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RESEARCH**

APPLICATION NUMBER:

21155Orig1s000

21155Orig2s000

REMS

Risk Evaluation and Mitigation Strategy (REMS) Document

COPIKTRA™ (duvelisib) REMS Program

I. Administrative Information

Application Number: NDA 211155

Application Holder: Verastem, Inc.

Initial REMS Approval: 9/2018

II. REMS Goal

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.

III. REMS Requirements

To inform healthcare providers about the REMS Program and the risks and safe use of COPIKTRA, Verastem, Inc. must disseminate REMS communication materials according to the table below:

Target Audience	Communication Materials & Dissemination Plans
<p>Healthcare providers who are likely to prescribe COPIKTRA</p>	<p>REMS Letters: Healthcare Provider REMS Letter, Professional Society REMS Letter with hyperlink to the Fact Sheet</p> <ol style="list-style-type: none"> 1. E-mail within 60 calendar days of the date COPIKTRA is first commercially distributed and again 12 months later. <ol style="list-style-type: none"> a. Send by mail within 30 calendar days of the date the first email was sent if a healthcare provider's 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 for 1 year from the date COPIKTRA is first commercially distributed. 4. Disseminate within 60 calendar days of the date COPIKTRA is first commercially distributed and again 12 months later through the following professional societies and request the letter or content be provided to their members. <ol style="list-style-type: none"> a. American Society of Clinical Oncology (ASCO); American Society of Hematology (ASH); Oncology Nursing Society (ONS); National Comprehensive Cancer Network (NCCN); Hematology Oncology Pharmacy Association (HOPA); American Pharmacists Association (APhA); American Society of Health-System Pharmacists (ASHP) 5. Disseminate at Professional Meetings where Verastem has a presence for 1 year from the date COPIKTRA is first commercially distributed. <p>Fact Sheet</p> <ol style="list-style-type: none"> 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 Fact Sheet during the visit with the healthcare provider. <p>Patient Safety Wallet Card</p> <ol style="list-style-type: none"> 1. Disseminate through field-based sales and medical representatives to healthcare providers for 1 year from the date COPIKTRA is first commercially distributed. <p>Website</p> <ol style="list-style-type: none"> 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.

Target Audience	Communication Materials & Dissemination Plans
	<p>The COPIKTRA REMS Program website must not link back to the promotional product website(s).</p> <p>3. Continue for as long as the COPIKTRA REMS is active.</p>

IV. REMS Assessment Timetable

Verastem, Inc. must submit REMS Assessments at 18 months, 3 years and 7 years from the date of initial REMS approval (09/24/2018). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Verastem, Inc. must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the COPIKTRA REMS:

Communication Materials

1. [Healthcare Provider REMS letter](#)
2. [Professional Society REMS letter](#)
3. [Fact Sheet](#)
4. [Patient Safety Wallet Card](#)

Other Materials

5. [COPIKTRA REMS Program website](#)



FDA-REQUIRED REMS SAFETY INFORMATION

COPIKTRA has the following risks of fatal and/or serious toxicities:

- Infections
- Diarrhea or Colitis
- Cutaneous Reactions
- Pneumonitis

Dear Healthcare Provider:

The Food and Drug Administration (FDA) has required this safety notice as part of the COPIKTRA REMS (Risk Evaluation and Mitigation Strategy) to inform you about the serious risks of COPIKTRA.

Serious Risks with Use of COPIKTRA

COPIKTRA can cause fatal and/or serious toxicities including **infections, diarrhea or colitis, cutaneous reactions, and pneumonitis.**

Counsel your patients on these risks. Provide your patients with the COPIKTRA Patient Safety Wallet Card available at www.COPIKTRAREMS.com.

Instruct your patients to seek immediate medical attention if they develop any of the following symptoms:

- | | |
|---|---|
| <ul style="list-style-type: none"> • Symptoms of infection (e.g. fever, chills) • New or worsening diarrhea, stool with mucus or blood, or abdominal pain | <ul style="list-style-type: none"> • New or worsening skin rash • New or worsening respiratory symptoms including cough or difficulty breathing |
|---|---|

Please see the non-promotional Fact Sheet, reviewed by the FDA, and the full Prescribing Information for more detailed safety information. Additional copies of the Patient Safety Wallet Card, Fact Sheet, and other important information are available at: www.COPIKTRAREMS.com.

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.
 - Relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies.
- 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.

Adverse Event Reporting

To report side effects during the use of COPIKTRA, contact Verastem Oncology at **1-877-779-8786** and/or to FDA at www.fda.gov/medwatch or call 1-800-FDA-1088.

