CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212018Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval
Breakthrough Therapy Designation Granted

NDA 212018
Review #1

Drug Name/Dosage Form	Erdafitinib Tablets
Strength	3, 4, and 5 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Janssen Biotech Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	08/02/2018	Pre-submission
Quality Amendment 0002	08/30/2018	All
Quality Amendment 0008	10/04/2018	DP/Process
Quality Amendment 0013	10/31/2018	DP
Quality Amendment 0016	11/16/2018	DP
Quality Amendment 0022	12/03/2018	DP
Quality Amendment 0027	12/26/2018	DP/Biopharm
Quality Amendment 0032	01/17/2019	DS/DP/Process

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Sithamalli Chandramouli	CDER/OPQ/ONDP/DNDAPI
Drug Product	Xing Wang	CDER/OPQ/ONDP/DNDP1
Process	Steve Rhieu	CDER/OPQ/OPF/DPA1
Facility	Steve Rhieu	CDER/OPQ/OPF/DPA1
Biopharmaceutics	Joan Zhao	CDER/OPQ/ONDP/DB
Regulatory Business Process Manager	Kristine Leahy	CDER/OPQ/OPRO/DRBPMI

Application Technical Lead	Xiao Hong Chen	CDER/OPQ/ONDP/DNDP1
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental	Xing Wang	CDER/OPQ/ONDP

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)	Adequate	Jan. 30, 2019	DMF not reviewed since sufficient information is in the NDA and Per MAPP 5015.5 (Rev. 1)
	Type IV			Adequate	Jan. 30, 2019	DMF has been reviewed and found adequate.
	Type III			Adequate	Jan. 30, 2019	DMF not reviewed since sufficient information is in the NDA and Per MAPP 5015.5 (Rev. 1).
	Type III			Adequate	Jan. 30, 2019	DMF not reviewed since sufficient information is in the NDA and Per MAPP 5015.5 (Rev. 1).
	Type III			Adequate	Jan. 30, 2019	DMF not reviewed since sufficient information is in the NDA and Per MAPP 5015.5 (Rev. 1).
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	Type III			Adequate	Jan. 30, 2019	DMF not reviewed since sufficient

						information is in the NDA and Per MAPP 5015.5 (Rev. 1).

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	117490	Initial IND for Erdafitinib (b) (4) [redacted]

2. CONSULTS
N/A

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA 212018, Erdafitinib Tablets, is recommended for Approval from the product quality perspective. The product quality team reviewed full CMC information in the NDA including the manufacturing facilities, and they are deemed acceptable. There are no outstanding product quality issues for the NDA.

II. Summary of Quality Assessments

A. Product Overview

Erdafitinib is a small molecule NME drug to be orally administered to patients with erdafitinib for the treatment of patients with locally advanced or metastatic urothelial carcinoma. This indication is approved under accelerated approval based on tumor response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Initial IND 117490 for erdafitinib (b) (4) The drug received breakthrough designation during development (3/13/2018). The NDA for erdafitinib was submitted as rolling submission and was reviewed under priority review clock. The drug substance is manufactured by (b) (4) . Janssen stated that erdafitinib is a BCS class 1 compound based on the aqueous solubility and the maximum clinical dose even though the aqueous solubility is very low. The drug product is immediate release film-coated tablet for oral administration, containing 3 mg, 4 mg, or 5 mg of erdafitinib drug substance. The tablets are manufactured (b) (4) and film coating processes. The different strengths are dose proportional. The drug product has a 24 months expiration dating period.

Proposed Indication(s) including Intended Patient Population	BALVERSA is a tyrosine kinase inhibitor indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma, which has * susceptible FGFR 3 or 2 genetic alterations, and * progress during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for BALVERSA.
Duration of Treatment	Until disease progression or unacceptable toxicity occurs

Maximum Daily Dose	Recommended initial dosage: 8 mg orally once daily with up-titration to 9 mg daily if criteria are met.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance

Erdafitinib is a small molecule NME drug that is a fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor. It is a yellow powder, which melts at about 141°C. The drug substance is insoluble in some organic solvents and freely soluble in some other organic solvents. It is slightly soluble to insoluble in aqueous media over a wide range of pH values. The drug substance has 2 dissociation constants, a pKa1 of 9.2 (basic amine moiety) and a pKa2 of 1.9 (basic pyrazole moiety). The drug substance does not have any chiral centers. It does not exhibit polymorphism, (b) (4) It is non-hygroscopic and only adsorbs water to a level that results in <0.1% change in mass at 90% RH. Janssen stated, but not officially claimed, that Erdafitinib is a BCS class 1 compound based on the aqueous solubility and the maximum clinical dose even though the aqueous solubility is very low.

