CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214783Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 21, 2021
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 214783
Product Name and Strength:	Rezurock (belumosudil) tablets, 200 mg
Applicant/Sponsor Name:	Kadmon Pharmaceuticals, LLC (Kadmon)
OSE RCM #:	2020-2047-3
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on June 14, 2021 for Rezurock. We reviewed the revised container label and carton labeling for Rezurock (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Iverson N. Label and Labeling Review Memo for Rezurock (NDA 214783). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 04. RCM No.: 2020-2047-2.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 4, 2021
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 214783
Product Name and Strength:	Rezurock (belumosudil) tablets, 200 mg
Applicant/Sponsor Name:	Kadmon Pharmaceuticals, LLC (Kadmon)
OSE RCM #:	2020-2047-2
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on April 16, 2021 for Rezurock. We reviewed the revised container label and carton labeling for Rezurock (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective. The Prescribing Information states the product must be stored and dispensed in the original container. To ensure this important information is not missed we recommend including the statement "Attention: Dispense and store Rezurock in original container with the desiccant to protect from moisture." on the principal display panel on the container label and carton labeling.

3 RECOMMENDATIONS FOR KADMON PHARMACEUTICALS, LLC (KADMON)

We recommend the following be implemented prior to approval of this NDA:

[a] Iverson N. Label and Labeling Review for Rezurock (NDA 214783). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 12. RCM No.: 2020-2047-1.

A. General Comments (Container label and Carton labeling)

1. The Prescribing Information states the product must be stored and dispensed in the original container. To ensure this important information is not missed we recommend including the statement "Attention: Dispense and store Rezurock in original container with the desiccant to protect from moisture." on the principal display panel on the container label and carton labeling.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 12, 2021
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 214783
Product Name and Strength:	Rezurock (belumosudil) tablets, 200 mg
Applicant/Sponsor Name:	Kadmon Pharmaceuticals, LLC (Kadmon)
OSE RCM #:	2020-2047-1
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on March 22, 2021 for Rezurock. We reviewed the revised container label and carton labeling for Rezurock (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective. The net quantity statement is in close proximity to the product strength and the linear barcode is presented in an horizontal position.

3 RECOMMENDATIONS FOR KADMON PHARMACEUTICALS, LLC (KADMON)

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container label and Carton labeling)
    1. The net quantity statement is in close proximity to the product strength. From post-marketing experience, the risk of numerical confusion between the

[a] Iverson N. Label and Labeling Review for Rezurock (NDA 214783). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 04. RCM No.: 2020-2047.

strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Product selection or dosing errors can occur if the net quantity statement is mistaken for the product strength, leading to over-dosing. We recommend relocating the net quantity statement away from and less prominent than the product strength, such as to the bottom of the principal display panel.

B. Container label

1. We recommend re-orientating the linear barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to bottle curvature.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 8, 2021

To: Rosa Lee-Alonzo, Regulatory Project Manager
Division of Hematologic Malignancies 1 (DHM1)

William Pierce, Associate Director for Labeling, DHM1

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for REZUROCK™ (belumosudil) tablets, for oral use

NDA: 214783

In response to DHM1's consult request dated October 6, 2020, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for the original NDA submission for REZUROCK™ (belumosudil) tablets, for oral use (Rezurock).

Labeling: OPDP's review of the proposed labeling was based on the draft labeling accessed from SharePoint on April 7, 2021, and we have no additional comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on April 8, 2021.

Thank you for your consult. If you have any questions, please contact Nisha Patel at (301) 796-3715 or nisha.patel@fda.hhs.gov.

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NISHA PATEL
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	April 8, 2021
To:	Rosa J. Lee-Alonzo, PharmD, RAC Senior Regulatory Project Manager **Division of Hematologic Malignancies 1 (DHM1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nisha Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	REZUROCK (belumosudil)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 214783
Applicant:	Kadmon Pharmaceuticals, LLC

1 INTRODUCTION

On September 30, 2020, Kadmon Pharmaceuticals, LLC submitted for the Agency's review an original New Drug Application (NDA) 214783 for REZUROCK (belumosudil) tablets. The proposed indication for REZUROCK (belumosudil) tablets is for the treatment of patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least (b) (4) of systemic therapy.

On March 9, 2021, the Applicant submitted a major amendment to the application; therefore, the Agency extended the goal date by three months in order to provide time for a full review of the submission.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematologic Malignancies 1 (DHM1) on October 6, 2020 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for REZUROCK (belumosudil) tablets.

