# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

## *APPLICATION NUMBER:*

**211155Orig1s000**
**211155Orig2s000**

| | |
|---|---|
| ***Trade Name:*** | COPIKTRA capsules 25 mg, 15 mg |
| ***Generic or Proper Name:*** | duvelisib |
| ***Sponsor:*** | Verastem Inc. |
| ***Approval Date:*** | September 24, 2018 |
| ***Indication:*** | Original 1: For the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies.<br><br>Original 2: 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. |

# CENTER FOR DRUG EVALUATION AND RESEARCH

# 211155Orig1s000
# 211155Orig2s000

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 211155Orig1s000
# 211155Orig2s000

# APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 211155/Original 1

**ACCELERATED APPROVAL**

Verastem Inc.
Attention: Mary Matthew
Vice President Regulatory Affairs
117 Kendrick Street, Suite 500
Needham, MA 02494

Dear Ms. Matthew:

Please refer to your New Drug Application (NDA) dated February 5, 2018, received February 5, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for COPIKTRA (duvelisib) capsules, 25mg, 15mg.

NDA 211155 provides for the use of COPIKTRA (duvelisib) for the following indications which, for administrative purposes, we have designated as follows:

- NDA 211155/Original #1 – treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies
- NDA 211155/Original #2 – treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after at least two prior therapies

The subject of this action letter is NDA 21115/Original #1. We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

## APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

## CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on August 22, 2018, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 211155**." Approval of this submission by FDA is not required before the labeling is used.

## ADVISORY COMMITTEE

Your application for duvelisib was not referred to an FDA advisory committee because this drug is not the first in its class.

## ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated August 29, 2018. This requirement, along with required completion dates, is listed below.

PMR 3494-1 Conduct a randomized phase 3 clinical trial in patients with relapsed or refractory follicular lymphoma that verifies and isolates the clinical benefit of duvelisib. The primary endpoint would be progression-free survival as determined by an independent review committee.

| | |
|---|---|
| Final Protocol Submission: | 03/2019 |
| Trial Completion: | 06/2024 |
| Final Report Submission: | 12/2024 |

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

## POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of the serious and fatal risks of infections, diarrhea or colitis, cutaneous reactions, pneumonitis, hepatotoxicity, and neutropenia, which should be characterized in longer term safety assessments.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

PMR 3494-2 Characterize the safety of long-term use of duvelisib monotherapy in patient with hematologic malignancies treated with a planned dose of 25 mg twice daily on Trials IPI-145-02, IPI-145-06, IPI-145-07, and IPI 145-12 combined. Submit a complete study report and datasets characterizing safety and exposure after patients have been followed for an additional 2 years on treatment. Include evaluations, supplemented by narratives, of deaths in the absence of treated progressive disease, serious adverse reactions, and adverse reactions of special interest.

The timetable you submitted on August 29, 2018, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 12/2018 |
| Interim Report Submission: | 11/2019 |
| Final Report Submission: | 11/2020 |

Submit clinical protocols to your IND 112486 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

## POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

PMC 3494-4 Conduct a clinical pharmacokinetic trial with repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of duvelisib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Submit Final Report with datasets.

The timetable you submitted on September 13, 2018, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission: | 10/2018 |
| Final Protocol Submission: | 02/2019 |
| Final Report Submission: | 01/2020 |

PMC 3494-5 To allow dose reduction of duvelisib in patients who do not tolerate 15 mg twice daily, develop and test the product characteristics of a lower strength (5 mg or 10 mg) duvelisib formulation. Include results of process validation in the final report.

The timetable you submitted on September 18, 2018, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Report Submission: | 12/2019 |

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 112486 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

## RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for COPIKTRA (duvelisib) to ensure the benefits of the drug outweigh the risks of fatal and/or serious toxicities including infections, diarrhea or colitis, cutaneous reactions, and pneumonitis.

Your proposed REMS must also include the following:

**Communication Plan**: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe COPIKTRA (duvelisib) is necessary to ensure the benefits of the drug outweigh the risks. The communication plan provides for the dissemination of information about fatal and/or serious toxicities including infections, diarrhea or colitis, cutaneous reactions, and pneumonitis.

The communication plan must include, at minimum, the following:

1. Communication materials to inform health care providers about the REMS Program and the risks and safe use of COPIKTRA.
2. A description of the audience for the communication plan, stating specifically the types of health care providers to which the communication plan will be directed as well as the professional societies.
3. A schedule for when and how the plan's materials are to be distributed to healthcare providers and professional societies.

Your proposed REMS, submitted on September, 10, 2018, amended and appended to this letter, is approved. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce COPIKTRA (duvelisib) into interstate commerce.

The REMS assessment plan must 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 (duvelisib) 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.

