APPLICATION NUMBER:

214783Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
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<th><strong>Application Type</strong></th>
<th>NDA</th>
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<td><strong>Application Number</strong></td>
<td>214783</td>
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<td><strong>PDUFA Goal Date</strong></td>
<td>August 30, 2021</td>
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<td><strong>OSE RCM #</strong></td>
<td>2020-2046; 2020-2048</td>
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<td><strong>Reviewer Name(s)</strong></td>
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<td><strong>Review Completion Date</strong></td>
<td>July 15, 2021</td>
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<td><strong>Subject</strong></td>
<td>Review to determine if a REMS is necessary</td>
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<tr>
<td><strong>Established Name</strong></td>
<td>belumosudil</td>
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<td><strong>Trade Name</strong></td>
<td>Rezurock</td>
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<tr>
<td><strong>Name of Applicant</strong></td>
<td>Kadmon Corp LLC</td>
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<tr>
<td><strong>Therapeutic Class</strong></td>
<td>kinase inhibitor</td>
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<tr>
<td><strong>Formulation(s)</strong></td>
<td>200 mg tablets</td>
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<tr>
<td><strong>Dosing Regimen</strong></td>
<td>200 mg taken orally once daily with food</td>
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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Rezurock (belumosudil) is necessary to ensure the benefits outweigh its risks. Kadmon Corp LLC submitted a New Drug Application (NDA) 214783 for belumosudil with the proposed indication for the treatment of patients 12 years and older with chronic graft-versus-host disease (cGVHD) after failure of at least \( (0.4) \) of systemic therapy. The serious risk associated with the use of belumosudil is embryo-fetal toxicity. The applicant did not submit a REMS with this application but proposed describing these risks in the Prescribing Information (PI) that includes Warnings and Precautions, as well as information to be included in Patient Counseling Information, and a Patient Package Insert (patient labeling or PPI).

The Division of Risk Management (DRM) and the Division of Hematologic Malignancies 1 (DHM1) have determined that if approved, a REMS is not necessary to ensure the benefits of belumosudil outweigh its risks. Chronic GVHD is the major cause of late nonrelapse death following HSCT. Chronic GVHD is a serious condition and, there is a clear need for therapeutic strategies with new alternative modalities that encompass a better tolerated treatment option for patients with cGVHD after failure of at least two prior lines of systemic therapy. Belumosudil appeared efficacious in its primary outcomes of overall response rate (ORR), and its risks can be communicated and managed through labeling. Based on the efficacy and safety information currently available, the clinical reviewer recommends approval of belumosudil for the treatment of adult and pediatric patients 12 years and older with cGVHD after failure of at least two prior lines of systemic therapy. The most concerning adverse reaction observed with the use of belumosudil is embryo-fetal toxicity. Based on its mechanism of action and findings from animal data, belumosudil can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of belumosudil to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes, including alterations to growth, embryo-fetal mortality, and embryo-fetal malformations at maternal exposures (AUC) approximately ≥ 3- (rat) were and ≥ 0.07 (rabbit) times the human exposure (AUC) at the recommended dose. Fetal-malformations in rat study included were absence of anus and tail, omphalocele, and dome shaped head. Embryo-fetal effects in rabbit study included were spontaneous abortion, increased post-implantation loss, decreased percentage of live fetuses, malformations, and decreased fetal body weight and the malformations included were those in the tail (short), ribs (branched, fused or deformed), sternebrae (fused), and neural arches (fused, misaligned, and deformed). DHM1 determined based on the available data that the risk of embryo-fetal toxicity did not rise to the level of a boxed warning.

If belumosudil is approved, labeling, including information in Warnings and Precautions, Patient Counseling Information, and in the PPI will be used to communicate the safety issues and management of toxicities associated with belumosudil. Besides being communicated in the Warnings and Precautions section of the label, recommended guidance to use effective contraception for females of reproductive potential and males with female partners of reproductive potential during treatment with belumosudil and for at least one week after the last dose will be communicated in the Use in Specific Populations section of the label.
1 Introduction

This review evaluates whether a REMS for the NME belumosudil is necessary to ensure the benefits outweigh its risks. Kadmon Corp LLC submitted a NDA 214783 for belumosudil with the proposed indication for the treatment of patients 12 years and older with chronic graft-versus-host disease (cGVHD) after failure of at least \( \text{2} \) of systemic therapy.\(^2\) The applicant did not submit a REMS with this application but proposed describing the risks in the PI that includes Warnings and Precautions, as well as information to be included in Patient Counseling Information, and a Patient Package Insert (patient labeling or PPI).

