CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211155Orig1s000
211155Orig2s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211155
PDUFA Goal Date	October 5, 2018
OSE RCM #	2018-296
Reviewer Name(s)	Joyce Weaver, Pharm.D.
Team Leader	Elizabeth Everhart, MSN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	Draft, September 10, 2018
Subject	Review of REMS
Established Name	Duvelisib
Trade Name	Copiktra
Name of Applicant	Verastem, Inc
Therapeutic Class	Kinase inhibitor
Formulation(s)	Capsules
Dosing Regimen	25 mg orally twice daily

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1 Introduction

This review by the Division of Risk Management (DRISK) reviews the REMS submitted by Verastem Inc. for Copiktra (duvelisib). Verastem, Inc. submitted a New Drug Application (NDA 211155) for duvelisib with the proposed indication the treatment of adult patients with:

- Relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after at least two prior therapies
- Relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies.

The risks associated with duvelisib include fatal or serious infections, fatal or serious infections diarrhea or colitis, and fatal or serious infections cutaneous reactions, fatal and/or serious pneumonitis, hepatotoxicity, neutropenia, and embryo-fetal toxicity. The Applicant submitted a proposed communication plan REMS after the Agency communicated to the Applicant that they needed to submit a REMS that included a communication plan.

The communication plan REMS submitted by Verastem for Copiktra is acceptable.

2 Background

2.1 PRODUCT INFORMATION

Duvelisib, a new molecular entity, is phosphoinositide 3-kinase (PI3K) inhibitor. Duvelisib inhibits growth of cell lines derived from malignant B-cells and in primary CLL tumor cells. Duvelisib inhibits cell-signaling pathways, including B-cell receptor signaling and chemokine ligand 12 (CXCR 12) mediated chemotaxis of malignant B-cells. Duvelisib is proposed for the treatment of adult patients with:

- Relapsed or refractory CLL or SLL after at least two prior therapies
- Relapsed or refractory FL after at least two prior systemic therapies.

Duvelisib will be supplied as (b) (4) 15 mg, and 25 mg capsules. Duvelisib will be administered 25 mg orally twice daily for a 28-day cycle.

Duvelisib was granted orphan drug designation for the treatment of CLL, SLL (April 15, 2013) and FL (August 1, 2013).

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761097 relevant to this review:

- 4/15/2013: Orphan designation granted for CLL and SLL
- 8/1/2013: Orphan designation granted for FL
- 10/17/2017: Pre-NDA meeting; Agency advised Applicant that a REMS likely needed
- 2/5/2018: Application submitted
- 4/6/2018: Priority review granted; PDUFA 10/05/18
- 5/17/2018: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference; the Agency stated a communication plan REMS was needed to ensure the benefits outweighed the risks

- 6/29/2018: Applicant submitted a communication plan REMS for duvelisib
- 8/21/2018: DRISK review of REMS submitted; comments sent to Applicant
- 9/4/2018: Applicant submitted email responding to Agency's 8/21 comments (REMS and materials submitted to Gateway 9/6/2018)
- 9/5/2018: DRISK review of REMS submitted; comments sent to Applicant
- 9/10/2018: Applicant submitted email responding to Agency's 9/5 comments (submission to Gateway pending)

3 Therapeutic Context and Treatment Options

The therapeutic context, including a description of the medical condition and current treatment options, is provided in the August 21, 2018 review, available in DARRTS.

4 Benefit Assessment

The efficacy of duvelisib is described in the August 21, 2018 DRISK review.

5 Risk Assessment & Safe-Use Conditions

The safety database comprised data from 442 patients who received duvelisib in clinical testing.

The most important serious adverse reactions are infections, diarrhea or colitis, cutaneous reactions, pneumonitis, hepatotoxicity, neutropenia, and embryo-fetal toxicity.

The risks with duvelisib treatment are described in the August 21, 2018 DRISK review.

6 Expected Postmarket Use

Duvelisib is likely to be used in both inpatient and outpatient healthcare setting. Because duvelisib will be taken orally, patients will be able to take duvelisib at home.

The patient population likely to receive duvelisib will be older patients (most patients clinical testing were in excess of 65 years of age) with relapsed or refractory CLL, SLL, or FL. Patients would be expected to be able to report their treatment-emergent signs and symptoms to their health care providers, and to undergo appropriate laboratory testing.

7 Risk Management Activities Proposed by the Applicant

This section describes the REMS submitted by the Applicant September 10, 2018.

