CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212526Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 212526

Review # 1

Drug Name/Dosage Form	**Alpelisib Film Coated Tablets**
Strength	**50 mg, 150 mg and 200 mg**
Route of Administration	**oral**
Rx/OTC Dispensed	**Rx**
Indication	**Treatment of postmenopausal women, and men, with hormone receptor positive, HER2-negative, advanced breast cancer**
Applicant	**Novartis**
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0000 (1)	*October 26, 2018*	*Facilities*
0001 (2)	*November 19, 2018*	*Labeling*
0004 (5)	*November 30, 2018*	*All CMC*
0006 (7)	*December 18, 2018*	*All CMC IR response*
0009 (10)	*January 11, 2019*	*IR response, all CMC*
0010 (11)	*January 11, 2019*	*IR response, Biopharmaceutics*
0011 (12)	*January 18, 2019*	*Labeling*
0016 (15)	*January 23, 2019*	*IR response, Process*
0017 (17)	*January 24, 2019*	*IR response, Biopharmaceutics*
0019 (19)	*January 31, 2019*	*IR response, Drug Product*
0026 (25)	*February 15, 2019*	*IR response, Process*
0028 (28)	*February 28, 2019*	*IR response, Process*
0029 (30)	*March 06, 2019*	*Labeling*
0030 (31)	*March 06, 2019*	*IR response, Biopharmaceutics, Drug Product*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Katherine Windsor	Suong T. Tran
Drug Product	Xing Wang	Xiaohong Chen
Process and Facility	Steve Rhieu	Dan Obrzut
Microbiology	NA	NA

Biopharmaceutics	Gerlie Gieser	Banu Zolnik
Regulatory Business Process Manager	Kristine Leahy	NA
Application Technical Lead	Anamitro Banerjee	NA
ORA Lead	NA	NA
Environmental	NA	NA

RELATED/SUPPORTING DOCUMENTS

DMFs:

DMF #	Type	Holder	Item Referenced	Status	Comments
(b) (4)	Type III		(b) (4)	Acceptable	Not reviewed for this NDA per ONDP policy
	Type III			Acceptable	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	119183	Alpelisib
IND	(b) (4)	Alpelisib

CONSULTS

None

OTHER

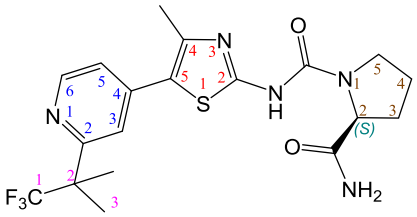
Refer to the full process review uploaded under NDA-212526-ORIG-1.

The Tables and Figures are numbered as per their eCTD locations.

Evaluation of the Quality Information

DRUG SUBSTANCE

The drug substance is a white to almost white powder that melts at ~208°C (by DSC) and is practically insoluble in water (0.02 mg/mL). Alpelisib is optically active with one stereocenter and shows pH dependent solubility: slightly soluble at pH 1 (3.42 mg/mL) to insoluble at pH 3 and up (<0.09 mg/mL). The applicant reports two pKa values of 3.3 and 9.4. Since the alpelisib is basic, these values are likely that of its conjugate acid. The drug substance is slightly hygroscopic (by DVS) and shows polymorphism (b) (4) and is used in the proposed product.



USAN: *Alpelisib*

(*S*)-*N*[1]-(4-methyl-5-(2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridin-4-yl)thiazol-2-yl)pyrrolidine-1,2-dicarboxamide

Chemical Formula: $C_{19}H_{22}F_3N_5O_2S$

Molecular Weight: 441.47

CAS# 1217486-61-7

The manufacturing process for the drug substance is shown below (b) (4)

(b) (4)

DRUG PRODUCT

The applicant is proposing 3 film coated tablets as immediate release dosage form for oral administration:

- 50 mg: Light pink, unscored, round and curved with beveled edges. Imprinted with L7 on one side and NVR on the other. 7.2 mm diameter.
- 150 mg: Pale red, unscored, ovaloid, and curved with beveled edges. Imprinted with UL7 on one side and NVR on the other. 14.2 mm length and 5.7 mm width.
- 200 mg: Light red, unscored, ovaloid, and curved with beveled edges. Imprinted with YL7 on one side and NVR on the other. 16.2 mm length and 6.5 mm width.

