REZUROCK® (belumosudil) tablets, for oral use

Initial U.S. Approval: 2021

INDICATIONS AND USAGE
REZUROCK is a kinase inhibitor indicated for the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy. (1)

Dosage and Administration (2.1, 2.4)

Recommended Dosage: 200 mg taken orally once daily with food. (2.1)

Dosage Modifications for Adverse Reactions

Table 1: Recommended Dosage Modifications for REZUROCK for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>REZUROCK Dosage Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatotoxicity (see Adverse Reactions [6.1])</td>
<td>Grade 3 AST or ALT (5x to 20x ULN) or Grade 2 bilirubin (1.5x to 3x ULN)</td>
<td>Hold REZUROCK until recovery of bilirubin, AST and ALT to Grade 0–1, then resume REZUROCK at the recommended dose</td>
</tr>
<tr>
<td></td>
<td>Grade 4 AST or ALT (more than 20x ULN) or Grade ≥3 bilirubin (more than 3x ULN)</td>
<td>Discontinue REZUROCK permanently</td>
</tr>
<tr>
<td>Other adverse reactions (see Adverse Reactions [6.1])</td>
<td>Grade 3</td>
<td>Hold REZUROCK until recovery to Grade 0–1, then resume REZUROCK at the recommended dose</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Discontinue REZUROCK permanently</td>
</tr>
</tbody>
</table>

Based on CTCAE v 4.03

2.3 Dosage Modification Due to Drug Interactions

Strong CYP3A Inducers
Increase the dosage of REZUROCK to 200 mg twice daily when coadministered with strong CYP3A inducers [see Drug Interactions (7.1)].

Proton Pump Inhibitors
Increase the dosage of REZUROCK to 200 mg twice daily when coadministered with proton pump inhibitors [see Drug Interactions (7.1)].
2.4 Recommended Dosage in Patients with Hepatic Impairment
Avoid use in patients with moderate hepatic impairment (Child-Pugh B) or severe hepatic impairment (Child-Pugh C) without liver GVHD [see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].
No dosage adjustment is recommended when administering REZUROCK to patients with mild hepatic impairment [see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

3 DOSAGE FORMS AND STRENGTHS
Each 200 mg belumosudil tablet is a pale yellow film-coated oblong tablet debossed with "KDM" on one side and "200" on the other side.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Embryo-Fetal Toxicity
Based on findings in animals and its mechanism of action, REZUROCK can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration ofbelumosudil to pregnant rats and rabbits during the period organogenesis caused adverse developmental outcomes including embryo-fetal mortality and malformations at maternal exposures (AUC) less than those in patients at the recommended dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with REZUROCK and for one week after the last dose [see Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)].

6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
Because clinical trials are conducted under widely variable conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

Chronic Graft versus Host Disease
In two clinical trials (Study KD025-213 and Study KD025-208), 83 adult patients with chronic GVHD were treated with REZUROCK 200 mg once daily [see Clinical Studies (14.1)]. The median duration of treatment was 9.2 months (range 0.5 to 44.7 months). Fatal adverse reaction was reported in one patient with severe nausea, vomiting, diarrhea and multi-organ failure. Permanent discontinuation of REZUROCK due to adverse reactions occurred in 18% of patients. The adverse reactions which resulted in permanent discontinuation of REZUROCK in ≥3% of patients included nausea (4%). 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, liver function test abnormal, nausea, pyrexia, edema, and renal failure with (2% each).

The most common (≥2%) adverse reactions, including laboratory abnormalities, were infections, asthenia, nausea, diarrhea, dyspnea, cough, edema, hemorrhage, abdominal pain, musculoskeletal pain, headache, phosphate decreased, gamma glutamyl transferase increased, lymphocytes decreased, and hypertension.

Table 2 summarizes the nonlaboratory adverse reactions.

Table 2: Nonlaboratory Adverse Reactions in ≥10% Patients with Chronic GVHD Treated with REZUROCK (continued)

<table>
<thead>
<tr>
<th>Table 2: Nonlaboratory Adverse Reactions in ≥10% Patients with Chronic GVHD Treated with REZUROCK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
</tr>
<tr>
<td>Muscle spasm</td>
</tr>
<tr>
<td>Arthralgia</td>
</tr>
<tr>
<td>Nervous system</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
</tr>
<tr>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Skin and subcutaneous</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Pruritus</td>
</tr>
</tbody>
</table>

*Infection with an unspecified pathogen includes acute sinusitis, device related infection, ear infection, folliculitis, gastroenteritis, gastrointestinal infection, hordilloid, infectious colitis, lung infection, skin infection, tooth infection, urinary tract infection, wound infection, upper respiratory tract infection, pneumonia, conjunctivitis, sinusitis, respiratory tract infection, bronchitis, sepsis, septic shock.