7.1.1. REMS Goals

The Applicant proposes the following:

The goal of the COPIKTRA REMS is to mitigate the risks of fatal and/or serious toxicities including infections, diarrhea or colitis, cutaneous reactions, and pneumonitis associated with the use of COPIKTRA by informing healthcare providers of these risks.

Reviewer Comment: This is acceptable.

7.1.1 REMS Requirements and Communication Pieces

The Applicant proposes a communication plan comprising the following:

REMS Letters: Healthcare Provider REMS Letter, Professional Society REMS Letter with (b) (4) REMS Fact Sheet

1. (b) (4) e-mail within 60 calendar days of the date COPIKTRA is first commercially distributed and again 1 year later.
2. Make available via a link from the COPIKTRA REMS Program Website.
3. Disseminate through professional societies - request the letter or content be provided to their members.
4. Disseminate at Professional Meetings for 1 year from the date COPIKTRA is first commercially distributed.

COPIKTRA REMS Fact Sheet

1. Disseminate and prominently display at Professional Meetings where Verastem Oncology has a presence for 1 year from the date COPIKTRA is first commercially distributed.
2. Disseminate through field-based sales and medical representatives during the initial and/or follow-up discussion with healthcare providers for 1 year after COPIKTRA is first commercially distributed. Field-based sales and/or medical representatives to orally review the risk messages contained in the COPIKTRA REMS Factsheet during the visit with the healthcare provider.

COPIKTRA Patient Safety Wallet Card

(b) (4)

COPIKTRA REMS Program Website

(b) (4)

2. Include a prominent REMS-specific link to the COPIKTRA (b) (4) website. The COPIKTRA REMS Program website will not link back to the promotional product website(s).
3. Continue for as long as the COPIKTRA REMS is active.

Reviewer Comment: This is acceptable.

7.1.2 REMS Assessment Plan

The following is the REMS Assessment Plan.

The REMS assessment plan should include, but is not limited to, the following:

1. An evaluation of healthcare providers' awareness and understanding of the risks of fatal and/or serious toxicities associated with the use of Copiktra including:
    - Infections
    - Diarrhea or colitis
    - Cutaneous reactions
    - Pneumonitis
2. A description of the implementation of the communication plan (current reporting period and cumulative), including:
    - Number of healthcare providers targeted by the REMS
    - Number and name of professional societies targeted by the REMS
    - Number of REMS letters sent to healthcare providers and professional societies via email, standard mail, and the dates the letters were sent. For letters sent via email, include the number of letters successfully delivered, and number of email letters opened by the recipients. Include the number of letters sent via mail because the emailed letter was undeliverable or the email unknown. For letters sent by mail include numbers of returned or undeliverable letters.
    - The sources of the recipient lists
    - Name of professional societies that distributed the REMS letters or content of the letter to their membership and date distributed
    - Name and date of scientific meetings and materials displayed
    - Date the REMS website went live
    - Number of unique site visits to the Copiktra REMS website each assessment period
    - Number of REMS fact sheets distributed by field-based sale and medical representatives during follow-up details/visits with healthcare providers
    - Number of Patient Safety Wallet Cards distributed by field-based sale and medical representatives during follow-up details/visits with healthcare providers.
3. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

Reviewer Comments: This is acceptable. This REMS Assessment Plan should be included in the NDA Approval Letter.

8 Discussion

DHP and DRISK agree that, should Copiktra (duvelisib) be approved, a communication plan REMS will be needed to ensure that the benefits of Copiktra outweigh its risks. The Applicant has made all required changes in the REMS document and REMS materials.

9 Conclusion & Recommendations

The risks of fatal and/or serious infections, fatal and/or serious diarrhea or colitis, fatal and/or serious cutaneous reactions, and fatal and/or serious pneumonitis associated with duvelisib are serious and it is necessary for prescribers to understand these risks. Based on the magnitude and severity of these risks, a REMS consisting of a communication plan is necessary to ensure that the benefits outweigh the risks.

DRISK recommends approval of the REMS submitted September 10, 2018.

10 Appendices

REMS Document and appended REMS materials.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOYCE P WEAVER
09/13/2018

CYNTHIA L LACIVITA
09/13/2018

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211155
PDUFA Goal Date	October 5, 2018
OSE RCM #	2018-296
Reviewer Name(s)	Joyce Weaver, Pharm.D.
	Kate Oswell, M.A.
Team Leader	Elizabeth Everhart, MSN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	August 21, 2018
Subject	Evaluation of Need for a REMS
Established Name	Duvelisib
Trade Name	Copiktra
Name of Applicant	Verastem, Inc
Therapeutic Class	Kinase inhibitor
Formulation(s)	Capsules
Dosing Regimen	25 mg orally twice daily

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) duvelisib is necessary to ensure the benefits outweigh its risks. Verastem, Inc. submitted a New Drug Application (NDA 211155) for duvelisib with the proposed indication[a] the treatment of adult patients with:

- Relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after at least two prior therapies
- Relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies.