The drug substance is manufactured (b) (4) Designation of starting materials has been agreed upon at the CMC EOP-2 meeting. The synthesis route used to produce drug substance batches remained unchanged through development. The optimization of the process leads to the increased purity of the drug substance while the impurities formed during the manufacturing processes remained same. The impurity profile of the proposed commercial synthesis method has been characterized by (b) (4) . Based on the understanding of the impurity formation and purging capacity of the synthesis process, appropriate specifications have been established for starting materials and drug substance. In addition, acceptable ranges have been established for critical process parameters (CPPs). Process validation has been conducted including successfully completed the production of 3 consecutive full-scale drug substance batches at the commercial facility. The proposed drug substance specifications are found to be acceptable. The related substances limits are based on ICH Q3A guidelines and the level of the specified impurity has been qualified. The acceptance limits for residual solvents are based on ICH Q3C guidelines. Batch analysis data for a total of 10 batches (5 clinical and 5 commercial) conform to the specifications. Based on stability data, the proposed (b) (4) months retest date is deemed acceptable.

Drug Product

Erdafitinib drug product is supplied as a round biconvex shaped, immediate release, film-coated tablet for oral administration, containing 3 mg, 4 mg, or 5 mg of erdafitinib in 40 cc HDPE (high-density polyethylene) bottles with child-resistant (b) (4) closure with heat induction seal (HIS) liners. All the excipients used in the formulation are of USP/Ph. Eur./JP compendial grade materials. Erdafitinib is highly soluble at the highest proposed clinical dose of 9 mg per administration. The particle size of the drug substance may impact dissolution and content uniformity due to the low drug loading.

Particle size test is included in the drug substance specification to help control product quality and performance. Erdafitinib tablets are manufactured (b) (4) followed by film coating. The three strengths of the formulation are manufactured (b) (4) Other than differing in size, shape, and a small difference in the amount of film coat applied to the tablets, the three strengths are dose proportional.

The drug product specifications are proposed based on ICH guidelines and consist of appearance, identification, assay, degradation products, dissolution, uniformity of dosage units, and microbial limits. Based on the primary and supportive stability data, a shelf life of 24 months when stored at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F) is deemed acceptable.

Process

(b) (4)

Facility

(b) (4)

Biopharmaceutics

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. Based on the provided dissolution data, the dissolution method and the revised acceptance criterion are acceptable. The Applicant provided adequate dissolution data for all three strengths to support the bridging between the clinical batches and the proposed commercial drug product (change in debossing). Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 212018 for BALVERSA™ (erdafitinib) Tablets, 3 mg, 4 mg and 5 mg, is recommended for approval.

C. Special Product Quality Labeling Recommendations (NDA only)
N/A

D. Final Risk Assessment (see Attachment)

Application Technical Lead Name and Date:
Xiao Hong Chen, Ph.D.
14-February-2019

Attachment

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	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	(b) (4)	Acceptable	Controls are in place and continue stability monitoring post approval
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place
Content uniformity	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	H		Acceptable	Controls are in place
Microbial limits	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place. Continue stability monitoring post approval
Dissolution – BCS Class I & III	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place. Continue stability monitoring post approval

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

Xiao Chen

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BIOPHARMACEUTICS

Application No: NDA 212018-ORIG-1 [505(b)(1)]
Drug Product Name / Strength: BALVERSA™ (Erdafitinib) tablets, 3 mg, 4 mg and 5 mg
Route of Administration: Oral
Applicant Name: Janssen Biotech, Inc.
Biopharmaceutics Review Team:
Primary Reviewer: Zhuojun Zhao, PhD
Secondary Reviewer: Banu Zolnik, PhD

Product Background:
Erdafitinib (NME drug substance) is a selective and potent pan-FGFR tyrosine kinase inhibitor. The proposed BALVERSA™ tablets is an immediate releast film-coated tablets, to be orally adminstered to patients with locally advanced and metastatic urothelial carcinoma.