2 MATERIAL REVIEWED

- Draft REZUROCK (belumosudil) tablets PPI received on September 30, 2020, and received by DMPP and OPDP on April 6, 2021.
- Draft REZUROCK (belumosudil) tablets Prescribing Information (PI) received on September 30, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 6, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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CLINICAL INSPECTION SUMMARY

Date	March 15, 2021
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Robert Q. Le, M.D., Ph.D., Medical Officer Donna Przepiorka, M.D., Ph.D., Clinical Team Leader R. Angelo de Claro, M.D., Division Director Rosa J. Lee-Alonzo, PharmD, RAC, Regulatory Project Manager Division of Hematology Malignancy 1 Office of Oncology Diseases
NDA	NDA 214783
Applicant	Kadmon Corporation, LLC
Drug	Belumosudil (KD025) (Rezurock™)
NME	Yes
Division Classification	Rho-associated coiled-coil kinase 2 (ROCK2) inhibitor
Proposed Indication	Treatment of patients 12 years and older with chronic graft-versus-host disease (cGvHD) after failure of at least (b) (4) of systemic therapy
Review Type	Priority
Consultation Request Date	October 14, 2020
Summary Goal Date	March 31, 2021
Action Goal Date	May 9, 2021
PDUFA Date	May 28, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from two studies (KD025-213 and KD025-208) were submitted to the Agency in support of a New Drug Application (NDA 214783) for Belumosudil (KD025, Rezurock™), proposed for treatment of patients 12 years and older with chronic graft-versus-host disease (cGvHD) after failure of at least (b) (4) of systemic therapy. Three clinical investigator sites (Zachariah M. DeFilipp, M.D., Marcello Rotta, M.D., and Behyar Zoghi, M.D.) and the sponsor (Kadmon Corporation) were inspected in NDA 214783.

Based on these inspections, the conduct of the above Studies KD025-213 and KD025-208 appears to be adequate, despite regulatory deficiencies observed at a clinical investigator site (Dr. Rotta) and the sponsor (Kadmon Corporation). The study data submitted to the Agency appear acceptable in support of this NDA for the proposed indication.

II. BACKGROUND

Glucocorticoids, with or without calcineurin inhibitors (i.e., cyclosporine and tacrolimus) remain the initial standard of therapeutic care for patients with chronic graft versus host disease, in patients requiring systemic therapy, with significant complications. Other non-first line systemic therapies under investigation and considered in clinical settings may include mammalian target of rapamycin (mTOR) inhibitors (i.e., sirolimus and everolimus), mycophenolate mofetil, rituximab and ibrutinib.

While B cells play a role, donor dendritic cells also help to mature the peripheral tissues in chronic graft versus host disease and is followed by antigen presentation to CD4+ and CD8+ T cells. Activated B cells with antibody production result in tissue destruction. Autoreactive T cell differentiation result in cytokine release.

Belumosudil (KD025) is a Rho-associated coiled-coil kinase 2 (ROCK2) inhibitor proposed for the treatment of chronic graft versus host disease. The data presented in this application is to support a single agent belumosudil from the Phase 2 trials KD025-213 and KD025-208 for the treatment of patients 12 years and older with chronic graft-versus-host disease (cGvHD) after failure of at least (b) (4) of systemic therapy. These two studies form the basis for the regulatory decision-making process for this application.

Study KD025-213

Study KD025-213 was a Phase 2, randomized, multicenter, open-label two-dose study arm study designed to evaluate the efficacy and safety of belumosudil in subjects with active cGvHD after at least 2 prior lines of systemic therapy.

The primary study objective of this study was to evaluate the efficacy and safety of belumosudil, at dose levels of 200 mg once daily and 200 mg twice daily, in subjects with cGvHD who had previously been treated with at least 2 prior lines of systemic therapy.

Subjects received belumosudil treatment in 28-day cycles until clinically significant progression of cGvHD (defined as progression that required the addition of new systemic therapy for cGvHD), histologic recurrence of underlying malignancy, unacceptable toxicity, Investigator decision, subject preference/withdrawal of consent, loss of follow-up, Sponsor decision, or death (whichever occurred first).

The primary efficacy endpoint was overall response rate (ORR). ORR was as defined by the 2014 NIH Consensus Development Project on Clinical Trials in cGvHD and as assessed by Investigators. Responders included subjects that achieved a response, defined as the study subjects who achieved complete response [CR] and partial response [PR].