The risks associated with duvelisib include fatal or serious infections, fatal or serious diarrhea or colitis, fatal or serious cutaneous reactions, and fatal or serious pneumonitis, hepatotoxicity, neutropenia, and embryo-fetal toxicity. On request from the Agency, the applicant submitted a proposed communication plan REMS.

DRISK and the Division of Hematology Products (DHP) agree that should duvelisib be approved, a REMS is needed to ensure its benefits outweigh its risks. The adverse events observed in clinical testing are similar to another in the class that required a communication plan REMS, idelalisib. Like idelalisib, a REMS is needed to communicate to prescribers the serious adverse events associated with the use of duvelisib.

1 Introduction

This review by the DRISK evaluates whether a REMS for the NME duvelisib is necessary to ensure the benefits outweigh its risks. Verastem submitted NDA 211155 for duvelisib with the proposed indication the treatment of adult patients with:

- Relapsed or refractory CLL or SLL after at least two prior therapies
- Relapsed or refractory FL after at least two prior systemic therapies.

This application is under review in DHP. The applicant submitted a communication plan REMS for this application.

This review is written by the Division of Risk Management (DRISK), in consultation with the Office of Prescription Drug Promotion (OPDP).[1]

2 Background

2.1 PRODUCT INFORMATION

[a] Applicant originally proposed the following indication statement: COPIKTRA is a kinase inhibitor indicated for the treatment of patients with— (b) (4)

(b) (4)

Duvelisib, a new molecular entity, is phosphoinositide 3-kinase (PI3K) inhibitor. Duvelisib inhibits cell-signaling pathways, including B-cell receptor signaling and chemokine ligand 12 (CXCR 12) mediated chemotaxis of malignant B-cells, thereby inhibiting growth of cell lines derived from malignant B-cells and in primary CLL tumor cells. Duvelisib is proposed for the treatment of adult patients with:

- Relapsed or refractory CLL or SLL after at least two prior therapies
- Relapsed or refractory FL after at least two prior systemic therapies.

Duvelisib will be supplied as (b) (4) 15 mg, and 25 mg capsules. Duvelisib will be administered 25 mg orally twice daily for a 28-day cycle.[b]

Duvelisib was granted orphan drug designation for the treatment of CLL, SLL (April 15, 2013) and FL (August 1, 2013).

2.2 Regulatory History

The following is a summary of the regulatory history for BLA 761097 relevant to this review:

- 4/15/2013: Orphan designation granted for CLL and SLL
- 8/1/2013: Orphan designation granted for FL
- 10/17/2017: Pre-NDA meeting; Agency advised Applicant that a REMS likely needed
- 2/5/2018: Application submitted
- 4/6/2018: Priority review granted; PDUFA 10/05/18
- 5/17/2018: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference; the Agency stated a communication plan REMS was needed to ensure the benefits outweighed the risks
- 6/29/2018: Applicant submitted a communication plan REMS for duvelisib

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Follicular lymphoma and SLL are two subtypes of indolent Non-Hodgkin's Lymphoma. Follicular lymphoma comprises about 20% of all NHL cases, and SLL comprises about 5% of all NHL cases. The average age of diagnosis in patients with these lymphomas is 65, with a slightly higher incidence in men. Over 70,000 people are diagnosed with indolent Non-Hodgkin's Lymphoma in the United States yearly, with about 19,000 patients dying from the disease.[2] Depending on the clinical staging of disease,

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

treatment may include a watch and wait period for several years, with mean survival rates of 7-10 years. However, many patients present after they have become symptomatic with advanced disease.

Chronic Lymphocytic Leukemia originates from lymphocytes in the bone marrow before it invades other areas of the body, most commonly the blood. There are about 21,000 new cases of CLL and 4,500 deaths from CLL yearly. [c,d] The average age at the time of diagnosis is about 70 years, and the risk is slightly higher in men compared to women. [3]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Treatment options for various presentations of FL and SLL include the following [4]:

- Radiation therapy
- Chemotherapy with rituximab followed by radiation therapy
- Radiation therapy to lymph nodes that are causing symptoms, or to a large localized mass, if one is present
- Single chemotherapy drugs in combination with rituximab (e.g., cyclophosphamide, chlorambucil, or bendamustine)
- R-CVP (rituximab plus cyclophosphamide, vincristine, and prednisone)
- R-CHOP (rituximab plus cyclophosphamide, hydroxydoxorubicin, vincristine and prednisone)
- A radioactive monoclonal antibody, such as yttrium-90+ibritumomab tiuxetan
- Stem cell transplantation
- Idelalisib
- Copanlisib
- Obinutuzumab in combination with bendamustine followed by obinutuzumab monotherapy.
- Obinutuzumab in combination with chemotherapy followed by obinutuzumab monotherapy

Like FL and SLL, CLL treatment can include a watch and wait period; however, most patients present with advanced disease after they have become symptomatic. Treatment options include rituximab, ibrutinib, idelalisib in combination with rituximab and venetoclax, and bendamustine hydrochloride. Alemtuzumab and ofatumumab in combination with chlorambucil are monoclonal antibodies that are approved for treatment of refractory CLL. [5]

4 Benefit Assessment[6, e]

The efficacy of duvelisib was examined in a randomized, multicenter, open-label trial that compared duvelisib with ofatumumab in 319 adult patients with CLL (N = 312) or SLL (N = 7) after at least one prior

[c] Section 505-1 (a) of the FD&C Act*: FDAAA factor (A): The estimated size of the population likely to use the drug.*

[d] Section 505-1 (a) of the FD&C Act*: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

therapy.[7] The median age of patients was 69 years (range, 40–90 years), and 59% were male. The study randomized patients 1:1 to receive either duvelisib 25 mg twice daily until disease progression or unacceptable toxicity or ofatumumab. Ofatumumab was administered intravenously at an initial dose of 300 mg, followed one week later by 2000 mg once weekly for 7 doses, and then 2000 mg once every 4 weeks for 4 additional doses.

Efficacy was assessed based on progression-free survival (PFS). Other efficacy measures included overall response rate (ORR). The median PFS for duvelisib was 16.4 months compared with 9.1 months for ofatumumab.

The efficacy of duvelisib in refractory FL was evaluated in a single-arm study (N = 83).[8] Duvelisib 25 mg was administered twice daily in patients with FL (N = 83) who were refractory to rituximab and to either chemotherapy or radioimmunotherapy.

The median age of patients in the study was 64 years (range: 30–82 years), 68% were male, and 37% had bulky disease assessed at baseline (target lesion ≥ 5 cm). Patients had a median of 3 prior lines of therapy (range: 1–10), with 94% being refractory to their last therapy and 81% being refractory to 2 or more prior lines of therapy.

Efficacy was based on ORR and duration of response (DOR). Thirty-five (42%) patients responded to treatment with Duvelisib. Fifteen of 35 patients (43%) maintained response at 6 months and 6 (17%) at 12 months.

5 Risk Assessment & Safe-Use Conditions[9, f]

The safety database comprised data from 442 patients who received duvelisib in clinical testing.

The most important serious adverse reactions are infections, diarrhea or colitis, cutaneous reactions, pneumonitis, hepatotoxicity, neutropenia, and embryo-fetal toxicity.

5.1 INFECTIONS

Section 5.1 of the draft labeling describes the risk serious, including fatal infections. Serious infections occurred in 31% of patients and fatal infections occurred in 18 (4%) patients receiving duvelisib. The most common infections were pneumonia, sepsis, and lower respiratory infections. The median time to onset of infection was 3 months (range, 1 day to 32 months). The draft labeling advises healthcare providers to withhold duvelisib for infections.

In addition to bacterial infections, serious, including fatal, cases of *Pneumocystis jirovecci* pneumonia (PJP) occurred in 1% of patients. The labeling advises that PJP prophylaxis should be provided for

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

patients receiving duvelisib. If PJP is suspected, duvelisib should be withheld. If PJP is confirmed, duvelisib should be discontinued.

Cytomegalovirus (CMV) reactivation/infection occurred in 1% of patients receiving duvelisib. Prophylaxis should be considered for patients receiving duvelisib. For clinical infection or reactivation, duvelisib should be withheld until the infection resolves.

5.2 DIARRHEA OR COLITIS

Section 5.2 of the draft labeling describes the risk of diarrhea or colitis. Serious diarrhea or colitis occurred in 18% of patients in clinical testing, and one fatal case occurred. The median time to onset of colitis was 4 months (range, 1 day to (b) (4) months). The draft labeling advises healthcare providers to hold duvelisib for severe colitis or diarrhea, and treat patients with supportive care. For life-threatening cases, duvelisib should be discontinued.