Review Summary:
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:
Based on the provided dissolution data, the following dissolution method and the revised acceptance criterion are acceptable and agreed upon:

Apparatus	Rotation Speed	Medium	Volume	Cumulative % of Drug Dissolved (Label Claim)
USP I (Basket)	75 RPM	0.01 N HCl (pH 2)	500 mL	NLT (b)(4)% (Q) at 30 minutes

Formulation Bridging:
The Applicant provided adequate dissolution data for all three strengths to support the bridging between the clinical batches and the proposed commercial drug product (change in debossing).

RECOMMENDATION:
Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 212018 for BALVERSA™ (erdafitinib) Tablets, 3 mg, 4 mg and 5 mg, is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

List of Submissions being reviewed:

Submissions Reviewed	Document Date
Original Submission	8/30/2018
IR Response	12/26/2018

I. Drug Substance

The Applicant only identified one form of the drug substance, Erdafitinib.

II. BCS Designation

The Applicant notes that the drug substance, Erdafitinib, behaves like a BCS Class 1 compound with high solubility and permeability at the highest proposed strength 5 mg. However, no BCS I designation is requested in the submission.

Drug Substance Solubility:

The Applicant provided the solubility of Erdafitinib over the physiologic pH range in Table 1.

Table 1. Solubility of Erdafitinib drug substance

Solvent	Solubility in Solution (g/100 mL)	pH of Solution	Descriptive Solubility[a]
Water	<0.001	7.7	Practically insoluble, or insoluble
0.1N HCl	0.23	1.1	Slightly soluble
0.01N HCl	0.073	1.9	Very slightly soluble
Citric acid-NaOH-HCl buffer pH 2	0.092	1.7	Very slightly soluble
Citric acid-NaOH buffer pH 5	0.037	5.3	Very slightly soluble
Phosphate buffer pH 7	0.65	7.4	Slightly soluble
Boric acid-KCl-NaOH buffer pH 9	0.001	9.0	Practically insoluble, or insoluble
Phosphate-NaOH buffer pH 12	<0.001	12.0	Practically insoluble, or insoluble
0.1N NaOH	<0.001	12.9	Practically insoluble, or insoluble

[a] Descriptive solubility according to USP and Ph. Eur. definitions

Permeability:

The Applicant provided the in vitro permeability of the drug substance in the Caco-2 cell line and MDCKII cell line as Papp A-to-B of 7.0×10^{-6} cm/s and 14.9×10^{-6} cm/s, respectively[1].

III. Formulation:

The proposed immediate-release BALVERSA™ (Erdafitinib) tablets are manufactured using (b) (4) film coating process.

Table 2 summarizes the qualitative and quantitative composition of the proposed Erdafitinib Tablets, 3 mg, 4 mg and 5 mg.

[1] \\cdsesub1\evsprod\nda212018\0002\m3\32-body-data\32s-drug-sub\erdafitnib-all\32s1-gen-info\general-properties.pdf

Table 2. Composition of the Proposed Erdafitinib Tablets

Component	Quality Reference[a]	Function	G023 (3-mg Film-Coated Tablet)		G024 (4-mg Film-Coated Tablet)		G025 (5-mg Film-Coated Tablet)	
			(mg/unit)	Theoretical % w/w	(mg/unit)	Theoretical % w/w	(mg/unit)	Theoretical % w/w
Tablet Core								
Erdafitinib	Company Standard	Active	3.00	(b) (4)	4.00	(b) (4)	5.00	(b) (4)
Mannitol	Ph. Eur./USP/JP							(b) (4)
Microcrystalline cellulose	Ph. Eur./NF/JP							
Meglumine	Ph. Eur./USP/JP							
Croscarmellose sodium	Ph. Eur./NF/JP							
Magnesium stearate[b]	Ph. Eur./NF/JP							
Core Tablet Weight:								
Film Coat								
Opadry® amb II (b) (4)	Company Standard							
Opadry® amb II	Company Standard							
Opadry® amb II	Company Standard							
(b) (4)	Ph. Eur./USP/JP							
Total Tablet Weight:								

[a] Where multiple compendia are listed, the compendium that is applied is specific to the applicable region of the submission.
[b] From vegetable source (b) (4)

NA: Not applicable

IV. Dissolution Method:

Table 3. lists the proposed commercial QC dissolution method as well as the dissolution method used in the early development.