The film coated tablets (FCT) are primary packaged in blisters, which are further assembled in cardboard based packs.

Composition and Batch formula of the proposed alpelisib tablets are provided in the Table P.1 below. All excipients are compendial. (b) (4)

Table P.1: Composition and Batch Formula of the Alpelisib Film Coated Tablets

Ingredients	Amount per film-coated tablet (mg)			Batch Formula§ (kg)	Function	Reference to standards
	50 mg	150 mg	200 mg			
(b) (4)				(b) (4)	(b) (4)	
Alpelisib[1]	50.00	150.00	200.00			Novartis monograph
(b) (4)			(b) (4)			
Microcrystalline cellulose						← Ph. Eur., USP/NF, JP →
(b) (4)						
Mannitol, (b) (4)						
(b) (4)						
Sodium starch glycolate (b) (4)						
Hypromellose						
Magnesium stearate[2]						
(b) (4)						
Film-coating						
(b) (4)						Novartis monograph Ph. Eur., USP/NF, JP
Hypromellose						
Iron oxide, black (b) (4)						Regulation (EU) 231/2012[6], USP/NF, JPE
(b) (4)						
Macrogol 4000, Polyethylene glycol (PEG) 4000						Ph. Eur., USP/NF
Talc						Ph. Eur., USP/NF, JP

(b) (4)		(b) (4)			(b) (4)	Novartis monograph Ph. Eur., USP/NF, JP
Iron oxide, red (b) (4) (b) (4)						Regulation (EU) 231/2012 6, USP/NF, JPE Ph. Eur., USP/NF Ph. Eur., USP/NF, JP
(b) (4						Novartis monograph Ph. Eur., USP/NF, JP Ph. Eur., USP/NF Ph. Eur., USP/NF, JP
						Ph. Eur., USP/NF, JP
(b) (4)						
Total weight of film-coated tablet:	**127.00**	**376.00**	**500.00**			

[1] Alpelisib (b) (4)

(b) (4)

Formulations A, B and C (10 mg, 50 mg, and 200 mg strengths) were used in Phase 1 trial, while formulation D (50 mg, and 200 mg strengths) were used in the pivotal (Phase 3) clinical trials. The proposed commercial formulation E (b) (4)

The evaluation of bridging of the formulations D and E is on Page 22 below.

The drug product is manufactured by (b) (4)

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(b) (4)

Assessment of Microbiological Controls

Microbial tests performed for release of commercial batches	No
Microbial tests performed during stability for commercial batches	No
Raw material specifications are in line with USP<1111> or otherwise justified	Yes
(b) (4)	
Hold times and time limits are justified with microbial limits data	No
Stability results for the exhibit batches are available and adequate	Yes

Incoming excipients and the drug substance are subjected to microbial limit testing as per USP <61> and <62>. (b) (4) The risk posed to microbial burden on each manufacturing process is deemed mitigated based on the results of microbial enumeration test as per UPS <1111>. In addition, a full waiver of microbial testing for the proposed drug product is supported by historical data of batches manufactured at the Stein facility.

No novel or excipients of human or animal origin are used. (b) (4) All excipients are compendial. (b) (4) The applicant provided CoA for all the excipients.

(b) (4)

Drug product specifications for the alpelisib tablets provided in the testing monographs for each strength are summarized in the Table P.5.1 below.