There are 33 clinical study sites in the United States. There were 135 subjects who were randomized. The study initiation date was on October 11, 2018. The end date of the reporting period for this ongoing study was on February 19, 2020.

Study KD025-208

Study KD025-208 was a Phase 2a study. Subjects who signed an Institutional Review Board-approved informed consent form and met all eligibility criteria were enrolled in the study. Subjects received orally administered belumosudil 200 mg once daily (Cohort 1), belumosudil 200 mg twice daily (Cohort 2), or belumosudil 400 mg once daily (Cohort 3). Study drug was administered with food, in 28-day cycles until disease progression or unacceptable toxicity occurred. From Protocol Amendment 5.0 (May 29, 2018) onward, subjects who had a response assessment, in the "Lack of Response (LR) - Mixed (LR-M)" category, were permitted to continue treatment with belumosudil, and remained in the study if the study investigator considered continued treatment to be in the subject's best interest.

The primary study objectives were (a) to evaluate the activity of belumosudil in subjects with active, steroid-dependent cGvHD in terms of partial response and complete response as defined by the 2014 National Institutes of Health (NIH) Consensus Development Project on Clinical Trials in cGvHD; and (b) to evaluate the safety and tolerability of belumosudil in subjects with cGvHD.

The Overall Response Rate (ORR), as per 2014 NIH criteria, was the primary endpoint of the study. Responses were assessed by investigators.

This Phase 2a study was conducted in seven study sites in the U.S. There were 54 study subjects who enrolled in this study. The study initiation date was on September 27, 2016. The end date of reporting period for this ongoing study was on February 19, 2020.

III. RESULTS (by site)

1. **Zachariah M. DeFilipp, M.D. / Site 004**
   55 Fruit St., Massachusetts General Hospital
   Boston, MA 02114
   Inspection dates: November 12 to 18, 2020

   Dr. DeFillip serves as principal investigator and Dr. Cutler (clinical site investigator initially requested in DHM1's consult) serves as sub-investigator at this site for Study KD025-213. A total of 19 study subjects were screened and 15 study subjects were enrolled and received study treatment. Six patients continue in this ongoing study. Nine enrolled study subjects with chronic Graft versus Host Disease discontinued, after receiving study treatment, for the following reasons: one subject died of an infection, two subjects had severe adverse events, two study subjects withdrew from the study, three subjects discontinued after treatment due to unspecified reasons, and a patient was withdrawn by study clinical investigator.

   Records reviewed included but were not limited to: investigator agreements, financial disclosure forms, Institutional Review Board (IRB) approvals and documentation, delegation log, screening and enrollment log, monitoring log and monitoring reports, electronic case report forms (eCRFs), subject source records, test article control records, adverse event/serious adverse event documentation, and informed consent documentation.

Source records for all enrolled study patients at the site were reviewed and compared with the submitted data listings for the site. The primary efficacy endpoint data were verified against the data line listings. No discrepancies were noted. There was no under-reporting of serious adverse events.

2. Marcello Rotta, M.D. / Site 098
1721 E 19th Avenue
Denver, CO 80218

Inspection dates: November 11 to 23, 2020

Dr. Rotta was inspected for Study KD025-213. A total of 21 subjects were screened and nine study patients enrolled. All nine enrolled study subjects received study treatment. This study is still ongoing with three subjects still receiving the investigational drug product, four subjects are in long-term follow up, one subject withdrew consent, and one subject died.

The inspection review covered the study protocol and amendments, IRB submissions and approvals, subject selection criteria and informed consents, clinical source data including subject evaluations, investigational new drug accountability records, sponsor monitoring activities, adverse event reporting, signed FDA Form 1572s, and financial disclosure statements.

Source records at the site were reviewed and compared against the case report forms and sponsor data line listings. Treatment assignments and patient disposition, concomitant study medications (background nonstudy treatments), and primary endpoints data were verifiable.

At the inspection close-out, Dr. Rotta was issued FDA Form 483, Inspectional Observations, for failure to conduct the investigation in accordance with the investigational plan and failure to maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. Specifically,

1) Delay in SAE Reporting: Subject# (b) (6) had two SAEs requiring hospitalization, that were not reported within 24 hours of onset. The first SAE (bronchopneumonia infection) occurred on (b) (6), and the second SAE (MSSA bacteremia infection) episode was on (b) (6).
2) Inadequate oversight of study staff: Two Clinical Research Coordinators at different visit time points, marked off on a single page section of the Provider's Survey response item form (cGVHD Activity Assessments) that they were not qualified to perform for Subject #s (b) (6).
3) Failure to prepare and maintain adequate and legible source documents: the source records were inadequate for Subject #s (b) (6).

