

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211155Orig1s000

211155Orig2s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

**NDA 211155
Review #1**

Drug Name/Dosage Form	COPIKTRA (duvelisib) Capsules
Strength	15 and 25 mg
Route of Administration	Oral
Rx/OTC Dispensed	R _x
Applicant	Verastem, Inc.
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	05-Feb-18	All
Amendment (SD 0018)	23-Feb-18	DP
Amendment (SD 0022)	19-Apr-18	DP
Amendment (SD 0025)	30-Apr-18	DP
Amendment (SD 0031)	24-May-18	Process, Biopharm
Amendment (SD 0037)	12-Jun-18	Process, Biopharm
Amendment (SD 0039)	21-Jun-18	Process
Amendment (SD 0040)	21-Jun-18	DP
Amendment (SD 0041)	25-Jun-18	Process
Amendment (SD 0052)	29-Aug-18	Process, Biopharm, DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Rajan Pragani	Charles Jewel
Drug Product	Xing Wang	Anamitro Banerjee
Process	Zhaoyang Meng	Rakhi Shah
Microbiology	n/a	n/a
Facility	Zhaoyang Meng	Zhihao Peter Qiu
Biopharmaceutics	Yang Zhao	Banu Zolnik
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a



QUALITY ASSESSMENT



Laboratory (OTR)	n/a	n/a
Environmental	Xing Wang	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	n/a	No Review	Adequate information provided in the NDA
	Type III		n/a	No Review	Adequate information provided in the NDA	
	Type III		n/a	No Review	Adequate information provided in the NDA	
	Type III		n/a	No Review	Adequate information provided in the NDA	
	Type III		n/a	No Review	Adequate information provided in the NDA	
	Type III		n/a	No Review	Adequate information provided in the NDA	
	Type III		n/a	No Review	Adequate information provided in the NDA	
	Type III		n/a	No Review	Adequate information provided in the NDA	
	Type III		n/a	No Review	Adequate information provided in the NDA	
	Type III		n/a	No Review	Adequate information provided in the NDA	
	Type III		n/a	No Review	Adequate information provided in the NDA	

(b) (4)	Type IV	(b) (4)	n/a	No Review	NDA
					Adequate information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	112486	duvelisib development

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of NDA 211155 for COPIKTRA (duvelisib) Capsules 25 and 15 mg. As part of this action, OPQ grants a (b) (4)-month re-test period for the drug substance when stored between (b) (4). Additionally, OPQ grants a 36-month expiration period for the 25 mg drug product and a 24-month expiration period for the 15 mg drug product when stored at “20°C to 25°C (68°F to 77°F) excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]. There are no outstanding issues and no post-approval quality agreements to be conveyed to the applicant.

II. Summary of Quality Assessments

A. Product Overview

NDA 211155 was originally submitted for COPIKTRA (duvelisib) Capsules 25, 15 (b) (4) mg in accordance with section 505(b)(1) of the Food, Drug and Cosmetic Act. (b) (4)
(b) (4)

(b) (4) Duvelisib is a twice daily, orally bioavailable, small-molecule, dual kinase inhibitor of phosphatidylinositol 3-kinases PI3K- δ and PI3K- γ indicated for the treatment of patients with Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Leukemia (SLL) (b) (4) and for the treatment of patients with Follicular B-cell non-Hodgkin lymphoma (FL) who have received at least two prior therapies. Duvelisib is an NME which was originally investigated under IND 112486. Duvelisib was granted orphan and fast-track drug designation for both indications (CLL/SLL and FL). Accelerated approval of NDA 211155 was granted for FL based on overall response rate.

Duvelisib is a small chiral molecule that is classified as a BCS class 4 compound. It has one stereogenic center and is manufactured (b) (4)

The drug product, COPIKTRA Capsules, is presented as 25, 15 (b) (4)-mg, immediate-release solid oral dosage form containing the duvelisib, microcrystalline cellulose, colloidal silicon dioxide, crospovidone and magnesium stearate. The 25 mg capsule is presented as opaque, (b) (4) capsules with white body and a Swedish Orange cap, with “duv 25 mg” printed in black ink on the body. The 15 mg capsule is presented as opaque, pink, (b) (4) capsules with “duv 15 mg” printed in black ink on the body.

The recommended dosing regimen for COPIKTRA Capsules is 25 mg orally twice daily (b) (4)

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 211155 and grants a ^(b)₍₄₎ month re-test period for the drug substance, a 36-month expiration period for the 25 mg and a 24 month expiration period for 15 mg drug product when stored at USP controlled room temperature in the proposed commercial packaging.

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of patients with CLL/SLL, ^(b) ₍₄₎ Indicated for the treatment of patients with FL who have received at least two prior therapies.
Duration of Treatment	^(b) ₍₄₎
Maximum Daily Dose	50 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

Duvelisib is a small chiral molecule that is classified as a BCS class 4 compound. It is a white to off-white non-hygroscopic crystalline solid that is practically insoluble in water, sparingly soluble in methanol and soluble in ethanol and isopropanol. Duvelisib has one stereogenic center and is manufactured ^(b)₍₄₎ as the S enantiomer ^(b)₍₄₎. It is manufactured ^(b)₍₄₎

The applicant includes specifications and suppliers for the regulatory starting materials as well as a detailed description of CPPs and IPCs and controls for all CQAs.

Batches used in the clinical, nonclinical, and stability studies were manufactured using 2 different processes (processes I and II). Process I was used to manufacture batches supporting early development toxicology studies. Process II was used to manufacture duvelisib drug substance for use in clinical and nonclinical studies. Process II is further divided into processes IIa through IIf. Processes IIa-IIf reflect operational changes. The drug substance manufacturing process is described in sufficient detail to clearly delineate how impurities are formed, how changes in the process could potentially affect the formation, fate, and purge of impurities and why the proposed control strategy is suitable for the drug substance manufacturing process.

^(b)₍₄₎

(b) (4)

The drug substance will be packaged and stored in (b) (4) which meet the requirements of 21 CFR 177.1520 and EU Regulation 10/2011. (b) (4)

(b) (4)

Specifications and acceptance criteria for the drug substance are consistent with ICH Q6A. The reviewer notes that the originally proposed particle size specification was (b) (4) The particle size specification was a contentious issue for the drug substance, biopharm, drug product and process reviewers throughout the review cycle. During the review cycle the D90 particle size specification was revised to (b) (4) μm based on a request by the biopharmaceutics reviewer. This revision was ultimately considered acceptable by all product quality reviewers.

The proposed specifications and acceptance criteria were deemed adequate to ensure the quality of the drug substance as it relates to the safety and efficacy of the drug product. All analytical methods are described in adequate detail and are appropriate for their intended use. All validation parameters (system suitability and system precision, specificity, linearity, range, precision, accuracy, ruggedness, robustness, and stability of solutions) are provided in the NDA.