†Includes influenza, rhinovirus infection, gastroenteritis viral, viral upper respiratory tract infection, bronchitis viral, Epstein-Barr virusemia, Epstein-Barr virus infection, parainfluenzae virus infection, Varicella zoster virus infection, viral infection.

‡Includes cellullitis, Helicobacter infection, Staphylococcal bacteremia, catheter site cellulitis, Closstridium difficile colitis, Escherichia urinary tract infection, gastroenteritis Escherichia coli, Pseudomonas infection, urinary tract infection bacterial.

§Includes fatigue, asthenia, malaise.

¶Includes edema peripheral, generalized edema, face edema, localized edema, edema.

**Includes nausea, vomiting.

Includes abdominal pain, abdominal pain upper, abdominal pain lower.

††Includes dyspnea, dyspnea exertional, apnea, orthopnea, sleep apnea syndrome.

‡‡Includes cough, productive cough.

Includes confusion, hemotoma, epistaxis, increased tendency to bruise, conjunctival hemorrhage, hematochezia, mouth hemorrhage, catheter site hemorrhage, hematura, hemophoral, purpure.

Includes pain in extremity, back pain, flank pain, limb discomfort, musculoskeletal chest pain, neck pain, musculoskeletal pain.

Includes headache, migraine.

Includes rash, rash musculo-papular, rash erythematous, rash generalized, dermatitis exfoliative.

Includes pruritus, pruritus generalized.

Table 3 summarizes the laboratory abnormalities in REZUROCK.

Table 3: Selected Laboratory Abnormalities in Patients with Chronic GVHD Treated with REZUROCK

<table>
<thead>
<tr>
<th>Table 3: Selected Laboratory Abnormalities in Patients with Chronic GVHD Treated with REZUROCK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>Chemistry</td>
</tr>
<tr>
<td>Phosphate decreased</td>
</tr>
<tr>
<td>Gamma Glutamyl Transferase increased</td>
</tr>
<tr>
<td>Calcium decreased</td>
</tr>
<tr>
<td>Alkaline Phosphatase increased</td>
</tr>
<tr>
<td>Potassium increased</td>
</tr>
<tr>
<td>Alanine Aminotransferase increased</td>
</tr>
<tr>
<td>Creatinine increased</td>
</tr>
<tr>
<td>Hematology</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
</tr>
<tr>
<td>Platelets decreased</td>
</tr>
<tr>
<td>Neutrophil Count decreased</td>
</tr>
</tbody>
</table>
7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on REZUROCK

Strong CYP3A4 Inducers

Co-administration of REZUROCK with strong CYP3A4 inducers decreases belumosudil exposure [see Clinical Pharmacology (12.3)], which may reduce the efficacy of REZUROCK. Increase the dosage of REZUROCK when coadministered with strong CYP3A4 inducers [see Dosage and Administration (2.3)].

Proton Pump Inhibitors

Co-administration of REZUROCK with proton pump inhibitors decreases belumosudil exposure [see Clinical Pharmacology (12.3)], which may reduce the efficacy of REZUROCK. Increase the dosage of REZUROCK when coadministered with proton pump inhibitors [see Dosage and Administration (2.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action [see Clinical Pharmacology (12.1)], REZUROCK can cause fetal harm when administered to pregnant women. There are no available human data on REZUROCK use in pregnant women to evaluate for a drug-associated risk. 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 \( \geq 3 \times \) (rat) and \( \geq 0.07 \) (rabbit) times the human exposure (AUC) at the recommended dose (see Data). Advise pregnant women and females of reproductive potential of the potential risk to the fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. Data

Animal data

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 (body weight) from gestation days 6 through 15. Among the effects observed was a dose-related increase post-implantation loss, decreased percentage of live fetuses, malformations, and increased 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 (reduced body weight gain) occurred at 150 and 300 mg/kg/day. Increased post-implantation loss occurred at 50 and 300 mg/kg/day. Fetal malformations were observed at 250 mg/kg/day and included absence of anus and tail, omphalocele, and dome shaped head. The exposure (AUC) at 50 mg/kg/day in rabbits is approximately 3 times the human exposure at the recommended dose of 200 mg. In an embryo-fetal developmental study in rats, 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 \( \geq 125 \) mg/kg/day. Embryo-fetal effects were observed at doses \( \geq 50 \) 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.