Table P.5.1 Drug Product Specifications for Alpelisib Tablets

Test, principle	Specifications			Comments
	50 mg	150 mg	200 mg	
Properties				
Appearance by visual examination				
Shape	Round and curved film-coated tablet with beveled edges	Ovaloid and curved film-coated tablet with beveled edges	Ovaloid and curved film-coated tablet with beveled edges	Acceptable
Color	Light pink	Pale red	Light red	Colors are not significantly different. However, tablet size, shape and debossment can further differentiate different strengths.
Score	Unscored	Unscored	Unscored	
Debossment	'L7' on one side and 'NVR' on other side	'UL7' on one side and 'NVR' on other side	'YL7' on one side and 'NVR' on other side	Acceptable
Approximate size	Diameter: 7.2 mm	Length: 14.2 mm Width: 5.7 mm	Length: 16.2 mm Width: 6.5 mm	Acceptable
Mean mass	Target: (b) (4) mg Range: (b) (4)	Target: (b) (4) mg Range: (b) (4)	Target: (b) (4) mg Range: (b) (4)	Acceptable. Range (b) (4) (b) (4)
Identity				
Identity by UV	Corresponds to the reference	Corresponds to the reference	Corresponds to the reference	(b) (4)
Identity by HPLC	Corresponds to the reference	Corresponds to the reference	Corresponds to the reference	Acceptable
Purity				
(b) (4)				
Performance and test combinations				
Dissolution by UV	NLT (b) (4) % (Q value) after 30 minutes (b) (4)	NLT (b) (4) % (Q value) after 30 minutes (b) (4)	NLT (b) (4) % (Q value) after 30 minutes (b) (4)	Acceptable
Uniformity of dosage units by mass variation	Meets the requirements of Ph. Eur., USP and JP	Meets the requirements of Ph. Eur., USP and JP	Meets the requirements of Ph. Eur., USP and JP	Acceptable. Low risk as DS PSD is controlled and strengths are relatively high.

assay and degradation products by HPLC				
Assay by HPLC	(b) (4) % of the declared content	(b) (4) % of the declared content	(b) (4) % of the declared content	(b) (4), but acceptable
Degradation products, based on the declared content of Alpelisib by HPLC Each specified, identified (b) (4) Each unspecified Total degradation products	NMT (b) (4)% NMT % NMT % NMT %	NMT (b) (4)% NMT % NMT % NMT %	NMT (b) (4)% NMT % NMT % NMT %	(b) (4)

The applicant provided a description of all the analytical methods in the testing monograph. The ID, assay, and degradation method uses a gradient reverse phase HPLC (Agilent 1290 or equivalent) with UV detection at 315 nm. Sample chromatogram for the resolution solution for related substances for the 50 mg capsule is shown below. The related substances methods have adequate resolution for the impurities.
The applicant is proposing not to include microbiology specifications as stringent microbiological and manufacturing controls are in place.
The applicant provided risk assessment for elemental impurities per (b) (4)
The applicant evaluated the drug substance, the excipients, equipment used in manufacturing process, and the container closure. The applicant also screened three registration stability batches and three pre-validation batches manufactured in the proposed manufacturing sites (b) (4) Based on this data, the applicant is proposing not to test for elemental impurities in the drug product.

The applicant provided detailed validation report for each method:

- ID by UV: specificity and precision (repeatability and intermediate precision). Acceptable
- ID by HPLC: Specificity and peak purity. Acceptable.
- Assay and Related Substances: Specificity, Precision (repeatability and intermediate precision), linearity and range, accuracy, LOD (0.01%, calculated), LOQ (0.03%, calculated) Robustness, stability of solutions. In the response to IR submitted on 1/11/2019, the applicant provided a summary of changes made from (b) (4) through (b) (4) that confirms that the method revisions do not have impact on the method validation status. This is acceptable.
- Dissolution: Precision (repeatability and intermediate precision), linearity, specificity, filter check, accuracy, Robustness, stability of solutions.