5.3 CUTANEOUS REACTIONS

Section 5.3 of the draft labeling describes the risk of serious, including fatal, cutaneous reactions. Serious cutaneous reactions occurred in 5% of patients; 2 cases were fatal. The fatal cases included one case of drug reaction with eosinophilia and systemic symptoms (DRESS) and one case of toxic epidermal necrolysis (TEN). The median time to onset of cutaneous reactions was 3 months (range, 1 day to (b) (4) months). For mild to moderate reactions, the draft labeling advises to provide supportive care while continuing duvelisib. For severe reactions, in addition to treatment for the cutaneous reaction, duvelisib should be discontinued.

5.4 PNEUMONITIS

Section 5.4 of the draft labeling describes the risk of pneumonitis. Pneumonitis occurred in 5% of patients, including one fatal case. The median time to onset of pneumonitis was 4 months (range, 9 days to 27 months). The draft labeling advises, in addition to treatment of pneumonitis, to withhold duvelisib for mild to moderate pneumonitis, and discontinuing duvelisib for severe pneumonitis.

5.5 HEPATOTOXICITY

Section 5.5 of the draft labeling describes the risk of hepatotoxicty. Grade 3 and 4 alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevation occurred in 8% and 2%, respectively, in patients receiving duvelisib. ALT or AST greater than 3 x the upper limit of normal (ULN) and total bilirubin greater than 2 x ULN within 7 days of transaminase elevation occurred in 2% of patients. Median time to onset of any grade transaminase elevation was 2 months (range: 3 days – (b) (4) months). The draft labeling advises healthcare providers to monitor patients for hepatotoxicity, and withhold duvelisib for Grade 3 ALT/AST elevation, and reintroduce duvelisib after ALT/AST returns to less than 3 times the ULN. For Grade 4 increases in ALT/AST (greater than 20 times the ULN), duvelisib should be discontinued.

5.6 NEUTROPENIA

Section 5.6 of the draft labeling describes the risk of neutropenia. Grade 3 or 4 neutropenia occurred in 42% of patients. The median time to onset of Grade 3 or higher neutropenia was 2 months (range, 3 days to 31 months). The draft labeling advises healthcare providers to monitor patients for neutropenia, and withhold duvelisib for Grade 4 neutropenia.

5.7 EMBRYO-FETAL TOXICITY

Section 5.7 of the draft labeling describes the potential, based on mechanism of action and animal data, for embryo-fetal toxicity. The draft labeling advises healthcare providers to counsel female patients of reproductive potential regarding contraception.

6 Expected Postmarket Use

Duvelisib is likely to be used in both inpatient and outpatient healthcare setting. Because duvelisib will be taken orally, patients will be able to take duvelisib at home.

The patient population likely to receive duvelisib will be older patients (most patients clinical testing were in excess of 65 years of age) with relapsed or refractory CLL, SLL, or FL. Patients would be expected to be able to report their treatment-emergent signs and symptoms to their health care providers, and to undergo appropriate laboratory testing.

7 Risk Management Activities Proposed by the Applicant

Pursuant to a request from the Agency, the Applicant proposed a communication plan REMS for duvelisib.

7.1.1. REMS Goals

The Applicant proposes the following:

(b) (4)

Reviewer Comment: The goal should be as follows—

The goal of the COPIKTRA REMS is to mitigate the risks of fatal and/or serious infections, fatal and/or serious diarrhea or colitis, fatal and/or serious cutaneous reactions, and fatal and/or serious pneumonitis associated with the use of COPIKTRA by informing healthcare providers of these risks.

7.1.1 REMS Requirements and Communication Pieces

The Applicant proposes a communication plan comprising the following:

REMS Letters: Healthcare Provider REMS Letter, Professional Society REMS Letter with (b) (4) REMS Fact Sheet

1. (b) (4) e-mail within 60 calendar days of the date COPIKTRA is first commercially distributed and again 1 year later.
2. Make available via a link from the COPIKTRA REMS Program Website.
3. Disseminate through professional societies - request the letter or content be provided to their members.
4. Disseminate at Professional Meetings for 1 year from the date COPIKTRA is first commercially distributed.

COPIKTRA REMS Fact Sheet

1. Disseminate and prominently display at Professional Meetings where Verastem Oncology has a presence for 1 year from the date COPIKTRA is first commercially distributed.
2. Disseminate through field-based sales and medical representatives during the initial and/or follow-up discussion with healthcare providers for 1 year after COPIKTRA is first commercially distributed. Field-based sales and/or medical representatives to orally review the risk messages contained in the COPIKTRA REMS Factsheet during the visit with the healthcare provider.