8.2 Lactation

Risk Summary

There are no data available on the presence of belumosudil or its metabolites in human milk or the effects on the breastfed child, or milk production. Because of the potential for serious adverse reactions from belumosudil in the breastfed child, advise lactating women not to breastfeed during treatment with REZUROCK and for one week after the last dose.

8.3 Females and Males of Reproductive Potential

REZUROCK can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating treatment with REZUROCK.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with REZUROCK and for one week after the last dose of REZUROCK. This drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with REZUROCK and for one week after the last dose of REZUROCK.

Infertility

Females

Based on findings from rats, REZUROCK may impair female fertility. The effect on fertility is reversible [see Nonclinical Toxicology (13.1)].

Males

Based on findings from rats and dogs, REZUROCK may impair male fertility. The effects on fertility are reversible [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

The safety and effectiveness of REZUROCK have been established in pediatric patients 12 years and older. Use of REZUROCK in this age group is supported by evidence from adequate and well-controlled studies of REZUROCK in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the pharmacokinetics of belumosudil. In the absence of drug substance, the exposure of drug substance is expected to be similar between adults and pediatric patients age 12 years and older, and that the course of disease is sufficiently similar in adult and pediatric patients to allow extrapolation of data in adults to pediatric patients. The safety and effectiveness of REZUROCK in pediatric patients less than 12 years old have not been established.

8.5 Geriatric Use

Of the 186 patients with chronic GVHD in clinical studies of REZUROCK, 26% were 65 years and older. No clinically meaningful differences in safety or effectiveness of REZUROCK were observed in comparison to younger patients.

8.6 Renal Impairment

Treatment with REZUROCK has not been studied in patients with pre-existing severe renal impairment. For patients with pre-existing severe renal impairment, consider the risks and benefits before initiating treatment with REZUROCK [see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment

Avoid use in patients with moderate hepatic impairment (Child-Pugh B) or severe hepatic impairment (Child-Pugh C) without liver GVHD [see Dosage and Administration (2.4), Clinical Pharmacology (12.3)].

No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A) [see Dosage and Administration (2.4), Clinical Pharmacology (12.3)].

11 DESCRIPTION

Belumosudil is a kinase inhibitor. The active pharmaceutical ingredient is belumosudil mesylate with the molecular formula \( \text{C}_{23} \text{H}_{29} \text{N}_{2} \text{O}_{5} \text{~S} \) and the molecular weight is 548.6 g/mol. The chemical name for belumosudil mesylate is \( 2-[2-(4-(1H-indazol-5-yl)-5)] \text{~N-(propan-2-yl)} \text{~acetamide methanesulfonate (1:1).} \) The chemical structure is as follows:

![Chemical Structure]

Belumosudil mesylate is a yellow powder that is practically insoluble in water, slightly soluble in methanol and DMF and soluble in DMSO. REZUROCK tablets are for oral administration. Each tablet contains 200 mg of the free base equivalent to 242.5 mg of belumosudil mesylate. The tablet also contains the following inactive ingredients: microcrystalline cellulose, hypromellose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The tablet film consists of polyvinyl alcohol, polyethylene glycol, taic, titanium dioxide and yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Belumosudil is an inhibitor of the-associated, coiled-coil containing protein kinase (ROCK) which inhibits ROCK2 and ROCK1 with IC\( _{50} \) values of approximately 100 nM and 3 \( \mu \text{M} \), respectively. Belumosudil down-regulated proinflammatory responses via regulation of STAT3/STAT5 phosphorylation and shifting Th17/Treg balance in ex-vivo or in vitro-human T cell assays. Belumosudil also inhibited aberrant pro-fibrotic signaling, in vitro. In vivo, belumosudil demonstrated activity in animal models of chronic GVHD.

12.2 Pharmacodynamics

Belumosudil exposure-response relationships and the time course of pharmacodynamic response are not established.