In addition, there were sporadic missing original assessment or procedure source documents at various specific calendar date visits for several patients, such as (a) missing a Provider Survey form in Subject #(b) (6), (b) missing original ECG in Subject #(b) (6), and (c) missing the cGVHD Activity Assessment-Patient Self Report Missing Provider Survey in Subject #(b) (6).

In response to the above inspectional observations (FDA Form 483) on December 14, 2020, responded adequately to the regulatory violation citations. Specifically,

- Dr. Rotta instituted retraining of study staff with urgent and timely serious adverse event reporting, completed additional standard operating procedures, and conducted staff retraining for clinical trial management adherence according to principles of Good Document Practices (GDP).
- The clinical investigator site (Dr. Rotta) noted that the corrections were made at the request of the application sponsor (Kadmon) at monitoring visits, or sponsor-requested EDC queries.
- Dr. Rotta mentioned that every response item change was re-reviewed by the site principal investigator (Dr. Rotta) or a site sub-investigator. The PI stated that the Clinical Research Coordinator was qualified to make corrections on the Provider's Survey response item form, and that the research coordinator completed protocol-specific training on how to compete these survey forms. Further, in Dr. Rotta's response, he stated that Kadmon (sponsor) was aware of Site #098's practice for completing these forms.
- Dr. Rotta indicated that these missing documents were misplaced but not lost. Subsequently, these study documents were scanned and reported accordingly to the sponsor.

Reviewer comments: GCPAB discussed the regulatory violations and clinical site responses with DHM1. Although the above findings are regulatory violations, these findings do not appear to have a significant impact on the safety and efficacy analyses.

3. Behyar Zoghi, M.D. / Site 079
4450 Medical Drive
San Antonio, TX 78229

Inspection dates: November 2 to 5, 2020

Dr. Zoghi was inspected for Study KD025-208 and Study KD025-213.

For Protocol KD025-208, there were six screened subjects and four subjects were randomized into the study. Three of the four enrolled subjects dropped out of the study, due to one progression of disease, one lost to follow up, and one removed by principal investigator due to drug non-compliance. One subject remains on this ongoing study.

For Study KD025-213, fourteen subjects were screened into the study. Eight subjects were randomized into the study and received study treatment. Seven of the eight study subjects who received treatment discontinued from the study: one study subject due to disease progression, two study subjects withdrew from the study, one patient died, two study subjects were lost to follow-up, and a single subject discontinued for unspecified reasons. One subject remains on this ongoing study.

The following study records were assessed protocol deviations, study inclusion criteria, exclusionary laboratory values, drug administration, concomitant medications, adverse event reporting, electronic medical records including physician and nurses' notes and imaging studies. Records review were conducted for study eligibility for all enrolled subjects for both studies. There were no limitations during conduct of the clinical investigation.

Source records at the site for all enrolled study patients in Study KD025-213 and Study KD025-208, respectively, were reviewed and compared against the case report forms and sponsor data line listings. The primary efficacy endpoint data were verified against the data line listings. No discrepancies were noted. No under-reporting of serious adverse events was noted.

4. **Kadmon Corporation, LLC**
55 Cambridge Parkway, Suite 300E
Cambridge, MA 02142

Inspection dates: December 3 to 8, 2020

An onsite inspection assessed Kadmon Corporation's responsibilities for oversight of Study KD025-213 and Study KD025-208.

The inspection included a review of the organizational charts, investigator agreements, transfer of obligations, financial disclosures with the sponsor, study master file, assessment of selection of clinical study site investigators, and selection of clinical study monitors and their training records. Standard operating procedures were evaluated, principally concerning clinical site monitoring, data collection, and handling of adverse event data.

Clinical study conduct in these clinical investigative sites and sponsor trial oversight were found to be appropriate, except for Site #098 (Dr. Marcell Rotta). With the exception of Site #098, no underreporting of significant adverse events (SAEs) to the Agency was noted. FDA did not encounter any barriers during the sponsor site audit. In general, study procedures, recordkeeping and reporting procedures were adequate.