The applicant included 36 month of long term stability data for the 3 primary batches and 18 months of long term stability data for 3 validation batches of the drug substance. The batches were manufactured at the commercial site according to the commercial process and packaged (b) (4)

The stability data for the registration batches demonstrated no notable changes after up to 36 months under long term storage condition. The applicant requested (b) (4) month retest for drug substance when stored between (b) (4) Based on the long term and accelerated stability data, forced degradation studies and stress testing data for the drug substance submitted in this application, the proposed retest of (b) (4) months for the drug substance when stored between (b) (4) is acceptable.

NDA 211155 is recommended for approval from a drug substance perspective.

Drug Product and Process

The drug product, COPIKTRA Capsules, is presented as 25 and 15 mg, (b) (4) gelatin capsule containing the active (duvelisib), microcrystalline cellulose, colloidal silicon dioxide, crospovidone and magnesium stearate. The 25 mg capsule is presented as opaque, (b) (4) capsules with white body and a Swedish Orange cap, with “duv 25 mg” printed in black ink on the body. The 15 mg capsule is presented as opaque, pink, (b) (4) capsules with “duv 15 mg” printed in black ink on the body. All excipients are compendial, commonly used in solid oral dosage forms and demonstrate good compatibility with the drug substance.

The formulation of 15 mg capsule is identical to that of the 25 mg capsule with the only difference being in the capsule fill weight. (b) (4)

(b) (4)

The QTPP was defined and the CQAs were identified. CQAs for the drug product include assay, content uniformity and dissolution.

The drug product is manufactured by (b) (4) at a commercial batch size (b) (4) for both the 25 and 15 mg capsules. The (b) (4) commercial batch of the 25 and 15 capsules translates to (b) (4), respectively. The drug product

(b) (4) The manufacturing process involves (b) (4)

(b) (4) The proposed process parameters and (b) (4) controls were described in sufficient detail and justified. The applicant demonstrated the suitability of the manufacturing process for the drug product at commercial scale. The description of the manufacturing process includes appropriate (b) (4) controls and operating parameters.

The 25 and 15 mg strengths will be packaged in HDPE bottles and in blisters. The commercial bottle packaging is a (b) (4) HDPE container with a (b) (4) cap. The bottles are sealed with

(b) (4). The commercial blister packaging is a (b) (4) blister card. Each blister card contains two rows of 14 capsules to a total of 28. Each carton contains 2 cards corresponding to a total of 56 capsules

The drug product specifications included appearance, identification, assay, content uniformity, individual and total degradants, (b) (4) dissolution, and microbial limits. The drug product specifications are consistent with ICH Q6A and are based on batch analyses and stability data. The drug product specifications provide adequate controls to ensure the quality of the drug product throughout the product expiry. The proposed specification and acceptance criteria for the drug product, together with controls for impurities in the drug substance are adequate to ensure that the critical quality attributes of this product are well controlled.

In support of the proposed 36-month expiry for the 25 drug product, the applicant provided 24 months of primary stability data for three pilot scale batches of the 25 drug product. In support of the proposed 24 month expiry for 15 mg drug product, the applicant provided 12 months of primary stability data for three pilot scale batches of the 15 mg drug product. All batches were manufactured according to the commercial process and packaged in the proposed commercial packaging. The samples were stored under the long-term (30°C/65% RH) and accelerated (40°C/75% RH) conditions.

The applicant completed a bulk hold study, photostability, and forced degradation studies for the drug product. The stability studies were executed in accordance with the ICH 1A and Q1B. No significant changes were observed in description, assay, or degradation products under any storage condition. While the (b) (4) increased slightly under some storage conditions, all results remained within the proposed acceptance criteria.

The available stability data shows consistency over time and support the proposed expiry. Based on the 24 months of stability data included in this application for the 25 capsule, Verastem, Inc. proposed and the FDA accepts the expiration dating period of **36 months** for the 25 mg drug product when stored at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Based on the 12 months of stability data included in this application for the 15 mg capsules, Verastem, Inc. proposed and the FDA accepts the expiration dating period of **24 months** for the 15 mg drug product when stored at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

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

Biopharmaceutics

The biopharmaceutics review focused on (1) the acceptability of the proposed dissolution method and acceptance criterion for the routine QC testing of the proposed drug product at batch release and on stability; (2) bridging of the different clinical

formulations; (3) the biowaiver request for the 15 mg capsule and (4) the evaluation of the adequacy of the proposed Physiologically Based Pharmacokinetic (PBPK) modelling and simulation, in support of the proposed drug substance particle size specifications.

Dissolution Specification and Method: The dissolution method includes a USP Apparatus 1 (Baskets) at 75 rpm in 900 mL of KCl in H₂O, 1.9. The proposed dissolution acceptance criterion for the 15 and 25 mg capsules is $Q = \frac{(b)}{(4)}\%$ in 45 minutes. (b) (4)

(b) (4). The proposed dissolution method and acceptance criteria were deemed acceptable for batch release and stability testing for the (b) (4) 15 mg, and 25 mg drug products.

Bridging of the Clinical Formulations: The Applicant established the bridge between the different formulations by way of a bioequivalence (BE) study. The bridging approach was deemed acceptable.

Biowaiver Request for 15 mg Capsules: The request to waive the requirement of an *in vivo* bioavailability/bioequivalence study for the 15 mg capsule is supported by the absolute bioavailability data on the 25 mg strength, the compositional proportionality of the formulations of the 25 mg and 15 mg strengths and comparative dissolution profile and, f_2 data. Accordingly, the biowaiver request is granted.

PBPK model to support of the drug substance particle size specifications: The proposed PBPK model was deemed acceptable to support the setting of the final drug substance particle size specifications.

This application is recommended for approval from a biopharmaceutics perspective.

(b) (4)

All facilities listed in NDA 211155 were deemed acceptable for the responsibility listed in the application. Accordingly, this application is recommended for approval from a compliance perspective.

Environmental Assessment

The approval of this application will increase the use of duvelisib; however, the estimated concentration of the substance at the point of entry into the aquatic environment is below 1 ppb (0.0090271 ppb). The applicant provided a claim for categorical exclusion and a statement of no extraordinary circumstances under 21 Code of Federal Regulations (CFR) Sections 25.31(b). The categorical exclusion cited is appropriate based on the estimated amount of drug to be produced for direct use. The claim of categorical exclusion is therefore acceptable and granted.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment (see Attachment)

Attached.



