceptable:

Method	USP II (Paddle) with a stainless steel cage sinker in 900 mL pH 4.5 Ammonium Acetate Buffer at 100 RPM
Acceptance Criterion	NLT (b) (4) % (Q) in 45minutes

No formulation bridging is needed, as the formulation of the proposed commercial BRAFTOVI Capsules, 50 mg is the same as the clinical batch. And the Applicant's biowaiver request of the proposed, Encorafenib Capsule, 75 mg is granted based on 21 CFR 320.22(b).

From the Biopharmaceutics perspective, NDA 210496 for encorafenib capsules, 50 and 75 mg is recommended for **APPROVAL**.

List of Submissions being reviewed:

Submissions Reviewed	Document Date
IND 113850 CMC Meeting Background Material	01/23/2017
NDA 210496 Original Submission	06/30/2017
IR Response	12/5/2017

BCS Designation

Reviewer's Assessment: Encorafenib is likely a BCS Class 2 (low solubility, high permeability) drug.

Drug Substance Solubility:

The aqueous solubility of encorafenib is pH dependent with a basic pK_{a1} of 4.49 and an acidic pK_{a2} of 7.21. The Applicant evaluated the solubility of encorafenib as shown in Table 1.

Table 1 Equilibrium Solubility of Encorafenib

FaSSIF v2
SGF (HCl 0.1N)

FeSSIF v2 = Fe
 FaSSIF v2 = Fe
 SGF = Simulat

The Applicant formulated encorafenib as an immediate release capsule

(b) (4)

(b) (4)

Permeability:

The Applicant examined the permeability and transporter interaction potential of encorafenib using an *in vitro* Caco-2 cell-based system. Encorafenib exhibits high intrinsic permeability (apical-to-basolateral permeability 71.5×10^{-5} cm/min) and the human ADME study (clinical study CLGX818A2101) demonstrated that the absolute bioavailability of encorafenib is \geq $\frac{(b)(4)}{(4)}\%$ following a single oral dose of 100 mg encorafenib drug substance $\frac{(b)(4)}{(b)(4)}$

Formulation:

The proposed drug product is an immediate release hard gelatin capsule for oral administration. Capsules are provided in two dosage strengths of 50 mg and 75 mg $\frac{(b)(4)}{(b)(4)}$

(b) (4)

Table 2 Qualitative / Quantitative Composition

(b) (4)			(b) (4)	(b) (4)
(b) (4)				
				(b) (4)
				(b) (4)

- d. Content
- e. the cap
- f. Quality

Dissolution Method and Acceptance Criteria

(b) (4)

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Dissolution Acceptance Criteria:

The Applicant proposed the dissolution acceptance criterion of NLT (b) (4) % in 45 minutes for the current proposed dissolution method.

Reviewer's Assessment:

No initial (release) data using the proposed dissolution method are available, as the Applicant analyzed the pivotal clinical study batches (b) (4) during pharmaceutical development. The Applicant reanalyzed the pivotal clinical batches, 50 mg (45-50 month) and 100 mg (24-45 month) using the proposed dissolution method. Based on the provided data of pivotal clinical batches (Appendix II and III) and registration batches (Appendix IV), the proposed dissolution acceptance criterion of NLT (b) (4) % (Q) in 45 minutes is accepted.

³ \\cdsesub1\evsprod\ind113850\0910\m1\us\pre-nda-cmc-meeting.pdf

Bridging of Formulations

N/A.

Encorafenib 50 mg and 100 mg strength capsules were used in the pivotal clinical study. The (b) (4) formulation used in the pivotal study (CMEK162B2301, CLGX818X2109 and CLGX818X2101) is the same formulation as the proposed commercial formulation.

Biowaiver Request

The Applicant used (b) (4) to manufacture capsule strengths of 10 mg, 25 mg, 50 mg, and 100 mg, for use during clinical development of encorafenib. The 50 mg and 100 mg strength capsules were used in the pivotal clinical studies (CMEK162B2301, CLGX818X2109 and CLGX818X2101). An additional 75 mg strength capsule was added using the proposed commercial (b) (4) and will be used as a proposed commercial formulation along with the 50 mg strength capsules.

Table 7 Unit Composition of Encorafenib Capsule Strengths Used in Clinical Studies and Proposed for Commercial Use

(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

The Applicant requests a biowaiver for the commercial 75 mg strength capsule in accordance with written responses by the Agency⁴. The Applicant conducted the comparative dissolution testing across the three strengths (i.e., 50, 75, and 100 mg) using the proposed dissolution method and calculated the similarity *f*₂ and difference *f*₁ factors.

⁴ IND 113850 DARRTS: COR-MEET-09 (Final written response), dated 04/26/2016

Figure 6. Comparative Dissolution Profiles (n=12) of 50 mg, 75 mg, and 100 mg Strength Encorafenib Capsules

u
Error

Table 8 Similarity Analysis of Dissolution Data

100 mg v.
Similarity
Differenc

Reviewer’s Assessment:

The biowaiver request for the proposed, Encorafenib Capsule, 75 mg is granted based on 21 CFR 320.22(b):

- The formulation of the 75 mg strength is (b) (4)
- Both 50 and 75 mg are the same dosage form, have the same release mechanism, and manufacturing process.
- Dissolution profile comparison between the strengths meets the f2 similarity requirements using the proposed dissolution method.