Sincerely,

Verastem Oncology





FDA-REQUIRED REMS SAFETY INFORMATION

COPIKTRA has the following risks of fatal and/or serious toxicities:

- Infections
- Diarrhea or Colitis
- Cutaneous Reactions
- Pneumonitis

Dear <PROFESSIONAL SOCIETY NAME>:

The Food and Drug Administration (FDA) has required this safety notice as part of the COPIKTRA REMS (**R**isk **E**valuation and **M**itigation **S**trategy) to inform you about the serious risks of COPIKTRA.

We would like to ask you to please distribute this information to your members so they are aware of the following risks.

Serious Risks with Use of COPIKTRA

COPIKTRA can cause fatal and/or serious toxicities including **infections, diarrhea or colitis, cutaneous reactions, and pneumonitis.**

Enclosed are the following materials:

- COPIKTRA Fact Sheet
- COPIKTRA Prescribing Information
- COPIKTRA Patient Safety Wallet Card

Please encourage your members to provide the Patient Safety Wallet Card to all patients being treated with COPIKTRA. The Patient Safety Wallet Card, Fact Sheet, and other important information are available at: www.COPIKTRAREMS.com.

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.
- Relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies.
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.

Sincerely,

Verastem Oncology





FDA-REQUIRED REMS* SAFETY INFORMATION (FACT SHEET)

COPIKTRA has a **BOXED WARNING** for the following fatal and/or serious toxicities:

Infections

- Serious, including fatal (4%) infections occurred in 31% of patients receiving COPIKTRA 25 mg BID (N=442).
- The most common serious infections were pneumonia, sepsis, and lower respiratory infections.
- Treat infections prior to initiation of COPIKTRA. Advise patients to report any new or worsening signs and symptoms of infection.
For Grade 3 or higher infection withhold COPIKTRA until infection has resolved. Resume COPIKTRA at the same or reduced dose.
- Serious, including fatal Pneumocystis jirovecii pneumonia (PJP) occurred in 1% of patients taking COPIKTRA. Provide prophylaxis for PJP during treatment with COPIKTRA. Following completion of COPIKTRA treatment, continue PJP prophylaxis until the absolute CD4+ T cell count is greater than 200 cells/ μ L. Withhold COPIKTRA in patients with suspected PJP of any grade, and permanently discontinue if PJP is confirmed.
- CMV reactivation/infection occurred in 1% of patients taking COPIKTRA. Consider prophylactic antivirals during COPIKTRA treatment to prevent CMV infection including CMV reactivation. For clinical CMV infection or viremia, withhold COPIKTRA until infection or viremia resolves. If COPIKTRA is resumed, administer a reduced dose and monitor patients for CMV reactivation by PCR or antigen test at least monthly.

Diarrhea or Colitis

- Serious, including fatal (<1%), diarrhea or colitis occurred in 18% of patients receiving COPIKTRA 25 mg BID (N=442).
- Advise patients to report any new or worsening diarrhea.
- For non-infectious diarrhea or colitis, follow the guidelines below:
 - For patients presenting with mild or moderate diarrhea (Grade 1-2) (i.e. up to 6 stools per day over baseline) or asymptomatic (Grade 1) colitis:
 - Initiate supportive care with antidiarrheal agents as appropriate, continue COPIKTRA at the current dose, and monitor the patient at least weekly until the event resolves.
 - If the diarrhea is unresponsive to antidiarrheal therapy, withhold COPIKTRA and initiate supportive therapy with enteric acting steroids (e.g. budesonide). Monitor the patient at least weekly. Upon resolution of the diarrhea, consider restarting COPIKTRA at a reduced dose.
 - For patients presenting with abdominal pain, stool with mucus or blood, change in bowel habits, peritoneal signs, or with severe diarrhea (Grade 3) (i.e. > 6 stools per day over baseline) follow the guidelines below:
 - Withhold COPIKTRA and initiate supportive therapy with enteric acting steroids (e.g. budesonide) or systemic steroids. A diagnostic work-up to determine etiology, including colonoscopy, should be performed. Monitor at least weekly. Upon resolution of the diarrhea or colitis, restart COPIKTRA at a reduced dose.
 - For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue COPIKTRA.
- Discontinue COPIKTRA for life-threatening diarrhea or colitis.

Cutaneous Reactions

- Serious, including fatal (<1%), cutaneous reactions occurred in 5% of patients receiving COPIKTRA 25 mg BID (N=442).
- Fatal cases included drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN).
- Advise patients to report any new or worsening cutaneous reactions.
- Review all concomitant medications and discontinue any medications potentially contributing to the event.
- For patients presenting with mild or moderate (Grade 1-2) cutaneous reactions, continue COPIKTRA at the current dose, initiate supportive care with emollients, anti-histamines (for pruritus), or topical steroids, and monitor the patient closely.
- Withhold COPIKTRA for severe (Grade 3) cutaneous reaction until resolution. Initiate supportive care with steroids (topical or systemic) or anti-histamines (for pruritus). Monitor at least weekly until resolved. Upon resolution of the event, restart COPIKTRA at a reduced dose. Discontinue COPIKTRA if severe cutaneous reaction does not improve, worsens, or recurs.
- For life-threatening cutaneous reactions, discontinue COPIKTRA.
- In patients with SJS, TEN, or DRESS of any grade, discontinue COPIKTRA.