(b) (4)

The Applicant provided the justification for the choice of dissolution apparatus, dissolution medium, and agitation speed in 3.2.P.2.2.3 Physicochemical and Biological Properties as detailed below:

1 Apparatus:

(b) (4)

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8. Dissolution Acceptance Criterion:

The Applicant proposed the dissolution acceptance criterion of Q(b) (4)% at 30 minutes using the proposed dissolution method. Based on the dissolution data as well as the Applicant's justification provided in Appendix I, the proposed acceptance criterion is acceptable.

9. Bridging of Formulations:

An overview of the formulations used across clinical studies is shown in Table 4.

The initial clinical formulation of erdafitinib was an oral solution (0.025 mg/mL (G001) and 0.5 mg/mL (G002 and G004)) which used in Studies EDI1001, EDI1002, and EDI1005. Then, capsule formulation (1 mg (G013) and 5 mg (G014)) for oral administration was used in Studies EDI1001 and GAC1001. The initial tablet formulation with Opadry® II (b) (4) (2 mg (G016), 3 mg (G017), 4 mg (G019), and 5 mg (G018)), was used in Studies EDI1002, EDI1003, GAC1001, and BLC2001.

[3] file://cdsesub1/evsprod/NDA212018/0004/m1/us/spl/8b28832f-8dee-4648-a88e-261f057a5d0e.xml#section-11.1

The final proposed commercial film-coated tablets, 3 mg (G023), 4 mg (G024), and 5 mg (G025) tablets, were used in studies EDI1004, EDI1006, EDI1007, and BLC2001.

Table 4. Overview of the Formulations used in Clinical Studies

G Number	Clinical Stage	Dosage Form	Dose	Remarks
G001	Phase 1	Oral solution	0.025 mg/mL	(b) (4)
G002	Phase 1	Oral solution	0.5 mg/mL	
G004	Phase 1	Oral solution	0.5 mg/mL	
G013[a]	Phase 1	Oral capsule	1 mg	
G014[a]	Phase 1	Oral capsule	5 mg	
G016[a]	Phase 1, 2	Film-coated tablet	2 mg	
G017[a]	Phase 1, 2	Film-coated tablet	3 mg	
G018[a]	Phase 1, 2	Film-coated tablet	5 mg	
G019[a]	Phase 1, 2	Film-coated tablet	4 mg	
G023[a]	Phase 1, 2, 3	Film-coated tablet	3 mg	
G024[a]	Phase 1, 2, 3	Film-coated tablet	4 mg	
G025[a]	Phase 1, 2, 3	Film-coated tablet	5 mg	

(b) (4)

During development and transfer to commercial scale at the commercial facility (from Johnson & Johnson Higi to Janssen Latina, Italy see **Error! Reference source not found.**), tablets debossed with corresponding strengths on both sides (the 3 mg, 4 mg, and 5 mg tablets were debossed with 3, 4, 5 , respectively). This embossing on the tooling was also used to manufacture the BLC2001 clinical batches and primary stability batches.

Table 5. Manufacturing Site and the Target Batch Size

(b) (4)

A change to the debossing (b) (4) of the tablet was introduced during the transfer to the commercial scale. Characterization batches were manufactured at commercial scale and the tablets (b) (4) of the tablet (the 3 mg, 4 mg and 5 mg tablets were debossed with 3, 4, and 5, respectively on one side and "EF" on the other side). The Applicant provided in vitro dissolution data

to bridge (1) the differences in manufacturing sites and scale used for the clinical BLC2001 batches and (2) the differences in debossing used for commercial production versus the primary stability/proposed clinical Phase 3/clinical BLC2001 batches.

Table 6. Relevant Manufacturing Information of Batches Used for Comparison towards Differences in Manufacturing Sites and Scale

Tablet Strength	DP Batch	Manufacturing Site	Scale (Tablets)	Commercial Debossment	Use
3-mg (G023)	HG-15J059	Higi	(b) (4)	No	Clinical BLC2001 trial
	HG-15L072	Higi		No	Clinical BLC2001 trial
	GCL30	Latina		No	Primary Stability, Clinical BLC2001 trial
4-mg (G024)	HG-15J061	Higi		No	Clinical BLC2001 trial
	HG-15L073	Higi		No	Clinical BLC2001 trial
	GCL27	Latina		No	Primary Stability, Clinical BLC2001 trial
5-mg (G025)	HG-15J063	Higi		No	Clinical BLC2001 trial
	HG-15L074	Higi		No	Clinical BLC2001 trial
	GCL1W	Latina		No	Primary Stability, Clinical BLC2001 trial

Higi = Johnson & Johnson Private Limited, Higi House, Opp. Ralli Wolf, L.B.S. Marg, Mulund (W), Mumbai (b) (4) India

Latina = Janssen-Cilag SpA, Via C. Janssen, Borgo S. Michele, 04100 Latina, Italy

The Applicant assessed the dissolution profiles of theses bathes using the proposed dissolution method (Table 6) towards differences in manufacturing sites and scale, as shown in Table 7.