2 Background

2.1 PRODUCT INFORMATION

Belumosudil is a NME NDA type 505(b)(1) pathway application.\(^a\) It is a rho-associated, coiled-coil containing protein kinase-2 (ROCK2) inhibitor. Belumosudil also demonstrated inhibitory activity for ROCK1, with approximately 30 times greater affinity for ROCK2 compared to ROCK1. Belumosudil reduced secretion of interleukin (IL)-17 and IL-21 in human T cells and down-regulation of signal transducer and activator of transcription 3 (STAT3) phosphorylation in ex-vivo assays. In vivo, belumosudil demonstrated activity in animal models of chronic GVHD.\(^1\) Belumosudil is available in 200mg tablet. The recommended dose of belumosudil is 200 mg given orally once daily until progression of chronic GVHD that requires new systemic therapy.\(^b\) Belumosudil was granted orphan drug designation for the treatment of cGVHD on October 5, 2017 and breakthrough therapy designation for the treatment of adult patients with cGVHD after failure of two or more lines of systemic therapy on October 16, 2018. Belumosudil is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for belumosudil (NDA 214783) relevant to this review:

- 01/08/2016: Investigation New Drug (IND) 125890 submission for belumosudil (KD025; SLx-2119) was received.
- 10/05/2017: Orphan Drug Designation granted
- 10/16/2018: Breakthrough Therapy Designation granted
- 09/30/2020: NDA 214783 submission for belumosudil with the proposed indication for the treatment of patients 12 years and older with cGVHD after failure of at least \( \text{2} \) of systemic therapy, received.
- 01/19/2021: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for belumosudil.

\(^a\) Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

\(^b\) Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.
3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

GVHD is an adverse immunologic phenomenon observed after allogenic hematopoietic stem cell transplant (HSCT). GVHD is a complex disease with acute and chronic presentations and multiorgan involvement. The incidence of GVHD is as high as 40% to 60% in patients receiving HSCTs.\(^2\)\(^,\)\(^3\) GVHD is a multisystem disorder that may involve several organs, including the lungs, hepatobiliary system, musculoskeletal system, gastrointestinal (GI) tract, and skin.\(^2\) Roughly half of the patients undergoing HSCT develop GVHD which requires treatment, and greater than 10% of patients may die because of it.\(^3\),\(^d\)

Acute GVHD (aGVHD) commonly occurs in the early posttransplant period. Previous definitions of aGVHD required onset of symptoms within 100 days after transplant; however, the current National Institutes of Health (NIH) consensus criteria uses clinical findings to differentiate between aGVHD and cGVHD rather than a 100-day cutoff. The diagnosis of aGVHD is made by clinical manifestations that develop in patients who have undergone allogeneic HSCT. Classically, patients present with a maculopapular rash, abdominal cramps with diarrhea, and increasing serum bilirubin level usually within the first 100 days. The NIH consensus criteria classify 2 categories of aGVHD that occur without diagnostic or distinctive features of cGVHD: (1) classic aGVHD, involving clinical features of aGVHD occurring within 100 days of HSCT; and (2) persistent, recurrent, late-onset aGVHD, involving clinical features of aGVHD after 100 days.\(^4\) Chronic GVHD generally manifests later (>100 days) and has some features of autoimmune diseases. It may develop either de novo or following resolution of - or as an extension of acute GVHD.\(^5\) In 2014, the NIH Working Group report for diagnosis and staging of cGVHD established criteria for diagnosis by various clinical manifestations, including cutaneous ones. The diagnosis of cGVHD requires the presence of at least 1 diagnostic manifestation or 1 distinctive feature confirmed by biopsy, laboratory tests, or radiology in the same or a separate organ.\(^5\) Chronic GVHD is the major cause of late nonrelapse death following HSCT.\(^6\),\(^d\) Its presentation may be progressive (active or aGVHD merging into chronic), or de novo (occurring without prior aGVHD). Chronic graft versus host disease pathology involves both T cells and B cells and is characterized by overproduction of pro-inflammatory cytokines interleukin (IL)-21 and IL-17 and over-activation of pro-inflammatory T follicular helper cells (Tfh) and B cells, leading to overproduction of antibodies.\(^6\) Manifestations may be systemic, involving multiple organs, with profound impact upon quality of life and nonrelapse mortality. Patients who develop cGVHD after an allogeneic HCT face a multifaceted burden, including physical, functional, and psychosocial deficits, which negatively influence quality of life.\(^7\)