Sherita
McLamore

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BIOPHARMACEUTICS**Drug Product Name/Strengths:** COPIKTRA (duvelisib) Capsules, 15 mg and 25 mg**Route of Administration:** Oral**Applicant Name:** Verastem, Inc.**List of Reviewed Submissions:****Original NDA 211155** submission dated 2/5/2018

eCTD Seq. 0030 Applicant's Response dated 5/24/2018

eCTD Seq. 0037 Applicant's Response dated 6/12/2018

eCTD Seq. 0052 Applicant's Response dated 8/29/2018

Biopharmaceutics Review Team:

Primary Reviewer: Yang Zhao, PhD

Secondary Reviewers: Banu Zolnik, PhD and Fang Wu, PhD (PBPK Advisor)

Tertiary Reviewer: Angelica Dorantes, PhD

RECOMMENDATION: ADEQUATE**REVIEW SUMMARY:****Submission:** Verastem, Inc. submitted NDA 211155 seeking approval for Duvelisib Capsules, (b) (4) 15 mg, and 25 mg under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for the treatment of:

- ✓ Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), (b) (4)
- ✓ Follicular B-cell non-Hodgkin lymphoma (FL) who have received at least two prior therapies.

(b) (4)

Review Objective: The Biopharmaceutics Review evaluated the adequacy of (1) the proposed dissolution method and acceptance criterion for QC testing of the proposed drug product 15 mg and 25 mg strengths at batch release and during stability, (2) bridging of different clinical formulations, (3) biowaiver request for 15 mg strength, and (4) evaluation of the adequacy of the proposed Physiologically Based Pharmacokinetic (PBPK) modelling and simulation, in support of the proposed drug substance particle size specifications.

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA 211155 COPIKTRA (duvelisib) Capsules (b) (4) 15 and 25 mg

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 At release and stability)	<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, continue stability monitoring post approval
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	Controls are in place, continue stability monitoring post approval
Content Uniformity	<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	Controls are in place, continue stability monitoring post approval
Microbial Limits	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	L	Assessed during Development and controlled via specs	Acceptable	Justification is provided, refer to OPF review.
Dissolution – BCS Class II & IV	<ul style="list-style-type: none"> • Formulation • Raw Materials • Process parameters • Scale/equipments • Site 	M	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval, refer to BioPharm review.



Sherita
McLamore

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Reviewer’s Assessment:

(1) Dissolution Method and Acceptance Criterion: The Applicant’s proposed dissolution method and dissolution acceptance criterion are acceptable for batch release and stability testing of the proposed Duvelisib Capsules, 15 mg, and 25 mg.

Final Dissolution Method and Acceptance Criterion for Duvelisib Capsules, 15 mg and 25 mg				
USP Apparatus	Speed (rpm)	Medium/Temp	Volume (mL)	Acceptance Criterion
USP 1 (basket)	75	3.7 g/L potassiumchloride in water solution (pH adjusted to 1.9)/37 °C	900	Q = ^(b) / ₍₄₎ % at 45 min for 15 mg and 25 mg strengths

(2) Bridging of Drug Products: The Applicant established the bridge between the DP-B and DP-A products with a bioequivalence (BE) study. The bridging approach is acceptable. It is noted that the assessment of the BE study is performed by the Clinical Pharmacology reviewer.

(3) Biowaiver Request: The Applicant’s request for a waiver of the requirement to submit an in vivo bioavailability/bioequivalence study for the proposed Duvelisib Capsules, 15 mg, is fully supported by the evidence of absolute bioavailability data on the highest 25 mg strength, compositional proportionality of the formulations of the 25 mg and 15 mg strengths, and comparative dissolution profile and similarity, *f*₂ data. Therefore, the biowaiver request for Duvelisib Capsules, 15 mg is granted.

(4) Proposed PBPK Model

- ✓ **Development:** The Applicant applied in vitro experimental data (e.g. solubility), predicted/fitted physicochemical parameters (e.g. Peff) and different physiology parameter (e.g. gastric emptying pH and gastric emptying time) values under fasted or fed conditions (using default values in GastroPlus™) in the PBPK absorption model. PK parameters of clearance, distribution volume and inter-compartmental kinetic rate constants were estimated in the disposition model using duvelisib intravenous administration clinical data. The prediction of nine clinical data sets with different product-formulations and/or dosing regimens demonstrated that the developed model well predicted the observed geometric mean for the parameters of maximum plasma concentration (C_{max}) and area under the curve (AUC_{0-inf}), with the % prediction errors (%PE) ranging from -42%–13% for AUC_{0-inf} and from -22%–23% for C_{max}. The PBPK model development is adequate to support the selection of particle size specifications.

- ✓ **Validation:** Based on the model, the prediction of independently 6 clinical data sets predicted well with % prediction errors (%PE) from -8%–13% for AUC and -19%–16% for C_{max}. The proposed PBPK model is found robust.

- ✓ **Application for Setting Particle Size Specifications:** The final drug substance particle size specifications for the proposed Duvelisib Capsules are supported by the evidence of parameter sensitivity analysis, simulation, and virtual bioequivalence results, based on the validated GastroPlus™ PBPK model. It is noted that any future application of the model for other purposes will be assessed separately with its supporting data.
- ✓ **Recommendation:** The proposed PBPK model is acceptable to support the setting of the particle size specifications. The final specification limits for the drug substance particle size distribution (PSD) are: $D_{10} \geq$ (b) (4) D_{50} : (b) (4) and $D_{90} \leq$ (b) (4)

OVERALL RECOMMENDATION:

From the Biopharmaceutics perspective, the provided information is ADEQUATE and NDA 211155 for Duvelisib Capsules, 15 mg and 25 mg is recommended for **APPROVAL**.

SIGNATURES

Primary Reviewer:

Yang Zhao, PhD 9/4/2018
Biopharmaceutics Reviewer
Division of Biopharmaceutics-Branch I
Office of New Drugs, OPQ

Secondary Reviewers:

Banu Zolnik, PhD 9/4/2018
Acting Biopharmaceutics Lead
Division of Biopharmaceutics-Branch I
Office of New Drugs, OPQ

Fang Wu, PhD 9/4/2018
Biopharmaceutics Reviewer (PBPK Advisor)
Division of Biopharmaceutics-Branch III
Office of New Drugs, OPQ

Tertiary Reviewer:

Angelica Dorantes, PhD 9/5/2018
Branch Chief
Division of Biopharmaceutics-Branch I
Office of New Drugs, OPQ

BIOPHARMACEUTICS ASSESSMENT

Duvelisib is a kinase inhibitor, proposed for the treatment of patients with (1) Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), (b) (4) (2) Follicular B-cell non-Hodgkin lymphoma (FL) who have received at least two prior therapies. Per Applicant’s proposed labeling, the recommended dose of Duvelisib Capsules is 25 mg taken orally twice daily with or without food. The main proposed strength is 25 mg strength.

1. DRUG SUBSTANCE:

1.1 Solubility:

The Applicant reported that duvelisib is a low water-solubility drug (Table 1).