- (b) (4)
- Microbial Enumeration Test:

(b) (4)

BCS Designation: The applicant considers alpelisib as a BCS II (low solubility, high permeability) drug substance. The pH-solubility profile data of alpelisib at 37°C is shown in Table 1-2 of the Section 3.2.S.1.3 in the submission dated November 30, 2018 shows solubility of 3.64 mg/mL at pH 1.0 (0.1N HCl) and 1.43 mg/mL at pH 1.1 (simulated gastric fluid). Solubility drops to less than 0.5 mg/mL at all higher pHs. Co-administered food significantly increases the oral bioavailability of alpelisib; thus, alpelisib tablets are recommended to be taken immediately following food intake.

Dissolution Method: (b) (4)

(b) (4)

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(b) (4)

[redacted]

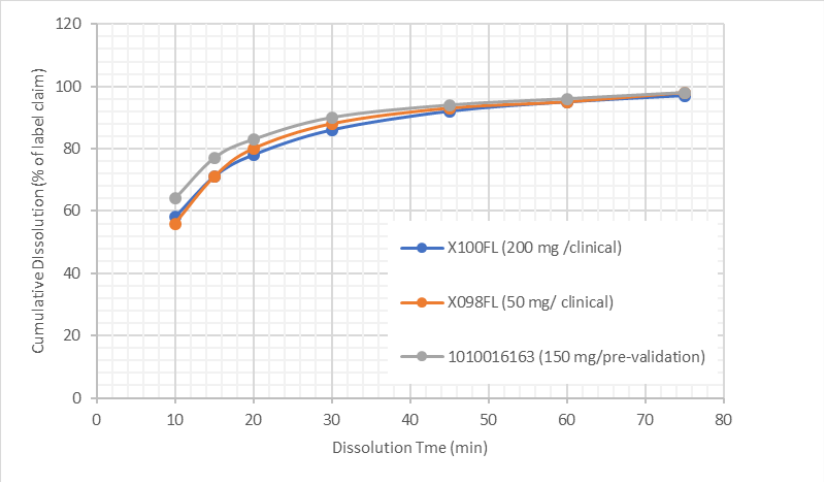
Dissolution Acceptance Criterion: The proposed dissolution acceptance criterion (Q (b) (4)% in 30 min) is reasonable based on the dissolution profile data provided for the

pre-validation and the commercial validation batches at Month 0 of stability testing, and representative Phase 3 clinical trial and registration stability lots.

Biowaiver Request: The applicant is seeking a waiver from conducting an in-vivo bioavailability studies in accordance with 21 CFR 320.22(d)(2) for 150 mg tablets based on comparability with the highest strength (200 mg).

Per 21 CFR 320.22(d)(2), the applicant's request to waive the requirement to conduct an *in vivo* bioavailability/bioequivalence study for 150 mg tablets is GRANTED based on evidence of: (1) compositional proportionality with the final to-be-marketed 50 mg and 200 mg strengths (b) (4) and (2) comparable in vitro dissolution profiles with the 200 mg tablets (which are evaluated in the pivotal clinical trial and the pre-validation/proposed commercial tablets, when tested in the proposed QC dissolution medium (Figure P.2.3). Additionally, the applicant indicated that linear PK was observed across the dose range of 30 to 450 mg under fed conditions. The proposed clinical dosage for the treatment of breast cancer is 300 mg once daily (with dose adjustment in 50 mg increments to 250 mg or 200 mg once daily); therefore, the proposed commercialization of the 150 mg strength (b) (4)

Figure P.2.3. Dissolution Profiles of the Three Strengths of Alpelisib Tablets



Bridging to the Proposed To-Be-Marketed Drug Product: The alpelisib drug product formulation and manufacturing process were optimized after the initiation of the Phase III program (b) (4)