(b) (4)

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10. Biowaiver Request:

The final proposed commercial film-coated tablets, 3 mg (G023), 4 mg (G024), and 5 mg (G025) tablets, were all used in clinical pharmacology studies (Phase 1) and in regimen 3 of the Phase 2 study BLC2001 (Table 4) and thus biowaiver request is not requested nor needed.

V. Regional Information

Comparability Protocols: N/A

Lifecycle Management Considerations: N/A

APPENDIX I: Biopharmaceutics Information Requests on December 17, 2018 and the Applicant's Response on December 26, 2018

Biopharmaceutics Request Comments:

Based on the dissolution data provided for the proposed Erdafitinib Tablets, 3, 4 and 5 mg, FDA recommends the dissolution acceptance criterion of Q= (b) (4)% at (b) (4) minutes. Be aware that setting of the dissolution acceptance criterion are based on stage 2 testing (n=12) and therefore sometimes stage 2 testing and occasional stage 3 testing maybe needed.

Applicant's Response to Biopharmaceutics-IR Comment:

Erdafitinib is a BCS class 1 drug. The current proposed single-point acceptance criterion of Q is (b) (4)% at 30 minutes is aligned with the FDA guidance, Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs.

The proposed dissolution method developed for the drug product is aligned with the FDA (b) (4)

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In conclusion, taking into account the available dissolution data and the biopharmaceutical risk assessment, the 75 rpm method, with an acceptance criterion of Q is (b) (4) at 30 minutes is deemed appropriate to ensure the release of, and the continuation of supply for, a quality drug product with the necessary in vivo performance.

Reviewer Note:
The Applicant's proposed dissolution acceptance criterion is found acceptable based on the following reasons:

1. (b) (4)
2. In vivo bioequivalence between the oral solution to oral dosage forms (tablet and capsule) in the BA studies EDI1002, EDI1003 and EDI1004, as discussed in Section IV.7.
3. Observed median of T_{max} of 2.5 hours (range: 2-6 hours)
4. Reported high solubility of Erdafitinib over the physiologic pH range at the highest strength of 5 mg
5. FDA draft guidance on Dissolution Testing and Specification Criteria for Immediate Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs.

The Applicant's response is satisfactory.

Zhuojun Zhao

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LABELING

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	BALVERSA (erdafitinib)
Dosage form, route of administration	tablets, for oral use
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Tablets: 3 mg, 4 mg, and 5 mg

2. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Tablets
Strengths: in metric system	3 mg, 4 mg, 5 mg
Active moiety expression of strength with equivalence statement (if applicable)	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	3 mg: Yellow, round biconvex (b) (4), film-coated, debossed with "3" on one side and "EF" on the other side. 4 mg: Orange, round biconvex (b) (4), film-coated, debossed with "4" on one side and "EF" on the other side. 5 mg: Brown, round biconvex (b) (4), film-coated, debossed with "5" on one side and "EF" on the other side.

3. *Section 11 Description*

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	BALVERSA erdafitinib
Dosage form and route of administration	Film-coated tablets for oral administration
Active moiety expression of strength with equivalence statement (if applicable)	N/A
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>)	Tablet Core: Croscarmellose sodium, Magnesium stearate (from vegetable source), Mannitol, Meglumine, and Microcrystalline Cellulose. Film Coating: (Opadry amb II): Glycerol monocaprylocaprate Type I, Polyvinyl alcohol-partially hydrolyzed, Sodium lauryl sulfate, Talc, Titanium dioxide, Iron oxide yellow, Iron oxide red (for the orange and brown tablets only), Ferrosoferric oxide/iron oxide black (for the brown tablets only).
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	(b) (4)FGFR3 tyrosine kinase inhibitor
Chemical name, structural formula, molecular weight	N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine $C_{25}H_{30}N_6O_2$ 446.56
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	Yellow powder. The drug substance is practically insoluble, or insoluble to freely soluble in organic solvents, and slightly soluble to practically insoluble, or insoluble in aqueous media over a wide range of pH values.