COPIKTRA Patient Safety Wallet Card

(b) (4)

COPIKTRA REMS Program Website

(b) (4)

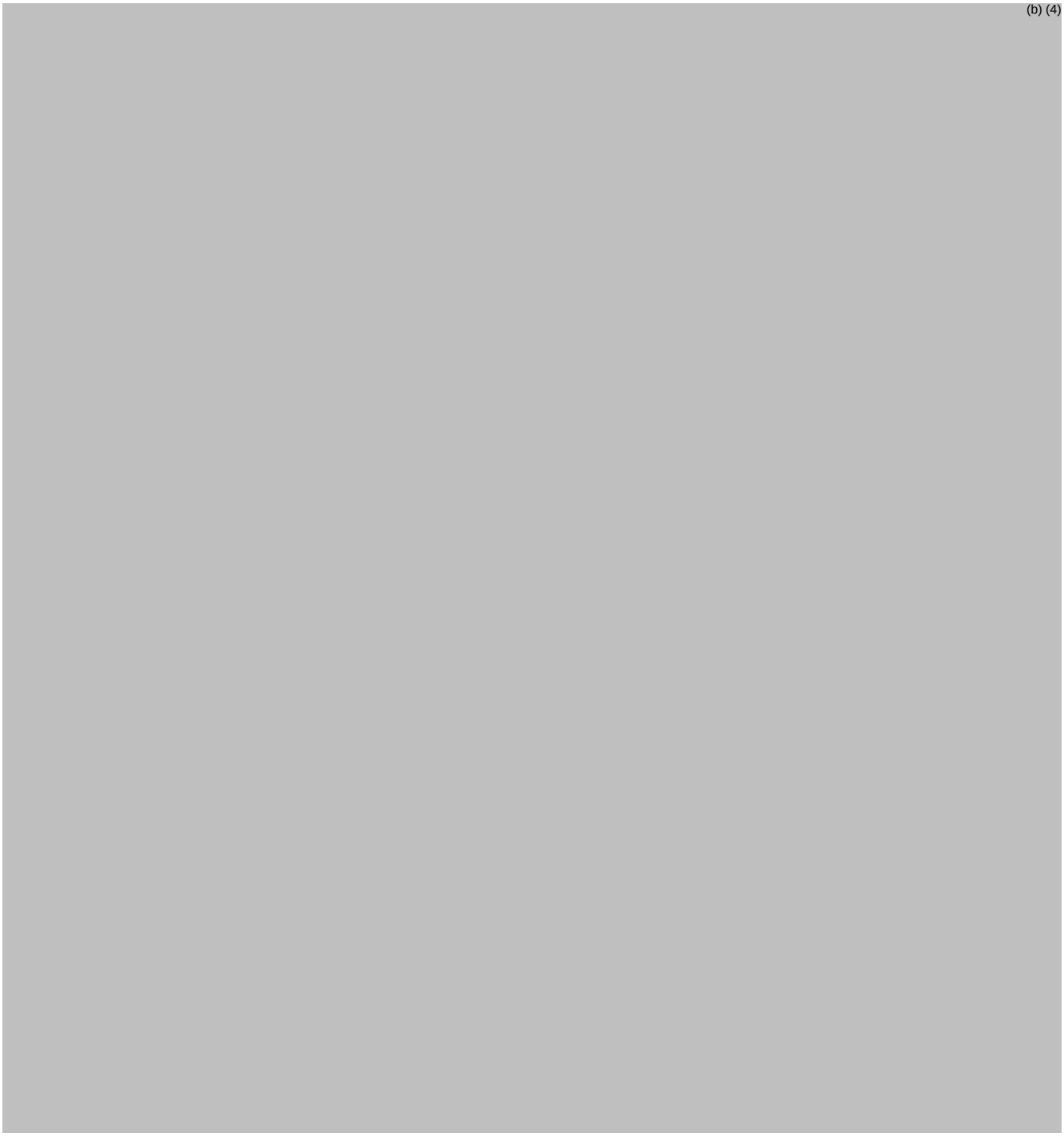
2. Include a prominent REMS-specific link to the COPIKTRA (b) (4) website. The COPIKTRA REMS Program website will not link back to the promotional product website(s).
3. Continue for as long as the COPIKTRA REMS is active.

Reviewer Comment: This is acceptable. We have comments for the Applicant on the communication pieces that were submitted.

7.1.2 REMS Assessment Plan

The Applicant proposes the following REMS Assessment Plan.

(b) (4)



The REMS Assessment will include evaluation of the distribution of the COPIKTRA REMS Program materials with the following program metrics:

Reviewer Comments: We will have comments on the REMS assessment plan and will provide them at a later date.