Formulation D (50 mg and 200 mg strengths) was used in the pivotal Phase 3 clinical study (C2301; SOLAR-1), as well as in Phase 1 clinical pharmacology studies in healthy subjects and in subjects with cancer (Studies A2103 [food-effect & ranitidine DDI], A2105 and Z2102 (PK in hepatic impairment, and dose-finding study) whereas Formulation E was used for the registration stability, pre-validation and validation batches and for the proposed commercial tablet. For the detailed comparison of Formulations D and E, refer to Table 1-6 of Section 3.2.P.2.7.1 Summary of

Biopharmaceutic Studies. Figure P.2.4 shows that the in vitro dissolution profiles of the pivotal clinical trial lots and the pre-validation lots are comparable for both 50 mg and 100 mg strengths in various pH media without surfactant and in the proposed QC dissolution medium. Although, there are differences in the API manufacturing sites and processes used during drug product development, the dissolution profiles are comparable. Based on the Applicant's GastroPlus® PBPK modeling, Formulations D and E are expected to be bioequivalent; however, as *in vitro* dissolution comparisons successfully bridged the pre-change to the post-change drug products, a thorough FDA review of the modeling results was not performed. FDA informed the applicant that any future biopharmaceutics application of the PBPK modeling can be submitted to the IND if the applicant wishes to use this model for a post approval change.
Although PK data are available to bridge the previous formulations (A, B, and C) to Formulation D. See Table 1-4 of 2.7.1 Summary of Biopharmaceutic Studies for the comparison of the compositions of these various developmental formulations, the evaluation of this study is not needed to support the approval, and therefore not reviewed. Per the applicant, based on inter-study comparison, there were no major differences in the overall PK of the different formulations given at the same or similar doses.

Figure P.2.4: Comparative Dissolution Profiles of Pre-Validation (Proposed Commercial) Drug Product Lots versus Phase 3 Clinical Lots (in various media)

The applicant provided historical batch data for all the batches used in clinical and toxicological studies through the development of this product. In this review, the registration batches manufactured using three different drug substance lots for each strength are evaluated. The registration batches are (b) (4) units for 50 mg, (b) (4) units for 150 mg, and (b) (4) units for 200 mg scale.
The batch release data for registration batches show minimal impurities (Total impurities (b) (4)%) and consistent assay for all strengths. A brief summary of certain CQAs for registration lots are shown in the Table P.5.4 below.

Table P.5.4: Observed Assay and Total Impurities for Alpelisib Drug Product Registration Lots

	Assay			Total Impurities		
	50 mg	150 mg	200 mg	50 mg	150 mg	200 mg
Proposed Specifications						(b) (4)
Ranges Reported						

Alpelisib 50 mg, 150 mg, and 200 mg film coated tablets are packaged in (b) (4) blisters and Aluminum Foil (b) (4) blister backing component. The applicant provided specifications for the components, indicated that they conform to relevant CFRs and provided LOA for the supplier DMFs. Per MAPP 5015.5 (Rev. 1), DMF are not reviewed since sufficient information is provided in the NDA. Based on the information provided in the Section 1.14.1.1 of the NDA (Draft Carton and Container Labels), the packaging is (b) (4)

Stability Study on Drug Product:
Photostability per ICH Q1B (1.2 million lux hours, 200 Watts/m^2 UV): Appears to be stable. No changes observed.
Open Petri Dish: No changes observed.
Freeze-Thaw Testing (-20 °C for 6 days then 1 day 25°C/60%RH): No effect observed.