Table 1. Aqueous solubility of Duvelisib at different pHs at room temperature

pH	pH Modifier Solution	Solubility ^a (mg/mL)	Solubility (parts solvent per part solute)	Descriptive Term ^b
1.2	85 mM HCl and 50 mM KCl	5.94	168	Slightly soluble
2.2	25 mM HCl and 25 mM potassium biphthalate	0.38	2632	Very slightly soluble
3.0	22 mM HCl and 50 mM potassium biphthalate	0.17	5882	Very slightly soluble
4.0	0.1 mM HCl and 50 mM potassium biphthalate	0.05	20000	Practically insoluble or insoluble
4.5	50 mM potassium biphthalate and 11 mM NaOH	0.03	33333	Practically insoluble or insoluble
5.5	50 mM potassium biphthalate and 39 mM NaOH	0.02	50000	Practically insoluble or insoluble
6.5	50 mM Monobasic potassium phosphate and 16 mM NaOH	0.02	50000	Practically insoluble or insoluble
7.4	50 mM Monobasic potassium phosphate and 39 mM NaOH	0.02	50000	Practically insoluble or insoluble

^a Solubility conducted at room temperature.
^b USP 39 General Notices and Requirements:
 Practically insoluble, or insoluble = ≥ 10000 parts solvent per 1 part solute
 Very slightly soluble = 1000-10000 parts solvent per 1 part solute
 Slightly soluble = 100-1000 parts solvent per 1 part solute
 Sparingly soluble = 30-100 parts solvent per 1 part solute
 Soluble = 10-30 parts solvent per 1 part solute

1.2 Permeability:

The Applicant reported that duvelisib membrane permeability (P_{app}) in Caco-2 cells ranged from $2.2-6.7 \times 10^{-6}$ cm/sec at drug concentrations of 3 and 100 μ M, respectively (pH of apical well at 7.4). The Applicant stated that these P_{app} values are in the moderate permeability range (typically $1-10 \times 10^{-6}$ cm/sec), projecting moderate absorption (typically 50 to 89%) in humans.

1.3 BCS Designation:

The Applicant stated that duvelisib is a low solubility and low permeability (BCS-Class IV) drug substance.

2. DRUG PRODUCT:

Duvelisib drug product is supplied as an immediate release (b) (4) gelatin capsule containing (b) (4) 15 mg, and 25 mg duvelisib drug substance (on anhydrous basis) (b) (4). Duvelisib capsules, 15 mg are supplied as opaque, pink, (b) (4) capsules with “duv 15 mg” printed in black ink on the body. Duvelisib capsules, 25 mg are supplied as opaque, (b) (4) capsules with white body and a Swedish Orange cap, with “duv 25 mg” printed in black ink on the body. The proposed Duvelisib Capsules, 25 mg and 15 mg are compositionally proportional (Table 2).

Table 2. Composition of commercial Duvelisib Capsules, 25 mg, 15 mg (b) (4)

Component	Quality Standard	Function	IIG limit	Amount per Capsule	
				25 mg	15 mg
				mg/capsule	mg/capsule
Duvelisib drug substance (on anhydrous basis) ^a	cGMP	Active Ingredient	NA	25.00	15.00
Microcrystalline Cellulose (MCC)	USP/NF, Ph. Eur., JP				
Colloidal Silicon Dioxide	USP/NF, Ph. Eur., JP				
Crospovidone	USP/NF, Ph. Eur., JP				
Magnesium Stearate	USP/NF, Ph. Eur./BP, JP				
Pre-printed opaque, white gelatin capsule					
Pre-printed opaque, pink gelatin capsule					
Pre-printed gelatin capsule with an opaque, Swedish Orange cap and opaque, white body					
Ink-Black					
Ink-Black					

Note: API = Active pharmaceutical ingredient, N/A = not applicable, USP = United States Pharmacopoeia, NF = National Formulary, Ph. Eur. = European Pharmacopoeia, BP = British Pharmacopoeia, JP = Japanese Pharmacopoeia, DMF = Drug Master File

3. PROPOSED DISSOLUTION METHOD AND ACCEPTANCE CRITERION:

The proposed dissolution method and dissolution acceptance criterion for Duvelisib Capsules, 15 mg and 25 mg are as follows:

Proposed dissolution method and acceptance criterion for Duvelisib Capsules, 15 mg and 25 mg				
USP Apparatus	Speed (rpm)	Medium/Temp	Volume (mL)	Acceptance Criterion*
USP 1 (basket)	75	3.7 g/L potassiumchloride in water solution (pH adjusted to 1.9)/37 °C	900	Q = $\frac{(b)}{(4)}$ % at 45 min for 25 mg and 15 mg strengths

(b) (4)

(b) (4)



Yang
Zhao

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Angelica
Dorantes

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CHAPTER IV: Labeling

Package Insert

(a) “Highlights” Section (21CFR 201.57(a))

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all information needed to use COPIKTRA safely and effectively. See full prescribing information for COPIKTRA.

COPIKTRA (duvelisib capsules), for oral use
Initial U.S. Approval: [Approval Year]

WARNING: FATAL AND SERIOUS TOXICITIES: INFECTIONS, DIARRHEA OR COLITIS, CUTANEOUS REACTIONS, and PNEUMONITIS

See full prescribing information for complete boxed warning

- Fatal and/or serious infections occurred in 31% of COPIKTRA-treated patients. Monitor for signs and symptoms of infection. Withhold COPIKTRA if infection is suspected. (5.1)
- Fatal and/or serious diarrhea or colitis occurred in 18% of COPIKTRA-treated patients. Monitor for the development of severe diarrhea or colitis. Withhold COPIKTRA. (5.2)
- Fatal and/or serious cutaneous reactions occurred in 5% of COPIKTRA-treated patients. Withhold COPIKTRA. (5.3)
- Fatal and/or serious pneumonitis occurred in 5% of COPIKTRA-treated patients. Monitor for pulmonary symptoms and interstitial infiltrates. Withhold COPIKTRA. (5.4)

INDICATIONS AND USAGE

COPIKTRA is a kinase inhibitor indicated for the treatment of adult patients with:

- Relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after at least two prior therapies. (1.1)
 - Relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies. (1.2)
- This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

DOSAGE AND ADMINISTRATION
25 mg orally, twice daily. Modify dosage for toxicity. (2.1, 2.2)

DOSAGE FORMS AND STRENGTHS
Capsules: 25 mg, 15 mg. (3)

CONTRAINDICATIONS
None.

- WARNINGS AND PRECAUTIONS**
- Hepatotoxicity: Monitor hepatic function. (5.5)
 - Neutropenia: Monitor blood counts. (5.6)
 - Embryo-Fetal toxicity: COPIKTRA can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception. (5.7)

ADVERSE REACTIONS
The most common adverse reactions (≥ 20%) are diarrhea or colitis, neutropenia, rash, fatigue, pyrexia, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain, and anemia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Verastem, Inc. (Verastem) at 877-7RXVSTM or 1-877-779-8786, or U.S. Food and Drug Administration (FDA) at 1-800-FDA-1088 or www.fda.gov/medwatch.