R Regional Information

Comparability Protocols: N/A

Lifecycle Management Considerations: N/A

Primary Biopharmaceutics Reviewer Name and Date: Zhuojun Zhao, 2/9/2018

Secondary Reviewer Name and Date: Okpo Eradiri, Ph.D. 2/13/2018

APPENDIX I: Biopharmaceutics Information Requests dated November 21, 2017 and Applicant’s Responses dated December 5, 2017

1. While a summary of the results of experiments conducted to validate the proposed dissolution method is in the NDA, a full validation report appears to be missing. Provide the dissolution method validation report or refer to its location of the report in the Application.
2. We acknowledge that you provided a SAS data file with individual vessel data for prevalidation, clinical, and registration/stability batches. As we requested in the Pre-NDA CMC meeting, please provide the complete dissolution profile data (individual, mean, SD, profiles) for those batches presented in graphical and tabular formats.

Please resubmit your data sets as shown in the example below:

Example - Reporting of individual vessel dissolution data

Cell A1 – Identifying Batch/Lot Label, and dissolution method/media used

	A	B	C	D	E	F	G	H	I	J
1	Test lot 12345 (QC method/QC media)									
2	Cell A2 – blank	1	2	4	6	8	10	12		Sampling Times (starting from cell B2 numerical values indicating collection times (minutes or hours))
3		3	15	62	98	99	99	98		Dissolution Data (starting from cell B3 numerical values indicating percent drug release)
4		3	15	64	94	92	95	95		
5		3	9	37	80	96	97	97		
6		4	13	44	79	97	98	99		
7		5	3	12	39	71	96	98		
8		6	3	14	60	98	97	99		
9		7	4	13	44	82	93	98		
10		8	5	22	89	97	98	97		
11		9	4	16	64	96	98	96		
12		10	4	14	57	98	96	99		
13		11	4	16	63	96	96	97		
14		12	6	22	87	96	93	96		
15										
16										
17										
18										
19										
20										
21										
22	Use one sheet for each unique batch/lot. Label accordingly in Cell A1									

Sheet1 Sheet2 Sheet3

3. The dissolution profiles of Encorafenib capsules, 75 mg, displayed in figure 8, Module 3.2.P.2.2 (rotation speed of 100 rpm) seem to be the same as those in figure 28 of the pre-NDA meeting briefing document (75 RPM; IND 113850). Please provide the related dissolution data and testing information (e.g. batch #, testing date, etc.) and clarify if the results are for the same batches of the proposed drug product.
4. If available, provide complete dissolution profile data for the prevalidation, clinical, and registration/stability batches using 1000 mL of pH 4.5 dissolution medium at a rotation speed of 75 rpm.

Provide justification for the use of a sinker in the proposed dissolution test and provide detailed information on the selected sinker.

Applicant’s Response to Biopharmaceutics-IR Comment 1:

Dissolution method validation report TTP-NQF-J0096.00 and supplemental validation report TTP-NQF-J0111.00 are provided with this response as appendices to NDA Section 3.2.P.5.3.

Reviewer Note:

The Applicant's response is satisfactory. The full dissolution method validation report is updated in [Appendix 1 and 2](#).

Applicant's Response to Biopharmaceutics-IR Comment 2:

The data are provided as an Excel workbook appendix to Section 3.2.P.5.6. During preparation of the Excel workbook a few data entry errors were discovered in the SAS data file. These have been corrected and the corrected file is also provided.

Reviewer Note:

The Applicant's response is satisfactory.

Applicant's Response to Biopharmaceutics-IR Comment 3:

The caption for Figure 8 in Section 3.2.P.2.2 is correct; the caption for Figure 28 in the pre-NDA briefing document is incorrect and should have read 100 RPM. With the exception of (b) (4) the method used is the same as the validated commercial method.

The drug product batch used to generate the dissolution profiles was 75 mg prevalidation batch 16JM-254 (see Section 3.2.P.5.4). The test dates were between 28 September 2016, when the analysis request was submitted, and 07 October 2016, when the laboratory report was approved.

The results in the pre-NDA briefing document and Section 3.2.P.2.2 are the same data set.

Reviewer Note:

The Applicant's clarification is satisfactory.

Applicant's Response to Biopharmaceutics-IR Comment 4:

The requested data are not available. The batches were tested using only the validated method (900 mL of pH 4.5 dissolution medium at a rotation speed of 100 rpm). (b) (4)

Reviewer Note:

The Applicant's response is satisfactory.

Applicant's Response to Biopharmaceutics-IR Comment 5:

Sinkers are used in the assay (b) (4)

(b) (4)

(b) (4)

Reviewer Note:

The Applicant's response is satisfactory.

APPENDIX II: Reanalysis of Pivotal Clinical Study Batch Samples: 50 mg Strength Batches⁵

(b) (4)

(b) (4)

(b) (4)

(b) (4)

⁵ \\cdsesub1\evsprod\nda210496\0017\m3\32-body-data\32p-drug-prod\encorafenib-50-mg-75-mg-hard-gelatin-capsule\32p5-contr-drug-prod\32p56-justif-spec\justification-of-specifications-dissolution-excel.xlsx

(b) (4)

(b) (4)

(b) (4)

Passes S2

APPENDIX III: Reanalysis of Pivotal Clinical Study Batch Samples: 100 mg Strength Batches⁵

(b) (4)

(b) (4)
Passes

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Passes :

APPENDIX IV: Encorafenib Primary Stability Batch Dissolution Profile Data⁶

Where anal.
Passes S2 t

⁶ \\cdsesub1\evsprod\nda210496\0017\m3\32-body-data\32p-drug-prod\encorafenib-50-mg-75-mg-hard-gelatin-capsule\32p5-contr-drug-prod\32p56-justif-spec\justification-of-specifications-dissolution-excel.xlsx



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Tiwari

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