Cardiac Electrophysiology

At 2.4 times the maximum exposure for approved recommended dose, REZUROCK does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

The following pharmacokinetic parameters are presented for chronic GVHD patients administered belumosudil 200 mg once daily, unless otherwise specified. The mean (percent coefficient of variation, %CV) steady-state AUC and C\( \text{max} \) of belumosudil was 22,700 (48%) ng·h/mL and 2390 (44%) ng/mL, respectively. Belumosudil C\( \text{max} \) and AUC increased in an approximately proportional manner over a dosage range of 200 and 400 mg (1 to 2 times once daily recommended dosage). The accumulation ratio of belumosudil was 1.4.

Absorption

Median Tmax of belumosudil at steady state was 1.26 to 2.53 hours following administration of 200 mg once daily or twice daily in patients. The mean (%CV) bioavailability was 64% (17%) following a single belumosudil dose in healthy subjects.

Effect of food

Belumosudil C\( \text{max} \) and AUC increased 2.2 times and 2 times, respectively, following administration of a single belumosudil dose with a high-fat and high-calorie meal (800 to 1,000 calories with approximately 50% of total caloric content of the meal from fat) compared to the fasted state in healthy subjects. Median Tmax was delayed 0.5 hours. Distribution

The geometric mean volume of distribution after a single dose of belumosudil in healthy subjects was 184 L (geo CV% 67.7%). Belumosudil binding to human serum albumin and human \( \alpha \)-acid glycoprotein was 99.9% and 98.9%, respectively, in vitro.

Elimination

The mean (%CV) elimination half-life of belumosudil was 19 hours (39%), and clearance was 8.83 (46%) L/hours in patients.

Metabolism

Belumosudil is primarily metabolized by CYP3A4 and to a lesser extent by CYP2C8, CYP2D6, and UGT1A9, in vitro.

Excretion

Following a single oral dose of radiolabeled belumosudil in healthy subjects, 85% of radioactivity was recovered in feces (30% as unchanged) and less than 5% in urine.

Specific Populations

No clinically significant differences in belumosudil pharmacokinetics were observed with regard to age (18 to 77 years), sex, weight (38.6 to 143 kg), or mild to moderate renal
improvement (eGFR ≥60 and <90 mL/min/1.72m² to eGFR ≥30 and <60 mL/min/1.72m²).

The effect of severe renal impairment on the pharmacokinetics of belumosudil has not been studied.

Patients with Hepatic Impairment

Following a single 200 mg dose ofbelumosudil, changes in belumosudil exposure in subjects with moderate degrees of hepatic impairment based on Child-Pugh score without liver GVHD relative to subjects with normal hepatic function is shown in Table 4.

<table>
<thead>
<tr>
<th>Hepatic Impairment Category</th>
<th>Changes in Belumosudil Exposure in Subjects with Hepatic Impairment Compared to Subjects with Normal Hepatic Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (Free + Bound) Concentrations</td>
</tr>
<tr>
<td></td>
<td>$C_{max}$</td>
</tr>
<tr>
<td>Mild (Child-Pugh A)</td>
<td>1.2-fold increase</td>
</tr>
<tr>
<td>Moderate (Child-Pugh B)</td>
<td>6% decrease</td>
</tr>
<tr>
<td>Severe (Child-Pugh C)</td>
<td>1.3-fold increase</td>
</tr>
</tbody>
</table>

Drug Interaction Studies

Clinical studies and model-informed approaches were conducted to assess the potential effects of other drugs on belumosudil exposure.

Strong CYP3A inducers: Coadministration of rifampin decreased belumosudil $C_{max}$ by 59% and AUC by 72% in healthy subjects. Moderate CYP3A Inducers: Coadministration of efavirenz is predicted to decrease belumosudil $C_{max}$ by 19% and AUC by 35% in healthy subjects. Proton Pump Inhibitors: Coadministration of rabeprazole decreased belumosudil $C_{max}$ by 87% and AUC by 90%, and omeprazole decreased belumosudil $C_{max}$ by 66% and AUC by 47% in healthy subjects. Effects of Belumosudil on other drugs:

CYP3A Substrates: Coadministration of belumosudil is predicted to increase midazolam (a sensitive CYP3A substrate) $C_{max}$ and AUC approximately 1.3- and 1.5-fold, respectively. CYP2C9 Substrates: Coadministration of belumosudil is not expected to have clinically meaningful effect on the exposure of CYP2C9 substrates (such as warfarin). CYP2C8 Substrates: Coadministration of belumosudil is not expected to have clinically meaningful effect on the exposure of CYP2C8 substrates that are not an OATP1B1 substrate.