- DRUG INTERACTIONS**
- CYP3A inducers: Avoid co-administration with strong CYP3A inducers. (7.1)
 - CYP3A inhibitors: Monitor for COPIKTRA toxicities when co-administered with strong or moderate CYP3A inhibitors. Reduce COPIKTRA dose to 15 mg twice daily when co-administered with strong CYP3A4 inhibitors. (7.1)
 - CYP3A substrates: Monitor for signs of toxicities when co-administering COPIKTRA with sensitive CYP3A substrates. (7.2)

USE IN SPECIFIC POPULATIONS
Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: XX/20XX

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	COPIKTRA (duvelisib) capsules, for oral use	Changed to COPIKTRA (duvelisib capsules), for oral use
Dosage form, route of administration	Capsules, for oral use	Adequate
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Capsules: 25 mg, 15 mg (b) (4)	Adequate

Conclusion: Adequate

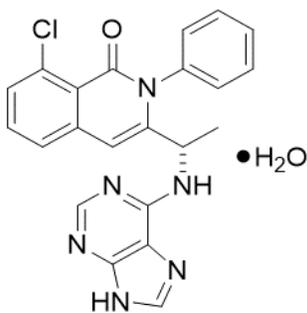
(b) “Full Prescribing Information” Section**# 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))**

Strength	Description
25 mg	White to off-white opaque and Swedish orange opaque capsule printed in black ink with “duv 25 mg”
15 mg	Pink opaque capsule printed in black ink with “duv 15 mg”

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	Capsule	Adequate
Strengths: in metric system	25 mg, 15 mg	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Provided. See above	Adequate

Conclusion: Adequate**#11: Description (21CFR 201.57(c)(12))**

COPIKTRA (duvelisib) is a dual inhibitor of phosphatidylinositol 3-kinases PI3K- δ and PI3K- γ . Duvelisib is a white-to-off-white crystalline solid with the empirical formula $C_{22}H_{17}ClN_6O \cdot H_2O$ and a molecular weight of 434.88 g/mol. Hydration can vary with relative humidity. Duvelisib contains a single chiral center as (S) enantiomer. Duvelisib is soluble in ethanol and practically insoluble in water. Duvelisib is described chemically as a hydrate of (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one and has the following chemical structure:



COPIKTRA capsules are for oral administration and are supplied as white to off-white opaque and Swedish orange opaque capsules (25 mg, on anhydrous basis) or pink opaque capsules (15 mg, on anhydrous basis), and contain the following inactive ingredients: colloidal silicon dioxide, croscopvidone, magnesium stearate, and microcrystalline cellulose. Capsule shells contain gelatin, titanium dioxide, black ink, and red iron oxide.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	COPIKTRA (duvelisib)	Adequate
Dosage form and route of administration	Capsule, for oral administration	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Free base, not salt, added "on anhydrous basis"	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Provided	Adequate
Statement of being sterile (if applicable)		N/A
Pharmacological/ therapeutic class	Provided	Adequate
Chemical name, structural formula, molecular weight	Provided	Adequate
If radioactive, statement of important nuclear characteristics.		N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Provided	Adequate

Conclusion: Adequate

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

COPIKTRA (duvelisib) capsules are supplied as follows:

Capsule Strength	Description	Package Configuration	NDC No.
25 mg	White to off-white and Swedish orange opaque capsules marked with "duv 25 mg" in black ink	<ul style="list-style-type: none"> 28 days carton (Each carton contains 2 × 28-count blister packs) 56 count HDPE bottles 	<ul style="list-style-type: none"> 71779-125-02 71779-125-01
15 mg	Pink opaque capsules marked with "duv 15 mg" in black ink	<ul style="list-style-type: none"> 28 days carton (Each carton contains 2×28-count blister packs) 56 count HDPE bottles 	<ul style="list-style-type: none"> 71779-115-02 71779-115-01

Abbreviations: HDPE = high-density polyethylene; NDC = National Drug Code; no. = number

Store at 20° to 25°C (68° to 77°F), with excursions permitted at 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Retain in original package until dispensing.

Conclusion: Adequate

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

Manufactured for:
Verastem, Inc.
117 Kendrick Street
Suite 500
Needham, MA 02494

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Missing information but format is acceptable	Adequate

Conclusion: Adequate

Container Labeling

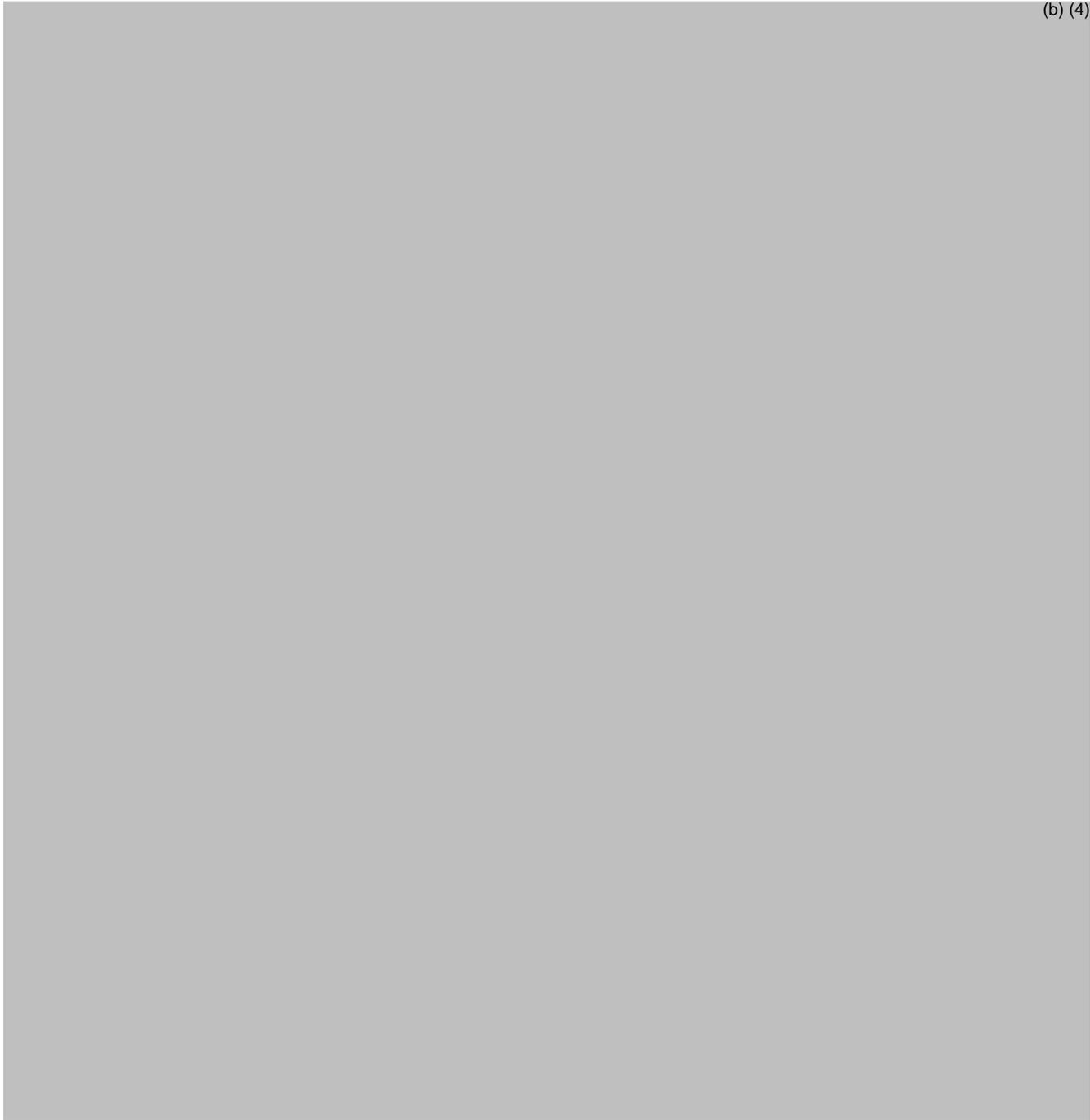
(b) (4)