3.2 Description of Current Treatment Options

Management of chronic GVHD has relied on corticosteroids as the mainstay of treatment for more than 3 decades. Systemic treatment typically begins with prednisone at 0.5 to 1 mg/kg per day, followed by a taper to reach an alternate-day regimen, with or without calcineurin inhibitors (CNIs) such as

\(\text{Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.}\)

\(\text{Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.}\)
cyclosporine or tacrolimus. Prolonged systemic corticosteroid treatment causes significant toxicity, including weight gain, bone loss, myopathy, diabetes, hypertension, mood swings, cataract formation, and increased risk of infection. Many of these toxicities can be mitigated by alternate-day administration of corticosteroids. Combination therapy with other immunosuppressive agents is often considered in hopes of minimizing toxicity caused by prolonged corticosteroid treatment.\(^8\) Approximately 50% to 60% of patients with chronic GVHD require secondary treatment within 2 years after initial systemic treatment. Indications for secondary treatment include worsening manifestations of chronic GVHD in a previously affected organ, development of signs and symptoms of chronic GVHD in a previously unaffected organ, absence of improvement after 1 month of standard primary treatment, inability to decrease prednisone below 1 mg/kg per day within 2 months, or significant treatment-related toxicity.\(^8\) Ibrutinib was approved by the Food and Drug Administration (FDA) for the treatment of adult patients with cGVHD after failure of 1 or more lines of systemic therapy.\(^9\) Chronic GVHD remains a common and potentially lifethreatening complication of allogeneic HSCT. There is a clear need for therapeutic strategies with new alternative modalities that encompass a better tolerated treatment option for patients with cGVHD after failure of at least two prior line of systemic therapy.

## 4 Benefit Assessment

The efficacy of belumosudil was evaluated in study KD025-213 (NCT03640481), a randomized, open-label, multicenter study for treatment of patients with chronic GVHD who had received 2 to 5 prior lines of systemic therapy and required additional treatment. Patients were excluded from the studies if platelets were \(< 50 \times 10^9/\text{L} \); absolute neutrophil count \(< 1.5 \times 10^7/\text{L} \); AST or ALT \(> 3 \times \text{ULN} \); total bilirubin \(> 1.5 \times \text{ULN} \); QTc(F) \(> 480 \text{ms} \); GFR \(< 30 \text{ mL/min/1.73 m}^2 \); or FEV1 \(\leq 39\% \). There were 66 patients treated with belumosudil 200 mg taken orally once daily. GVHD prophylaxis was continued, and concomitant treatment with supportive care therapies for chronic GVHD was permitted.\(^1\)

The following section is a summary of relevant efficacy information to date for belumosudil. The main efficacy outcome measure was overall response rate (ORR) through Cycle 7 Day 1 where overall response included complete response or partial response according to the 2014 NIH Response Criteria. The ORR was 75\% (95\% CI: 63, 85). The results of the ORR is summarized in Table 1.\(^1,10,11\) The median time to first response was 1.8 months (95\% CI: 1.0, 1.9). The median duration of response, calculated from first response to progression, death, or new systemic therapies for chronic GVHD, was 1.9 months (95\% CI: 1.2, 2.9). In patients who achieved response, no death or new systemic therapy initiation occurred in 62\% (95\% CI: 46, 74) of patients for at least 12 months following response. ORR results were supported by exploratory analyses of patient-reported symptom based on a bother score, which showed at least a 7-point decrease in the modified Lee Symptom Scale summary score through Cycle 7 Day 1 in 52\% (95\% CI: 40, 65) of patients.