8 Discussion of Need for a REMS

DHP and DRISK agree that, should Copiktra (duvelisib) be approved, a communication plan REMS will be needed to ensure that the benefits of Copiktra outweigh its risks. Although the prescribing community likely is somewhat familiar with the nature of the adverse events with this class of drugs, the severity of the adverse events differs between products. Copanlisib (Aliqopa), another drug in the class, approved in 2017, did not require boxed warning or a REMS. Idelalisib (Zydelig), a product of the same class, was approved in 2014 for similar indications.[g] A communication plan REMS was determined to be necessary for the approval of idelalisib. The adverse event profile of duvelisib is of similar severity to idelalisib. A communication plan REMS is needed to inform prescribers about the fatal and/or serious adverse events associated with duvelisib. Although REMS are required for idelalisib and duvelisib, future approvals for products in this class for similar indications may not necessarily need a REMS if prescribers are knowledgeable about these risks.

8.1 REMS Requirements and Design

A communication plan REMS is needed to inform prescribers about the fatal and/or serious adverse events associated with duvelisib. The adverse events that will be addressed in the REMS include fatal and/or serious infections, fatal and/or serious diarrhea or colitis, fatal and/or serious cutaneous reactions, and fatal and/or serious pneumonitis.

[g] Zydelig is a kinase inhibitor indicated for the treatment of patients with:
- Relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities
- Relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies.
- Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.

8.1.1 REMS Goals

The REMS goals should be as follows:

The goal of the COPIKTRA REMS is to mitigate the risks of fatal and/or serious infections, fatal and/or serious diarrhea or colitis, fatal and/or serious cutaneous reactions, and fatal and/or serious pneumonitis associated with the use of COPIKTRA by informing healthcare providers of these risks.

8.1.2 REMS Requirements

The following shows the requirements for dissemination of the REMS communication materials to Healthcare Providers likely to prescribe Copiktra.

REMS Letters: Healthcare Provider REMS Letter, Professional Society REMS Letter with (b) (4) Fact Sheet

1. E-mail within 60 calendar days of the date COPIKTRA is first commercially distributed and again 12 months later.
    a. Send by mail within 30 calendar days of the date the first email was sent if a healthcare providers email address is not available or the email is undeliverable.
    b. Send a second email within 30 calendar days of the date the first email was sent if the first email is marked as unopened.
    c. Send by mail within 30 calendar days of the date the second email was sent if the second email is marked as unopened.
2. Make available via a link from the COPIKTRA REMS Program Website.
3. Disseminate through field-based sales and medical representatives.
4. Disseminate through the following professional societies and request the letter or content be provided to their members.
    a. American Society of Clinical Oncology (ASCO)
    b. American Society of Hematology (ASH)
    c. Oncology Nursing Society (ONS)
    d. National Comprehensive Cancer Network (NCCN)
    e. Hematology Oncology Pharmacy Association (HOPA)
    f. American Pharmacists Association (APhA)
    g. American Society of Health-System Pharmacists (ASHP)
5. Disseminate at Professional Meetings for 1 year from the date COPIKTRA is first commercially distributed.

Fact Sheet

1. Disseminate and prominently display at Professional Meetings where Verastem has a presence for 1 year from the date COPIKTRA is first commercially distributed.
2. Disseminate through field-based sales and medical representatives during the initial and/or follow-up discussion with healthcare providers for 1 year after COPIKTRA is first commercially distributed. Field-based sales and medical representatives to orally review the risk messages

contained in the Factsheet during the visit with the healthcare provider.

Patient Safety Wallet Card

1. Disseminate through field-based sales and medical representatives to healthcare providers for 1 year from the date COPIKTRA is first commercially distributed. Disseminate throughfield-based sales and medical representatives, to healthcare providers for 1 year from the date COPIKTRA is first commercially distributed.

Website

1. Make the REMS Program website fully operational and all REMS materials available through the website by the date COPIKTRA is first commercially distributed.
2. Include a prominent REMS-specific link to the COPIKTRA REMS Program website on all product websites for consumers and healthcare providers. The COPIKTRA REMS Program website must not link back to the promotional product website(s).
3. Continue for as long as the COPIKTRA REMS is active.

8.1.3 REMS Assessment Plan

The REMS assessment plan will be provided at a later date.