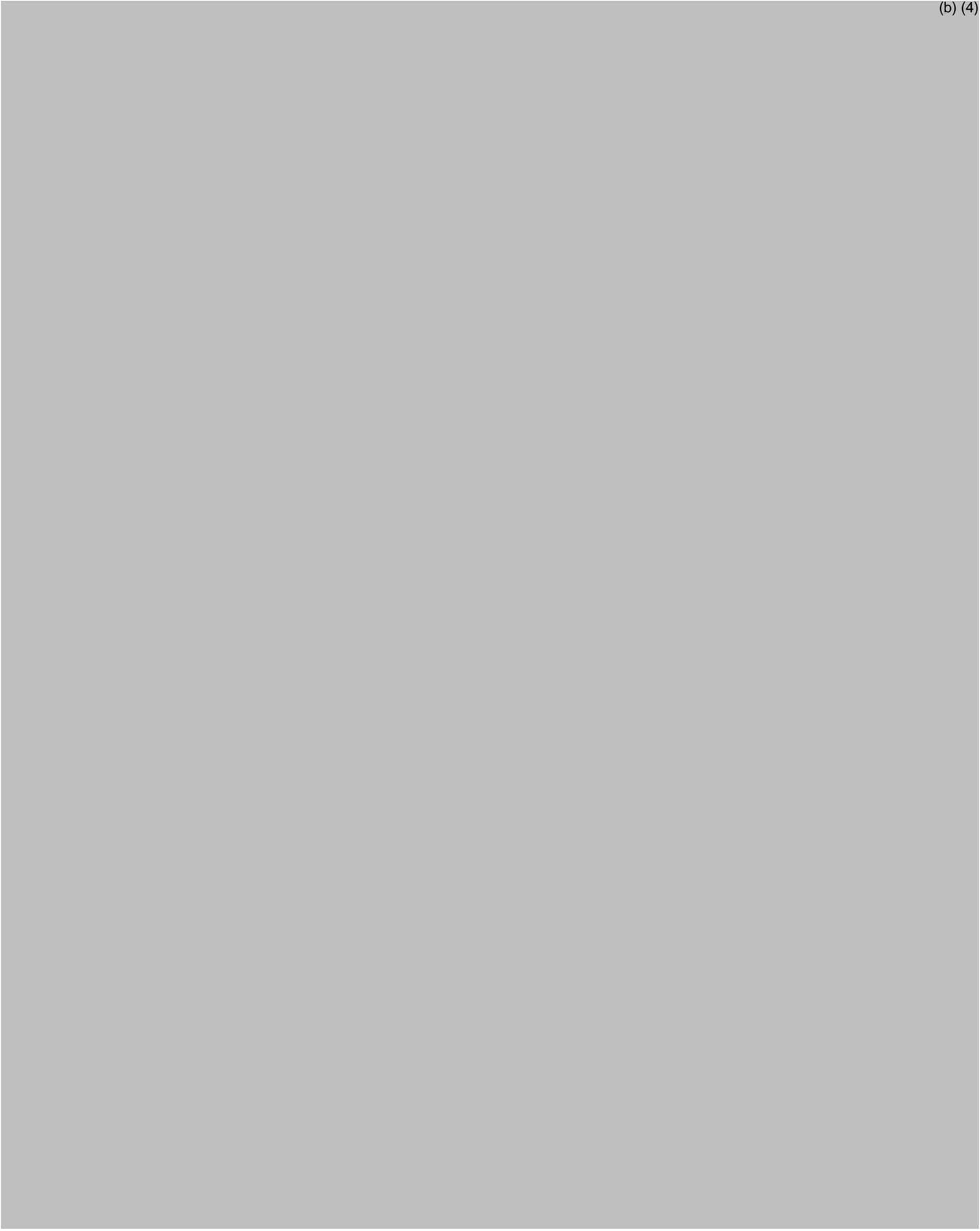
Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Copiktra (duvelisib)	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	25 mg, 15 mg (b) (4)	Adequate
Route of administration 21.CFR 201.100(b)(3))	for oral use, not required	Adequate
Net contents* (21 CFR 201.51(a))	Provided	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	“See package insert for full prescribing information”	Adequate
Lot number per 21 CFR 201.18	Reserved space	Adequate
Expiration date per 21 CFR 201.17	Reserved space	Adequate
“Rx only” statement per 21 CFR	Provided	Adequate
Storage (not required)	Provided, will change to USP controlled room temperature	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(h)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Provided	Adequate
Name of manufacturer/distributor or (21 CFR 201.1)	Provided	Adequate
Others		Adequate

Reviewer's Assessment: Will change the storage temperature to USP controlled room temperature. Acceptable.

Blister Labeling

(b) (4)





Reviewer's Assessment: Adequate

List of Deficiencies: Comments/Edits have been conveyed DHP during labeling review.

Primary Drug Product Reviewer Name and Date:

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

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

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



Xing
Wang

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Anamitro
Banerjee

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NDA 211155 Summary

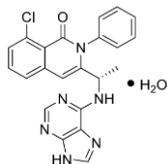
NDA 211155 was submitted as a 505(b)(1) NDA under the Federal Food, Drug and Cosmetic Act. The drug product, COPIKTRA (duvelisib) Capsules (b) (4) 15 and 25 mg is an oral monotherapy indicated for the treatment of patients with Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Leukemia (SLL) (b) (4) (b) (4) and for the treatment of patients with Follicular B-cell non-Hodgkin lymphoma (FL) who have received at least two prior therapies. The applicant is seeking full approval for the indication of CLL/SLL and accelerated review with conditional approval for the indication of FL. Duvelisib is an orally bioavailable, kinase inhibitor. It is an NME that was granted orphan drug designation and fast-track designation for both indications (CLL/SLL and FL). The applicant has requested a priority review of this application.