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

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	3 mg, 4 mg, 5 mg
Available units (e.g., bottles of 100 tablets)	3 mg tablets: bottle of 56 tablets, bottle of 84 tablets, two dose pack wallets of 28 tablets each in a box of 56 tablets, two dose pack wallets of 42 tablets each in a box of 84 tablets 4mg tablets: bottle of 28 tablets, bottle of 56 tablets, one starter pack wallet of 14 tablets in a box, one dose pack wallet of 28 tablets in a box, two dose pack wallets of 28 tablets each in a box of 56 tablets 5 mg tablets: bottle of 28 tablets, one dose pack wallet of 28 tablets in a box
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Identification of dosage forms refer to section 3 of the PI. NDC numbers are provided – refer to DMEPA review.
Special handling (e.g., protect from light)	N/A
Storage conditions	Store at 20°C-25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Product of Switzerland (b) (4) Manufactured for: Janssen Products, LP Horsham, PA 19044

Reviewer's Assessment of Package Insert: ***Adequate***
See IRs and Responses about country of origin in section below. CMC sections of PI have been found adequate after edits in the labeling meeting. Refer to the updated PI for those edits.

II. Labels:

(b) (4)

[redacted]

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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))	Balversa™ (erdafitinib) tablets	Balversa™ (erdafitinib) tablets
Dosage strength	3 mg, 4 mg, 5 mg	3 mg, 4 mg, 5 mg
Net contents	Yes	Yes
"Rx only" displayed prominently on the main panel	Yes	Yes
NDC number (21 CFR 207.35(b)(3)(i))	Yes	Yes
Lot number and expiration date (21 CFR 201.17)	Provided	Provided
Storage conditions	Store at 20°C-25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].	Store at 20°C-25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].
Bar code (21CFR 201.25)	Provided	Provided
Name of manufacturer/distributor	Provided	Provided
And others, if space is available	Take # of tablets once daily (inner and outer wallets)	# of tablets once day (box)

Reviewer's Assessment of Labels: ***Adequate***

Container and carton labels are considered adequate from CMC perspective after labeling edits during the labeling meeting. Refer to updated labels.

IR sent on 1/22/2019:

"Product of Switzerland" should be removed from all container and carton labels.

Applicant response received on 1/28/2019:

In accordance with 19 CFR Part 134.11 requires that every article of foreign origin (or its container) imported into the United States shall be marked with the country of origin. In order to comply with these regulations, "Product of Switzerland" should remain printed on all the packaging components.

Another IR was sent on 1/29/2019:

FDA does not agree to your response to Question #2 in A. General Comments dated on 01/28/2019. Drug labeling should follow 21 CFR 201.1 instead of 19 CFR Part

(b) (4)

Information and container and carton labels. The following statement is acceptable and consistent with 21 CFR 201.1:

(b) (4)

Manufactured for:
Janssen Products, LP
Horsham, PA 19044"

<u>Applicant response received on 2/4/2019:</u>

The applicant proposed the following change to fulfill both 21 CFR 201.1 and 19 CFR 134.11

Original text	Revised text
(b) (4)	Product of Switzerland Manufactured for: Janssen Products, LP Horsham, PA 19044

<u>Evaluation:</u> Acceptable per email from LCDR Jibril Abdus-Samad, PharmD, OPQ/OPPQ/DRGS/Compendial Operations and Standards Branch, dated on 2/5/2019, "Either of the Applicant's proposed labeling is acceptable as they fulfill both 21 CFR 201.1 and 19 CFR 134.11." The revised text is accepted.

List of Deficiencies: None

Overall Assessment and Recommendation: Adequate

Primary Labeling Reviewer Name and Date:

Xing Wang, Ph.D., Reviewer, ONDP/DNDPI/NDPBII

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

Anamitro Banerjee, Ph.D., Branch Chief, ONDP/DNDPI/NDPBII

Xing Wang

Digitally signed by Xing Wang
Date: 2/06/2019 01:18:49PM
GUID: 525daca300039122a4daaad45e49c6fb

Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 2/06/2019 01:22:53PM
GUID: 5075764700003844b7bc89632228509f

Xiao Chen

Digitally signed by Xiao Chen
Date: 2/15/2019 02:57:54PM
GUID: 508da7220002a138fcc70fbccbfd08bf