Pneumonitis

- Serious, including fatal (<1%), pneumonitis reactions occurred in 5% of patients receiving COPIKTRA 25mg BID (N=442).
- Withhold COPIKTRA in patients who present with new or progressive pulmonary signs and symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates on a radiologic exam, or a decline by more than 5% in oxygen saturation, and evaluate for etiology. If the pneumonitis is infectious, patients may be restarted on COPIKTRA at the previous dose once the infection, pulmonary signs and symptoms resolve.
- For moderate non-infectious pneumonitis (Grade 2), treat with systemic corticosteroids, and resume COPIKTRA at a reduced dose upon resolution.
- If non-infectious pneumonitis recurs or does not respond to steroid therapy discontinue COPIKTRA.
- For severe or life-threatening non-infectious pneumonitis, discontinue COPIKTRA and treat with systemic steroids.

Indication

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.
 - Relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies.
- 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.

***AREMS (Risk Evaluation and Mitigation Strategy)** is a program required by the FDA to manage known and potential serious risks associated with a drug product. FDA has determined that a REMS is necessary to inform healthcare providers that COPIKTRA can cause fatal and/or serious toxicities including infections, diarrhea or colitis, cutaneous reactions, and pneumonitis. This Fact Sheet is required by the FDA as part of the COPIKTRA REMS Program.

Adverse Event Reporting

To report side effects during the use of COPIKTRA, contact Verastem Oncology at 1-877-779-8786 and/or to FDA at www.fda.gov/medwatch or call 1-800-FDA-1088.

For the complete safety profile of COPIKTRA, please see the full Prescribing Information, available at www.COPIKTRAREMS.com.





PATIENT SAFETY WALLET CARD



Prescriber Phone Number

COPIKTRA Prescriber Name

Patient Name

FOR HEALTHCARE PROVIDERS

 I am taking COPIKTRA for my treatment of leukemia or lymphoma.

+ IMPORTANT SAFETY INFORMATION YOU SHOULD KNOW:

COPIKTRA can cause fatal and/or serious toxicities including infections, diarrhea or colitis, cutaneous reactions, and pneumonitis. Contact the healthcare provider on this card **immediately** if your patient reports any signs or symptoms.



+ IMPORTANT SAFETY INFORMATION

FOR THE PATIENT

COPIKTRA can cause these serious side effects that may lead to death:

- Infections
- Diarrhea or inflammation of your intestine (colitis)
- Skin reactions
- Inflammation of the lungs

If you have any of these symptoms, call your healthcare provider right away:

- Fever, chills, or other signs of infection
- New or worsening diarrhea
- Stool with mucus or blood
- Severe stomach-area (abdominal) pain
- New or worsening skin rash or other skin reactions, including:
 - Painful sores or ulcers on your skin, lips, or in your mouth
 - Severe rash with blisters or peeling skin
 - Rash with itching
 - Rash with fever
- New or worsening cough or difficulty breathing



IMPORTANT TO REMEMBER: Call your doctor or get emergency medical care right away if you have any of these symptoms! Show this card to any doctor involved in your care!



PURPOSE

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

The purpose of the COPIKTRA™ REMS is to mitigate the risk of fatal and serious toxicities including:

- **Infections**

○ Serious, including fatal (4%) infection occurred in 31% of patients receiving COPIKTRA 25 mg twice daily (N=442).

- **Diarrhea or Colitis**

○ Serious, including fatal (<1%), diarrhea or colitis occurred in 18% of patients receiving COPIKTRA 25 mg twice daily (N=442).

- **Cutaneous Reactions**

○ Serious, including fatal (<1%) cutaneous reactions occurred in 5% of patients receiving COPIKTRA 25 mg twice daily (N=442).

- **Pneumonitis**

○ Serious, including fatal (<1%) pneumonitis without an apparent infectious cause occurred in 5% of patients receiving COPIKTRA 25 mg twice daily (N=442).

For more detailed information on these risks, please see the [Fact Sheet](#).

INDICATION

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.
- Relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies.
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.

Counsel patients using the COPIKTRA Patient Safety Wallet Card. Provide the COPIKTRA [Patient Safety Wallet Card](#) to your patients.

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/

RICHARD PAZDUR
09/24/2018