Pharmaceutical Information

Reference Listed Drug Name:	n/a
Innovator Company Name:	n/a
Established Product Name:	duvelisib
Applicant Name:	Verastem, Inc.
Drug Substance:	duvelisib
Strength(s):	(b) (4) 15 and 25 mg
Route of Administration:	Oral
Dosage Form:	Capsules
Chemical Abstracts Service (CAS) Index Name	(S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one hydrate
CAS Registry Number	
Molecular Formula	C ₂₂ H ₁₇ ClN ₆ O•H ₂ O (as monohydrate) C ₂₂ H ₁₇ ClN ₆ O (anhydrous form)
Molecular Weight	434.88 g/mol (as monohydrate) 416.86 g/mol (anhydrous form)

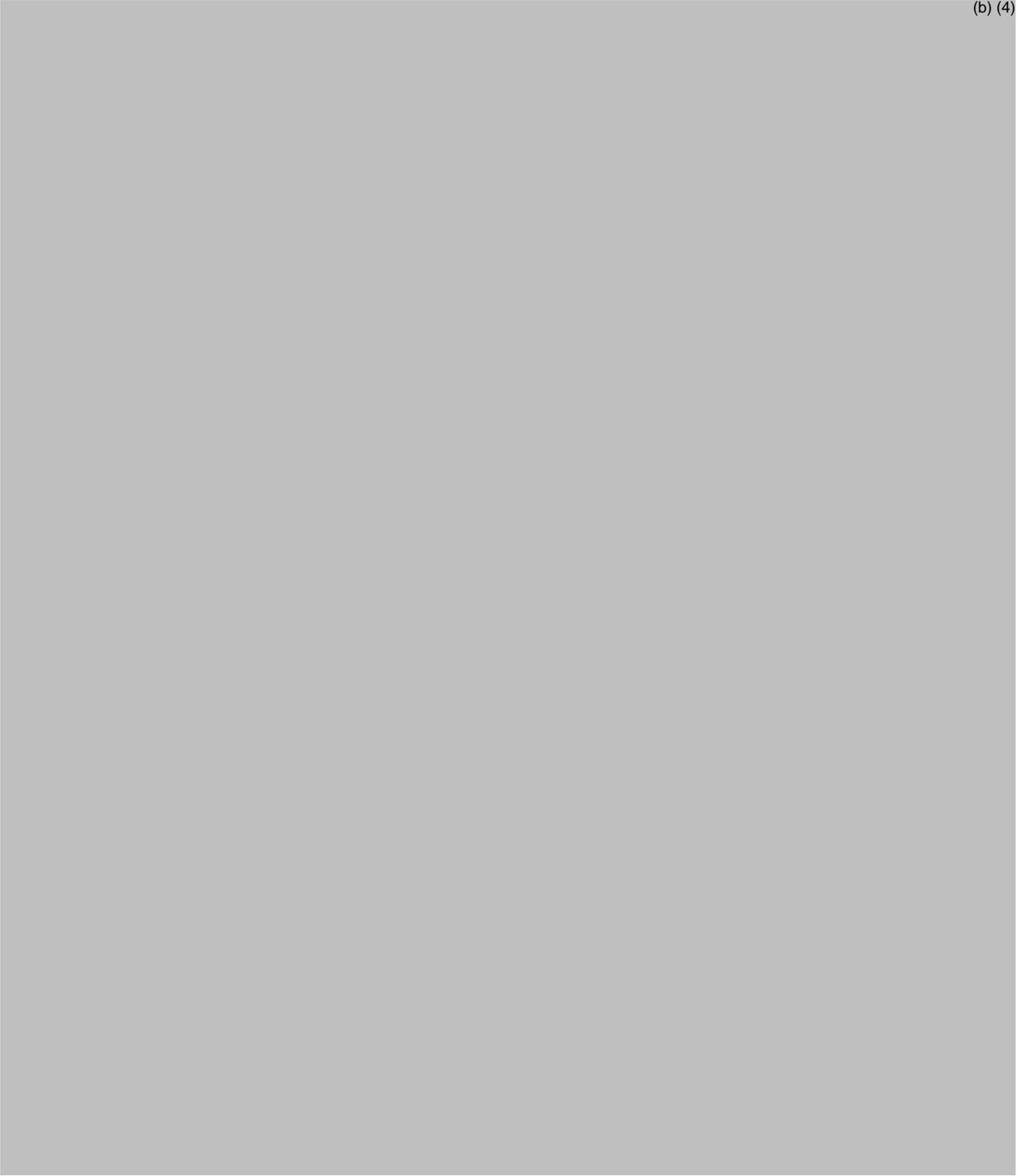
Drug Substance:

Duvelisib was originally investigated under IND 112486.



Duvelisib is a small chiral molecule that is classified as a BCS class 4 compound. It is a white to off-white non-hygroscopic crystalline solid that is practically insoluble in water, sparingly soluble in methanol and soluble in ethanol and isopropanol. Duvelisib has one stereogenic center and is manufactured as a single enantiomer (b) (4)

(b) (4) It is manufactured (b) (4) (b) (4) at a commercial batch size of (b) (4) The applicant includes specifications and suppliers for the regulatory starting materials as well as a detail description of CPPs (b) (4) and controls for all CQAs (there were discussion on the designation of the starting materials in 2014 and 2017). It seems that batches used in the clinical, nonclinical, and stability studies were manufactured using 2 different processes (processes I and II). Process I was used to manufacture batches supporting early development toxicology studies. Process II was used to manufacture duvelisib drug substance for use in clinical and nonclinical studies. Process II is further divided into processes IIa through IIc. Processes IIa-IIc reflect operational changes.





(b) (4)

The drug substance will be packaged (b) (4)

. The applicant includes 36 months long term stability data and 6 months of accelerated stability data for 3 registration stability batches. The applicant has requested a (b) (4) month retest period for the drug substance when stored between (b) (4)

DRUG PRODUCT

The drug product is an immediate release oral dosage form available in (b) (4) 15 and 25 mg strengths. The drug product is presented as a (b) (4) gelatin capsules containing the active, microcrystalline cellulose, colloidal silicon dioxide, crospovidone and magnesium stearate. The capsule shells and printing ink are both comprised of compendial excipients. The 25 mg capsule is presented as opaque, (b) (4) capsules with white body and a Swedish Orange cap, with “duv 25 mg” printed in black ink on the body. The 15 mg capsule is presented as opaque, pink, (b) (4) capsules with “duv 15 mg” printed in black ink on the body. (b) (4)

The formulation of 15 mg capsule is identical to that of the 25 mg capsule with the only difference being the capsule fill weight. (b) (4)

The drug product has a recommended dose of 25 mg twice daily with or without food.