Stability data for registration batches is summarized below.
Freezer Conditions (-20 °C/ambient RH): 6 months data for 1 batch for each strength. Total degradants (b) (4)%. Small decrease in assay (b) (4)% change. No OOS result.
Refrigerated Conditions (5 °C/ambient RH): 12 months data for 3 batches for each strength. Total degradants (b) (4)%. Minor decrease in assay (b) (4)% change. No OOS result. Crushing strength appears to slightly decrease over time for some batches.
Long Term Storage Conditions (25 °C/60% RH): 12 months data for 3 batches for each strength. Total degradants (b) (4)%. Minor decrease in assay (b) (4)% change. No OOS result. Crushing strength appears to slightly decrease over time for some batches.
Intermediate Storage Conditions (30 °C/75% RH): 12 months data for 3 batches for each strength at timepoints. Total degradants (b) (4)%. No trends or OOS results. Crushing strength appears to slightly decrease over time for some batches.
Accelerated Storage Conditions (40 °C/75% RH): 6 months data for 3 batches for each strength. Up to about (b) (4)% variability in assay observed. (b) (4)% of the impurity (b) (4) at 6 months. No OOS results. Crushing strength appears to slightly decrease over time for some batches.
50 °C/75% RH: 3 months data for 1 batch for each strength. About (b) (4)% variability in assay observed. (b) (4)% of the impurity (b) (4) at 6 months. No OOS results. Crushing strength appears to slightly decrease over time for some batches.
Dissolution on Stability: Up to 18 months of long-term (25 °C/60%RH) and up to 6 months of accelerated (40 °C/75%RH) stability data are available for Clinical trial lots X098FL (50 mg), X100FL (200 mg), and X101FL (200 mg), as well as the registration stability lots. The final QC dissolution method (b) (4) was used for QC testing starting at the 12 month long-term stability time point. Based on the

initial and 12, and 18 month long-term stability data, there were no trends in the dissolution data of the registration stability lots of all three strengths of the proposed generic drug product.
The applicant provided standard stability commitment. The protocol is shown below (Table P.8).

Table P.8: Testing Plan for Stability Commitment Program

Code	Storage conditions	Test times [months]										
		0	1	3	6	9	12	18	24	36	48	60
F_1	- 20°C/ambient RH	-	-	-	X	-	-	-	-	-	-	-
	5°C/ambient RH	-	-	X	X	X	X	[X]	[X]	[X]	[X]	[X]
	25°C/60% RH	X	-	X	X	X	X	X	X	X	[X]	[X]
	30°C/65% RH [2]	-	-	[X]	[X]	[X]	[X]	-	[X]	[X]	-	-
	30°C/75% RH [4]	-	-	X	X	X	X	X	X	X	[X]	[X]
	40°C/75% RH	-	X	X	X	-	-	-	-	-	-	-
	50°C/75% RH [3]	-	X	X[5]	-	-	-	-	-	-	-	-
F_2	5°C/ambient RH	-	-	X	X	X	X	[X]	[X]	[X]	[X]	[X]
	25°C/60% RH	X	-	X	X	X	X	X	X	X	[X]	[X]
	30°C/65% RH [2]	-	-	[X]	[X]	[X]	[X]	-	[X]	[X]	-	-
	30°C/75% RH [4]	-	-	X	X	X	X	X	X	X	[X]	[X]
	40°C/75% RH	-	X	X	X	-	-	-	-	-	-	-

[ ] Optional testing
X Mandatory and denotes the tests to be performed as defined in Table 3-1. (Quality characteristics tested)
[2] ICH intermediate condition, only tested if significant change is observed at 30°C/75% RH and 40°C/75% RH.
[3] Stress testing at 50°C/75% RH performed to collect supportive data for the evaluation of possible transport excursions.
[4] For climatic zones I and II, data from 30°C/75% RH are used as ICH intermediate condition if significant change is observed at 40°C/75% RH
- Not tested
[5] Analyzed due to an OOE at 1M time point

The applicant is proposing an expiration dating period of 24 months for the drug product packaged in the proposed commercial package when stored between 20 °C and 25 °C (68 °F to 77 °F) with excursions permitted between 15 °C and 30°C (59 °F to 86 °F). Based on the submitted stability data it may be granted.

FACILITIES

Drug substance manufacturing, packaging and testing facilities are listed below:

Site/address	FEI	Responsibility	Recommendation
(b) (4)			Acceptable based on profile.
			Acceptable based on profile.