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\(^{\text{e}}\) Section 505-1 (a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition
Table 1: Overall Response Rate through Cycle 7 Day 1 for Patients with Chronic GVHD in Study KD025-213 $^{1,10,11}$

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<th>Belumosudil 200 mg once daily (N=65)</th>
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<tr>
<td><strong>Overall Response Rate (ORR)</strong></td>
<td>49 (75%)</td>
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<tr>
<td><strong>95% Confidence Interval$^{a}$</strong></td>
<td>(63%, 85%)</td>
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<tr>
<td><strong>Complete Response</strong></td>
<td>4 (6%)</td>
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<td><strong>Partial Response</strong></td>
<td>45 (69%)</td>
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$^{a}$ Estimated using Clopper-Pearson method

## 5 Risk Assessment & Safe-Use Conditions

At the time of this review, labeling negotiations were still ongoing with the applicant. The following section is a summary of relevant safety information to date for belumosudil. The safety of belumosudil was evaluated in two clinical trials (Study KD025-213 and Study KD025-208), 83 adult patients with chronic GVHD were treated with belumosudil 200 mg once daily. The median duration of treatment was 9.2 months (range 0.5 to 44.7 months).$^1$

The most common (≥20%) adverse reactions, including laboratory abnormalities, were infections (53%), asthenia (46%), nausea (42%), diarrhea (35%), dyspnea (33%), cough (30%), edema (27%), hemorrhage (23%), abdominal pain (22%), musculoskeletal pain (22%), headache (21%), phosphate decreased (76%), gamma glutamyl transferase increased (47%), lymphocytes decreased (62%), and hypertension (21%).$^{1,11}$

### Deaths

A total of 4 deaths were reported in Study KD025-213, in which adult patients with chronic GVHD were treated with belumosudil 200 mg once daily. Most deaths were related to the subjects’ underlying disease. One of the patients died due to hemothorax, the second patient’s death was reported as respiratory failure and the third patient died due to a relapse of acute myeloid leukemia (AML).$^{11}$ The forth patient’s death was in a 75 year old with AML complicated by neutropenic shock secondary to acute pneumonia, who died from infection and septic shock.$^{11,12}$

### Serious Adverse Events (SAE)

Fatal adverse reactions was reported in one patient with severe nausea, vomiting, diarrhea and multi-organ failure. Permanent discontinuation of belumosudil due to adverse reactions occurred in 18% of patients. Nausea resulted in permanent discontinuation of belumosudil in 4% of patients included nausea. Adverse reactions leading to dose interruption occurred in 29% of patients. The adverse reactions leading to dose interruption in ≥ 2% were infections (11%), diarrhea (4%), and asthenia,
dyspnea, hemorrhage, hypotension, abnormal liver function tests, nausea, edema, and renal failure with (2% each).

If approved, labeling will include the following risks in the Warnings and Precautions section.

5.1 EMBRYO-FETAL TOXICITY

Based on its mechanism of action and findings from animal data, belumosudil can cause fetal harm when administered to a pregnant woman. Embryo-fetal development studies were conducted in rats with administration of belumosudil to pregnant animals during the period of organogenesis at oral doses of 25, 50, 150, and 300 mg/kg/day in a pilot study and doses of 15, 50, and 150 mg/kg/day in a pivotal study. In the pilot study, maternal toxicity and embryo-fetal developmental effects were observed. Maternal toxicity (reduced body weight gain) occurred at 150 and 300 mg/kg/day doses. Increased post-implantation loss occurred at 50 and 300 mg/kg/day. Fetal malformations were observed at ≥ 50 mg/kg/day and included absence of anus and tail, omphalocele, and dome shaped head. The exposure (AUC) at 50 mg/kg/day in rats is approximately 3 times the human exposure at the recommended dose of 200 mg.

In an embryo-fetal developmental study in rabbits, pregnant animals administered oral doses of belumosudil at 50, 125, and 225 mg/kg/day during the period of organogenesis resulted in maternal toxicity and embryo-fetal developmental effects. Maternal toxicity (body weight loss and mortality) was observed at doses ≥ 125 mg/kg/day. Embryo-fetal effects were observed at doses ≥ 50 mg/kg/day and included spontaneous abortion, increased post-implantation loss, decreased percentage of live fetuses, malformations, and decreased fetal body weight. Malformations included those in the tail (short), ribs (branched, fused or deformed), sternebrae (fused), and neural arches (fused, misaligned, and deformed). The exposure (AUC) at 50 mg/kg/day in rabbits is approximately 0.07 times the human exposure at the recommended dose of 200 mg.

Besides being communicated in the Warnings and Precautions section of the label, recommended guidance to use effective contraception for females of reproductive potential and males with female partners of reproductive potential during treatment with belumosudil and for at least one week after the last dose will be communicated in the Use in Specific Populations section of the label.