9 Conclusion & Recommendations

The risks of fatal and/or serious infections, fatal and/or serious diarrhea or colitis, fatal and/or serious cutaneous reactions, and fatal and/or serious pneumonitis associated with duvelisib are serious and it is necessary for prescribers to understand these risks. Based on the magnitude and severity of these risks, we agree that requiring a REMS consisting of a communication plan is necessary to ensure that the benefits outweigh the risks. We believe that educating prescribers regarding the risks via a communication plan will be sufficient to mitigate the risks without causing undue burden to stakeholders.

We have provided edited versions of the REMS document and REMS materials for the Applicant. The comments for the Applicant, the REMS document, and the REMS materials attached should be sent to the Applicant. The Applicant should be asked to resubmit the REMS and REMS materials within 1 week.

9.1 COMMENTS FOR THE APPLICANT

Overall Comments:

- To facilitate review of your submission, submit your proposed REMS and other REMS-related materials in Microsoft Word format, in track-change and clean versions. Additionally, submit REMS communications materials as .PDF files to show the to-be-used formatting and design. If certain

materials are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format to facilitate review.

- Phone numbers used by the Copiktra REMS may not link to information that is promotional in tone. When referring to the phone number use 1-877-779-8786 (b) (4).
- All REMS communication materials must be revised to be consistent with the final FDA approved labeling and resubmitted for review.
- We will supply comments on the REMS Supporting Document, including the REMS assessment plan, at a later date.

We request a response to these comments within one week.

REMS Letter for HCP:

- We made edits to the letter to better display the key risk information and symptoms associated with Copiktra, along with other REMS information. Please see redlined version of the REMS Letter for Healthcare Providers attached.

REMS Letter for Professional Societies:

- We made edits to the letter to better display the key risk and other REMS information. Please see redlined version of the REMS Letter for Healthcare Providers attached.

Fact Sheet

- The indication, order of risk information, along with all other content must reflect the final approved labeling. Significant changes will need to be made.
- Move the indication further down in the factsheet, after the risk information.
- Add a statement that Copiktra includes a Boxed Warning for the risks.
- See other edits on the redlined version of the Factsheet.

Patient Wallet Card

- The wallet card should have colors showing a sense of emergency and importance if presented at an Emergency Department or to a healthcare provider. Incorporate red and yellow font along with graphics/symbols used in an emergency department that represent importance or urgency (e.g., exclamation point). Other wallet cards for REMS programs with may be viewed at the REMS@FDA website.
- Include the key risk information and the actions that a healthcare provider would need to take on the healthcare provider side of the card.
- The section of the card with the Copiktra logo and title of the card needs to be shortened so that the space for the patient name, prescriber name and phone number lines are larger.

REMS Website

- The Copiktra logo size and placement needs to be modified. The product logo should be in the upper left or right hand corner of the website. The Verastem Oncology logo should be at the bottom of the page. REMS website pages are not designed to look like promotional product websites, as they are primarily for risk and safety information. Other REMS websites are available at the REMS@FDA website for examples.
- Include a section on patient counseling on the website and have a link to the Patient Safety Wallet Card within this section. See our suggested text on the attached edited version of the REMS webpage.
- Include a link on the COPIKTRA promotional product website that links to the REMS webpage for the duration of the REMS.

10 Appendices

REMS document and materials

10.1 REFERENCES

[1] OPDP REMS Consult Review; signed in DARRTS on August 1, 2018 by Patel, Nisha.

[2] http://www.cancer.org/cancer/non-hodgkinlymphoma/detailedguide/non-hodgkin-lymphoma-keystatistics accessed 14 August 2018

[3] American Cancer Society. https://www.cancer.org/cancer/chronic-lymphocytic-leukemia.html accessed August 15, 2018.

[4] Leukemia and Lymphoma Society. https://www.lls.org/lymphoma/non-hodgkin-lymphoma/treatment/treatment-for-indolent-nhl-subtypes. Accessed August 15, 2018.

[5] Leukemia and Lymphoma Society. https://www.lls.org/lymphoma/non-hodgkin-lymphoma/treatment/treatment-for-indolent-nhl-subtypes. Accessed August 15, 2018.

[6] Efficacy data summarized from presentations at the Mid-cycle Team Review Meeting, May 9, 2018, and from the FDA-edited labeling as of Aug 16, 2018.

[7] ClinicalTrials.gov Identifier: NCT02004522

[8] ClinicalTrials.gov Identifier: NCT01882803

[9] Robertson N. Clinical presentation of NDA 211155 at mid-cycle meeting, May 9, 2018, and from the FDA-edited labeling as of Aug 16, 2018.

13 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOYCE P WEAVER
08/21/2018

ELIZABETH E EVERHART
08/21/2018
I concur

CYNTHIA L LACIVITA
08/21/2018
concur