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 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.
e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the

proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 211155 REMS CORRESPONDENCE**
**(insert concise description of content in bold capital letters, e.g.,**
**UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**NDA 211155 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 211155/S-000**
**CHANGES BEING EFFECTED IN 30 DAYS**
**PROPOSED MINOR REMS MODIFICATION**

***or***

**NEW SUPPLEMENT FOR NDA 211155/S-000**
**PRIOR APPROVAL SUPPLEMENT**
**PROPOSED MAJOR REMS MODIFICATION**

***or***

**NEW SUPPLEMENT FOR NDA 211155/S-000**
**PRIOR APPROVAL SUPPLEMENT**
**PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)**
**FOR NDA 211155/S-000**
**REMS ASSESSMENT**
**PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

**REMS REVISION FOR NDA 211155**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

## SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

## PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved prescribing information (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration

Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

## REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

## MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

## POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Rachel McMullen, Senior Regulatory Project Manager, at (240) 402-4574.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, MD
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
REMS

---

**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.**

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/s/

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RICHARD PAZDUR
09/24/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 211155/Original 2

**NDA APPROVAL**

Verastem Inc.
Attention: Mary Matthew
Vice President Regulatory Affairs
117 Kendrick Street, Suite 500
Needham, MA 02494

Dear Ms. Matthew:

Please refer to your New Drug Application (NDA) dated February 2, 2018, received February 5, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for COPIKTRA (duvelisib) capsules, 25mg, 15mg.

NDA 211155 provides for the use of COPIKTRA (duvelisib) for the following indications which, for administrative purposes, we have designated as follows:

- NDA 211155/Original #1 – treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies

- NDA 211155/Original #2 – treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after at least two prior therapies

The subject of this action letter is NDA 211155/Original #2. We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances

/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

## CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on August 22, 2018, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3).* For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 211155**." Approval of this submission by FDA is not required before the labeling is used.

## ADVISORY COMMITTEE

Your application for duvelisib was not referred to an FDA advisory committee because this drug is not the first in its class.

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

## POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of the serious and fatal risks of infections, diarrhea or colitis, cutaneous reactions, pneumonitis, hepatotoxicity, and neutropenia, which should be characterized in longer term safety assessments.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

PMR 3494-2 Characterize the safety of long-term use of duvelisib monotherapy in patients with hematologic malignancies treated with a planned dose of 25 mg twice daily on Trials IPI-145-02, IPI-145-06, IPI-145-07, and IPI145-12 combined. Submit a complete study report and datasets characterizing safety and exposure after patients have been followed for an additional 2 years on treatment. Include evaluations, supplemented by narratives, of deaths in the absence of treated progressive disease, serious adverse reactions, and adverse reactions of special interest.

The timetable you submitted on August 29, 2018, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 12/2018 |
| Interim Report Submission: | 11/2019 |
| Final Report Submission: | 11/2020 |

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of fatal adverse reactions, such as infections, in the absence of treated disease progression.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

PMR 3494-3 Submit reports and datasets for overall survival from trial IPI-145-07 with 5 years of follow-up, with an interim report after 3 years of follow-up, measured from the last patient’s randomization date. Include causes of death and narratives for death in the absence of treated disease progression.

The timetable you submitted on August 29, 2018, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Interim Report Submission: | 06/2019 |
| Final Report Submission: | 06/2021 |

Submit clinical protocols to your IND 112486 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at

the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

## POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

PMC 3494-4 Conduct a clinical pharmacokinetic trial with repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of duvelisib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Submit Final Report with datasets.

The timetable you submitted on September 13, 2018, states that you will conduct this study according to the following schedule:

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| Draft Report Submission: | 10/2019 |
| Final Report Submission: | 01/2020 |

PMC 3494-5 To allow dose reduction of duvelisib in patients who do not tolerate 15 mg twice daily, develop and test the product characteristics of a lower strength (5 mg or 10 mg) duvelisib formulation. Include results of process validation in the final report.

The timetable you submitted on September 18, 2018, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Report Submission: | 12/2019 |

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 112486 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

## RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for duvelisib to ensure the benefits of the drug outweigh the risks of fatal and/or serious toxicities including infections, diarrhea or colitis, cutaneous reactions, and pneumonitis.

Your proposed REMS must also include the following:

**Communication Plan**: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe COPIKTRA (duvelisib) is necessary to ensure the benefits of the drug outweigh the risks. The communication plan provides for the dissemination of information about fatal and/or serious toxicities including infections, diarrhea or colitis, cutaneous reactions, and pneumonitis.

The communication plan must include, at minimum, the following:

1. Communication materials to inform health care providers about the REMS Program and the risks and safe use of COPIKTRA.
2. A description of the audience for the communication plan, stating specifically the types of health care providers to which the communication plan will be directed as well as the professional societies.
3. A schedule for when and how the plan's materials are to be distributed to healthcare providers and professional societies.

Your proposed REMS, submitted on September 10, 2018, amended and appended to this letter, is approved. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce COPIKTRA (duvelisib) into interstate commerce.

The REMS assessment plan must 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 (duvelisib) 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.

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 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.
e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 211155 REMS CORRESPONDENCE**
**(insert concise description of content in bold capital letters, e.g.,**
**UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**NDA 211155 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 211155/S-000**
**CHANGES BEING EFFECTED IN 30 DAYS**
**PROPOSED MINOR REMS MODIFICATION**

***or***

**NEW SUPPLEMENT FOR NDA 211155/S-000**
**PRIOR APPROVAL SUPPLEMENT**
**PROPOSED MAJOR REMS MODIFICATION**

***or***

**NEW SUPPLEMENT FOR NDA 211155/S-000**
**PRIOR APPROVAL SUPPLEMENT**
**PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)**
**FOR NDA 211155/S-000**
**REMS ASSESSMENT**
**PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

**REMS REVISION FOR NDA 211155**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

## SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf ).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

## REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

## MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

## POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Rachel McMullen, Senior Regulatory Project Manager, at (240) 402-4574.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, MD
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
REMS

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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.**

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/s/

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RICHARD PAZDUR
09/24/2018