	(b) (4)	
(b) (4)	Testing of X-ray diffraction and microbial enumeration tests (release and stability) if drug substance	Acceptable based on profile.
	Drug substance particle size and all stability testing except microbial enumeration tests	Acceptable based on profile.

Drug product manufacturing, packaging and testing facilities are listed below:

Site/address	FEI	Responsibility	Recommendation
Novartis Pharma Stein AG, Schaffhauserstrasse, 4332 Stein, Switzerland	3002653483	Manufacturing and testing of drug product. In-process testing. Excipient testing.	Acceptable based on profile.
(b) (4)		Excipient testing	No evaluation necessary
		Excipient testing	No evaluation necessary
		Stability testing of the drug product	Acceptable based on profile.
		Primary and secondary packaging and stability testing of the drug product	Acceptable based on profile.
		Secondary packaging of the drug product	No evaluation necessary

Environmental Analysis

The applicant has submitted a claim of categorical exclusion. The categorical exclusion cited at 21 CFR 25.31(b) is appropriate for the estimated amount of drug to be produced

for direct use. A statement of no extraordinary circumstances has been submitted. The claim of categorical exclusion is acceptable.

LABELING

Refer to the EDR and the DMEPA reviews for the most recent USPI and Carton Container label.
The adequacy of the USPI is currently being evaluated by the clinical division.

HIGHLIGHTS: The proprietary name has been found acceptable by DMEPA. The CMC content and formatting of the highlights section is adequate: PIQRAY^{TM}(alpelisib) tablets, for oral use, and all the three tablet strengths are listed.

FULL PRESCRIBING INFORMATION:
Section 3: Adequate description of all the three tablet strengths consistent with the proposed specifications provided.
Section 11: Description of the drug substance ("white to almost white powder"), molecular formula, weight, and structure provided. A description of the three strengths of the tablets along with a listing of all the excipients provided.
Section 16: After edits, description of all the configurations are found adequate. The applicant provided statement on storage between 20°C and 25 °C with permitted excursions but did not mention "USP storage conditions", but was added during labeling review.

Included name and address of the distributor: Novartis Pharmaceuticals Corporation.

Final Risk Assessments

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/equipment • Site	L	(b) (4)	L	
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		L	
Dosing accuracy	• Dosing device • Formulation • Process Parameters • Scale/equipment • Site	M		L	
Palatability	• Formulation • Excipient change • Process parameters • Scale/equipment • Site	M		L	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		L	
Leachables	• Formulation • Container closure • Process parameters • Scale/equipment • Site	N/A		L	
Dissolution	• Raw Materials • Formulation • Container closure • Process parameters • Scale/equipment • Site	M		L	(b) (4)

Recommendation Page

Drug Substance: Approval

Primary Reviewer: Katherine Windsor Date: 03/07/2019
Secondary Reviewer: Suong T. Tran Date: 03/07/2019

Drug Product: Approval

Primary Reviewer: Xing Wang Date: 01/31/2019
Secondary Reviewer: Xiao Hong Chen Date: 01/31/2019

Process and Facility: Approval

Primary Reviewer: Steve Rhieu Date: 02/20/2019
Secondary Reviewer: Daniel L. Obrzut Date: 02/20/2019

Biopharmaceutics: Approval

Primary Reviewer: Gerlie Gieser Date: 3/18/2019
Secondary Reviewer: Banu Zolnik Date: 3/18/2019

Application Technical Lead: Approval

Anamitro Banerjee Date: 03/18/2019

Katherine Windsor

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Su (Suong) Tran

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Xing Wang

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Xiao Chen

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Steve Rhieu

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Daniel Obrzut

Digitally signed by Daniel Obrzut
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Gerlie Gieser

Digitally signed by Gerlie Gieser
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Banu Zolnik

Digitally signed by Banu Zolnik
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Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 3/20/2019 03:04:07PM
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