Component	Amount (kg) per Batch		(b) (4)
	Duvelisib Capsule, 25 mg	Duvelisib Capsule, 15 mg	
Duvelisib (on anhydrous basis) ^a	(b) (4)		(b) (4)
Microcrystalline Cellulose (MCC) ^a			
Colloidal Silicon Dioxide (CSD)			
Crospovidone			
Magnesium Stearate			
(b) (4)			
Gelatin Capsules (# of capsules) ^b			

^a Duvelisib capsule, 25 mg: opaque, (b) (4) with a white to off-white body and Swedish Orange cap, pre-printed with black ink. Duvelisib capsule, 15 mg: opaque, pink (b) (4) pink cap and body), pre-printed with black ink. (b) (4)

(b) (4)

Component	Quality Standard	Function	IIG limit	Amount		(b) (4)
				25 mg	15 mg	
				mg/cap sule	mg/cap sule	
Duvelisib drug substance (on anhydrous basis) ^a	cGMP	Active Ingredient	NA	25.00	15.00	(b) (4)
Microcrystalline Cellulose (MCC) ^{a, b}	USP/NF, Ph. Eur., JP					(b) (4)
Colloidal Silicon Dioxide	USP/NF, Ph. Eur., JP					
Crospovidone	USP/NF, Ph. Eur., JP					
Magnesium Stearate	USP/NF, Ph. Eur./BP, JP					
Total fill weight per capsule	N/A					N/A

The drug product is manufactured by (b) (4) at a commercial batch size (b) (4) kg for the 25 and 15 mg capsules (b) (4). The (b) (4) kg commercial batch of the 25 and 15 capsules translates to (b) (4) capsules, respectively. (b) (4)

(b) (4)

(b) (4)

Table : Drug Product Specification

Test	Method	Acceptance Criterion
Appearance	Visual	25 mg: Opaque, size 2 capsule with a white to off-white body and Swedish Orange cap with "duv 25 mg" printed on the body in black ink
		15 mg: Opaque, size 2 pink capsule with "duv 15 mg" printed on the body in black ink
		(b) (4)
Identification by HPLC ^a	RP-HPLC-1	Consistent with reference
Identification by UV Spectrum ^a	RP-HPLC-1	Consistent with reference
Assay (Duvelisib content)	RP-HPLC-1	(b) (4)
Content Uniformity ^a	RP-HPLC-1	Conforms to USP <905>
Total Degradants (area %) ^b	RP-HPLC-1	(b) (4)
Individual Degradants (area %) - unspecified ^b	RP-HPLC-1	Each individual degradant ≤ (b) (4)
		(b) (4)
Dissolution	USP <711> Apparatus 1 RP-HPLC	25 mg and 15 mg: Q = (b) (4)% at 45 minutes (b) (4)
Microbial Enumeration Test	USP <61>	Total Yeast and Mold Count: ≤ (b) (4) cfu/g Total Aerobic Microbial Count: ≤ (b) (4) cfu/g
Tests for Specified Microorganisms	USP <62>	<i>Escherichia coli</i> : Absent in 1g

*Justification for the absence of test for solid form?

*Applicant needs to add test for Elemental Impurities USP <232>/<233> or provide a risk assessment consistent with ICH Q3D.

Container Closure System:

The drug product will be supplied as 25 mg, 15 mg, (b) (4) capsules. The (b) (4) (b) (4) (b) (4) 25 mg and 15 mg strengths will be packaged in bottles and blisters.

Bottle Packaging

The commercial product (25 mg, 15 mg, (b) (4)) is packaged in (b) (4) HDPE containers with a (b) (4) (b) (4) cap. The bottles are sealed with (b) (4) seals. Each bottle contains 56 capsules.

Blister Packaging

The commercial product (25 mg and 15 mg) is packaged in (b) (4) blister cards. Each blister card contains two rows of 14 capsules to a total of 28. Each carton contains 2 cards corresponding to a total of 56 capsules

Stability:

Twenty-four months long-term and 6 months accelerated stability data are included for the (b) (4) 25 mg capsules packaged in HDPE bottles or (b) (4) blisters and manufactured according to the proposed commercial manufacturing process. Nine months of long-term and 6-months accelerated stability data are included for the 15 mg capsules packaged in HDPE bottles and (b) (4) blisters. The stability assessment and expiration date assessment are performed based upon the stability data described in the following subsections.

Bulk stability data are include for one commercial size lot each of the, 25 mg, 15 mg (b) (4) capsules (b) (4) (b) (4). The bulk capsules are stored at or below 25°C. One registration stability lot each of duvelisib capsules, 25 mg (b) (4) was evaluated in the bulk packaging stability study for 24 months. One lot of duvelisib capsules, 15 mg is being evaluated in the bulk packing stability study and 12-month data is included---The study is planned for 24 month but I did not see a bulk hold time proposed.

The applicant proposes a 36 month shelf life for the 25 (b) (4) capsules and an (b) (4) shelf life for the 15 mg capsule when sored at CRT in bottles and blisters.

Biopharm:

There seems to have been two different capsule formulations (Formulation A and Formulation B) used throughout drug development.

Apparatus	USP Apparatus 1 (Baskets)
Paddle Speed	75 rpm
Volume	900 mL
Medium	KCl in H ₂ O, pH 1.9
Acceptance Criteria	15 and 25 mg capsules: Q= (b) (4) in 45 min (b) (4)

Facilities: (no insection schedule at the time of kickoff)



LOAs are included for the following DMFs and IND:

IND 112486 (Verastem for Duvelisib Oncology)



Review Team:

RBPM – Rabiya
ATL - Sherita

Drug Product- Xing/Anamitro
Drug Substance- Rajan/Chuck
Facilities- Zhaoyang /Peter
Biopharm- Yang/Okpo
Drug Process - Zhaoyang Rakhi

NDA 211155 Initial Risk Assessment Table

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	
Assay, Stability	<ul style="list-style-type: none"> • Formulation • Container closure • Process parameters • Scale/equipments • Site 	(b) (4)	4	2	Release (1)	8	
					Stability (3)	24	
Physical stability (solid state)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 		Crystalline (3)	3	4	36	
Content Uniformity	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 		(b) (4)	3	4	16	
Microbial Limits	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 		1	2	5	10	
Dissolution – BCS Class II & IV	<ul style="list-style-type: none"> • Formulation • Raw Materials • Process parameters • Scale/equipments • Site 			4	2	4	32



Sherita
McLamore

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