A FDA Form 483 was issued at the close of the sponsor inspection for failure to promptly bring an investigator site who did not comply with the signed agreement, the general investigational plan, and applicable regulatory requirements into compliance. The sponsor did not bring promptly into compliance, Dr. Marcell Rotta's clinical investigation site #098 in Study KD024-213. Specifically, 21 of 24 Interim Monitoring Visit Reports showed that sponsor did not maintain adequate study oversight.

Problems found in the sponsor Interim Monitoring Visit Reports and Site Corrective Action Preventive Action plans included the following examples: subject personal health information not redacted; response assessments for Provider Surveys not completed correctly; missing source documentation; source data discrepancies; multiple adverse events not entered into the electronic data capture system; adverse events not assessed appropriately; protocol deviations not reported to the IRB; concomitant medications not documented appropriately; study questionnaires not signed or dated by subjects, or queries not resolved in a timely fashion.

In sponsor's response to the FDA observations on December 24, 2020, sponsor implemented (b) (4) plus sponsor retraining clinical study sites of sponsor responsibilities covering 21 CFR Part 312, specifically section 312.56 (b). Further, a total of three subjects are still actively receiving study drug (Subjects (b) (6)) who will be transferred to a new study site. On December 23, 2020, Kadmon ended site KD024-213-098 participation, and notified Dr. Rotta this clinical site is closed, due to failure to secure compliance during the course of the study.

Kadmon Corporation's response dated December 24, 2020, to the FDA Form 483, was found to be adequate.

Additional Comments:
The application was submitted under a Real-Time Oncology Review Submission. (b) (4) *was the Contract Research Organization (CRO) for data management oversight and analysis programming for the submitted studies. During the NDA review, the sponsor submitted Study KD025-208, Study KD025-213, Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) datasets, with 12-month data on November 25, 2020 (SN0021) and updated datasets on November 30, 2020 (SN0022). On December 10, 2020, in response to the review division's information request to clarify which submission contained the most updated datasets, the sponsor stated that they noted that many of the Study KD025-208 and Study KD025-213 dataset files failed to be exported to a submission output. Consequently, these datasets were not submitted to the Agency due to the errors that occurred in their publishing tool. On December 10, 2020 (SN0026), the sponsor also submitted all corrected Study KD025-208 and Study KD025-213 datasets with 12-month data. The OSI AB review team discussed this with the review division. DHM1 confirmed that all corrected datasets were submitted to the Agency. Further, the DHM1 Medical Team had no additional concerns. Considering the programing errors were identified and corrected timely and there is no impact on the efficacy and safety analyses of the submitted studies, the additional CRO inspection was not requested in the current COVID-19 pandemic situation.*

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
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Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 04, 2021
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 214783
Product Name, Dosage Form, and Strength:	Rezurock (belumosudil) 200 mg, tablets
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Kadmon Corporation, LL (Kadmon)
FDA Received Date:	May 20, 2020 and July 24, 2020
OSE RCM #:	2020-2047
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process for NDA 214783 Rezurock (belumosudil) tablets, 200 mg, this review evaluates the proposed container label, carton labeling, Prescribing Information (PI) and Patient Information for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C– N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F– N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Kadmon submitted a 505(b)(1) application to obtain marketing approval of Rezurock (belumosudil) tablets. Rezurock is proposed for the treatment of patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least (b) (4) of systemic therapy.

The proposed PI includes instructions to store and dispense Rezurock tablets in the original container only versus simply retaining original packaging until dispensing. We considered that it may be necessary for pharmacies to dispense a quantity less than a full bottle (e.g. cash payers, vacation supply, or an emergency supply until patients can see the doctor for a new prescription). Furthermore, hospital pharmacies may repackage Rezurock (belumosudil) tablets in unit-dose blister packs because drugs are routinely dispensed in unit-doses in the usual

hospital setting. After discussion with the review team it was determined that the proposed product will be used as third line of therapy primarily in the outpatient setting. Therefore, the review team decided to not pursue a unit-dose blister packaging. Based on this reasoning and the fact that the current proposed packaging configuration is 30-count tablet bottles, we find this approach acceptable from a medication safety perspective.