6 Expected Postmarket Use

According to the current proposed indication, if approved, belumosudil will be used in both inpatient and outpatient settings. It is expected that oncolgists, familiar with screening and counseling patients who may be at risk for embryo-fetal toxicity, will be the likely prescribers of belumosudil.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for belumosudil beyond routine pharmacovigilance and labeling. The applicant proposed describing these risks in the PI that includes Warnings and Precautions, as well as information to be included in Patient Counseling Information, and a PPI to address the risk of embryo-fetal toxicity.
8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for belumosudil, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population.

Belumosudil is a kinase inhibitor, with the proposed indication for the treatment of patients 12 years and older with chronic GVHD after failure of at least one line of systemic therapy. Based on the efficacy and safety information currently available, the clinical reviewers stated that belumosudil shows clinically meaningful benefit, and recommends approval of belumosudil for the treatment of adult and pediatric patients 12 years and older with chronic GVHD after failure of at least two prior line of systemic therapy.1,10,11

Chronic GVHD is the major cause of late nonrelapse death following HSCT. Manifestations may be systemic, involving multiple organs, with profound impact upon quality of life and nonrelapse mortality. Patients who develop cGVHD after an allogeneic HSCT face a multifaceted burden, including physical, functional, and psychosocial deficits, which negatively influence quality of life. Chronic GVHD is a serious condition and, there is a clear need for therapeutic strategies with new alternative modalities that encompass a better tolerated treatment option for patients with cGVHD after failure of at least two prior lines of systemic therapy. Belumosudil appeared efficacious in its primary outcomes and its risks can be communicated and managed through labeling.1,10,11 The likely prescribers for belumosudil will be oncologists. Based on its mechanism of action and findings from animal data, belumosudil can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of belumosudil to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes, including alterations to growth, embryo-fetal mortality, and embryo-fetal malformations at maternal exposures (AUC) approximately ≥ 3·(rat) and ≥ 0.07 (rabbit) times the human exposure (AUC) at the recommended dose. Fetal-malformations in rats studied included absence of anus and tail, omphalocele, and dome shaped head. Embryo-fetal effects in rabbit study included were spontaneous abortion, increased post-implantation loss, decreased percentage of live fetuses, malformations, and decreased fetal body weight and the malformations included were those in the tail (short), ribs (branched, fused or deformed), sternebrae (fused), and neural arches (fused, misaligned, and deformed). DHM1 determined based on the available data that the risk of embryo-fetal toxicity did not rise to the level of a boxed warning. The risks identified are risks that these providers have likely encountered in their practice experience and can manage without additional risk mitigation measures.

DRM and DHM1 have determined that if approved, a REMS is not necessary to ensure the benefits of belumosudil outweigh its risks. The most concerning adverse reactions observed with the use of belumosudil is embryo-fetal toxicity; this is based on nonclinical data. At the time this review was completed, labeling negotiations were still ongoing with the Applicant; if belumosudil is approved, Warnings and Precautions in the labeling, will be used to communicate the safety issues and management of toxicities associated with belumosudil, as well as information to be included in Patient Counseling Information and a PPI to inform patients. The recommended guidance as per the label will be to use effective contraception for females of reproductive potential and males with female partners of reproductive potential during treatment with belumosudil and for at least one week after the last dose. This will be communicated in the Use in Specific Populations section of the label. To better characterize
safety the Agency has issued eleven post-marketing required (PMR) studies and one post-marketing commitment (PMC).\textsuperscript{13}

9 Conclusion & Recommendations

If approved, DRM has determined that a REMS is not necessary to ensure the benefits outweigh the risks of belumosudil. The management of the risks associated with belumosudil treatment will be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile, so that this recommendation can be reevaluated if necessary.

10 References

\textsuperscript{1} Draft Prescribing Information for belumosudil as currently edited by the FDA, last updated July 7, 2021.


\textsuperscript{8} Flowers ME, Martin PJ. How we treat chronic graft-versus-host disease. \textit{Blood.} 2015;125(4):606-615.

\textsuperscript{9} Imbruvica. Prescribing Information (last updated 12/2020)


\textsuperscript{12} Kadmon Corp LLC. Summary of Clinical Safety for belumosudil, dated September 30, 2020.

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/

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