We performed a risk assessment of the proposed container label, carton labeling, PI, and Patient Information for Rezurock tablets to determine whether there are significant concerns in terms of safety related to preventable medication errors. We identified areas of the proposed label and labeling that could be revised to improve clarity and readability of important information. For the Division, we note that the PI lacks clarity in the administration instructions and contains abbreviations and symbols. For the Applicant, we note the linear barcode is missing, the format for the expiration date is not defined, prominence of the Rx only statement, and missing product identifiers. In addition, we note the use of terminology inconsistent with the PI. These factors may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed container labels, carton labeling, and PI, that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Kadmon to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 1 (DHM 1)

A. Prescribing Information

1. Dosage and Administration Section
    a. Section 2.1 Recommended Dosage
        i. We note the Patient Information indicates that Rezurock should be not cut, crushed, or chewed. However, this information is missing from the Section 2 Dosage and Administration of the PI. We recommend revising the statement, "(b) (4) ." to "Swallow REZUROCK tablets whole. Do not cut, crush, or chew REZUROCK tablets."
    b. As currently presented, Section 2.2 *Dose Modifications for Adverse Reactions* of the PI contains the symbols, ">", "≥", and "≤". Error prone symbols may lead to misinterpretation and medication error. We

recommend replacing the symbols, ">", "≥", and "≤" with their intended meanings.

c. Section 2.4 (b) (4)

i. We recommend deleting this section as this information is already located in Section 2.1 *Recommended Dosage* of the Prescribing Information.

2. (b) (4)

3. How Supplied/Storage and Handling Section

a. As currently presented, the description of the container closure, uses the abbreviation, "(b) (4)". Error prone abbreviations may lead to misinterpretation and medication error. We recommend deleting "(b) (4) " as this may cause confusion. Revise statement to read "200 mg tablets in 30 count bottle: NDC 79802-200-30".

4.2 RECOMMENDATIONS FOR KADMON CORPORATION, LL (KADMON)

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. The established name is the active ingredient plus the dosage form. Thus, we recommend relocating the dosage form to appear next to the established name as follows:

   Rezurock

   belumosudil tablets

2. The linear barcode is missing on the container label or carton labeling. The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2). Add the product's linear barcode to the container label and carton labeling as required per 21CFR 201.25(c)(2).

3. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.
4. The terminology within the Dosage statement is inconsistent with the terminology in the Prescribing Information. To ensure consistency with the terminology in the Prescribing Information revise the dosage statement to read, "Recommended Dosage: See prescribing information."
5. The Rx Only statement appears as prominent. We recommend decreasing the prominence of the Rx only by debolding.

1. The PI states the product must be stored and dispense in the original container. To ensure this important information is not missed we recommend including the statement "Attention: Dispense and store Rezurock in original container with the desiccant to protect from moisture." on the principal display panel.
2. We recommend adding the statement "Store in the original container with the desiccant to protect from moisture." next to the storage information on the side panel.

B. Container Label

1. If space permits, consider adding the statements, "Swallow tablets whole. Do not cut, crush, or chew the tablets." on the principal display panel of the container labels. We recommend this revision to mitigate the risk of product administration errors.

C. Carton Labeling

1. Add the statements, "Swallow tablets whole. Do not cut, crush, or chew the tablets." on the principal display panel of the carton labeling. We recommend this revision to mitigate the risk of product administration errors.
2. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.1 The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction

in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

[1]The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Rezurock received on July 24, 2020 from Kadmon Corporation, LL (Kadmon).

Table 2. Relevant Product Information for Rezurock	
Initial Approval Date	N/A
Active Ingredient	belumosudil
Indication	For the treatment of patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least (b) (4) of systemic therapy.
Route of Administration	Oral
Dosage Form	200 mg
Strength	tablets
Dose and Frequency	The recommended dose of REZUROCK is 200 mg given orally once daily.
How Supplied	REZUROCK 200 mg tablets are supplied as pale yellow oblong tablets containing 200 mg of belumosudil (equivalent to 242.5 mg belumosudil mesylate). Each tablet is debossed with "KDM" on one side and "200" on the other side and is packaged as follows: 200 mg tablets: 30 count (b) (4) bottle
Storage	Store at room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C and 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 14, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Rezurock. Our search did not identify previous labeling reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Rezurock labels and labeling submitted by Kadmon Corporation, LL (Kadmon).

- Container label received on July 24, 2020
- Carton labeling received on July 24, 2020
- Prescribing Information and Patient Information (Image not shown) received on July 24, 2020, available from \\CDSESUB1\evsprod\nda214783\0003\m1\us\114-labeling\114a-draft-label\prop-lbl-pdf.pdf

G.2 Label and Labeling Images

Container label

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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