In Vitro studies

Transporter Systems: Belumosudil is a substrate of P-gp. Belumosudil inhibits BCRP, P-gp, and OATP1B1 at clinically relevant concentrations. Enzymes Systems: Belumosudil is an inhibitor of CYP1A2, CYP2C19, CYP2D6, UGT1A1 and UGT1A9.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been conducted with belumosudil.

Mutagenesis

Belumosudil was not genotoxic in an in vitro bacterial mutagenicity (Ames) assay, in vitro chromosome aberration assay in human peripheral blood lymphocytes (HPBL) or an in vivo rat bone marrow micronucleus assay.

Impairment of Fertility

In a combined male and female rat fertility study, belumosudil-treated male animals were mated with untreated females, or untreated males were mated with belumosudil-treated females. Belumosudil was administered orally at doses of 50, 150 or 275 mg/kg/day to male rats 70 days prior to and throughout the mating period, and to female rats 14 days prior to mating and up to Gestation Day 7. At the dose of 275 mg/kg/day, adverse findings in female rats (treated with belumosudil or untreated but mated with treated males) included increased pre- or post-implantation loss and decreased number of viable embryos. Administration of belumosudil to male rats at a dose of 275 mg/kg/day resulted in abnormal sperm findings (reduced motility, reduced count, and increased percentage of abnormal sperm), and testes/epididymis organ changes (reduced weight and degeneration). Fertility was reduced in both treated males or females at the 275 mg/kg/day dose and reached statistical significance in males. Adverse changes in male and female reproductive organs also occurred in general toxicology studies; findings included spermatozoa degeneration at a belumosudil dose of 35 mg/kg/day in dogs and decreased follicular development in ovaries at 275 mg/kg/day in rats. Changes were partially or fully reversed during the recovery period. The exposure (AUC) at the doses of 35 mg/kg/day in dogs, and 275 mg/kg/day in rats is 0.5 times and 8-9 times, respectively, the clinical exposure at the recommended dose of 200 mg daily.

14 CLINICAL STUDIES

14.1 Chronic Graft versus Host Disease

Study KD025-213 (NCT03640481) was a randomized, open-label, multicenter study of REZUROCK 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 x 10^9/L, absolute neutrophil count <1.5 x 10^9/L, AST or ALT >3 x ULN, total bilirubin >1.5 x ULN, QTcF >480 ms; eGFR <30 mL/min/1.73 m²; or FEV1 <50%. There were 66 patients treated with REZUROCK 200 mg taken orally once daily. Concomitant treatment with supportive care therapies for chronic GVHD was permitted. Concomitant treatment with GVHD prophylaxis and standard care systemic chronic GVHD therapies was permitted as long as the subject has been on a stable dose for at least 2 weeks prior to study. Initiation of new systemic chronic GVHD therapy while on study was not permitted.

Demographics and baseline characteristics are summarized in Table 5.

Table 5: Demographics and Baseline Characteristics of Patients with Chronic GVHD

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Prior Lines of Therapy</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2</td>
<td>23</td>
<td>(35)</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>(19)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>15</td>
<td>(23)</td>
</tr>
<tr>
<td>Prior chronic GVHD treatment with brutinib, n (%)</td>
<td>21 (32)</td>
<td></td>
</tr>
<tr>
<td>Prior chronic GVHD treatment with ruxolitinib, n (%)</td>
<td>20 (31)</td>
<td></td>
</tr>
<tr>
<td>Refractory to Last Therapy, n (%)</td>
<td>43/55 (78)</td>
<td></td>
</tr>
<tr>
<td>Severe chronic GVHD, n (%)</td>
<td>46 (71)</td>
<td></td>
</tr>
<tr>
<td>Median (range) Global Severity Rating</td>
<td>7 (2, 9)</td>
<td></td>
</tr>
<tr>
<td>Median (range) Lee Symptom Scale Score at baseline</td>
<td>27 (7, 56)</td>
<td></td>
</tr>
<tr>
<td>Median (range) Corticosteroid dose at baseline (PE/kg)</td>
<td>0.19 (0.03, 0.95)</td>
<td></td>
</tr>
</tbody>
</table>

Table 6: Overall Response Rate through Cycle 7 Day 1 for Patients with Chronic GVHD in Study KD025-213

<table>
<thead>
<tr>
<th>Overall Response Rate (ORR)</th>
<th>49 (75%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% Confidence Interval*</td>
<td>(63%, 85%)</td>
</tr>
<tr>
<td>Complete Response</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>45 (69%)</td>
</tr>
</tbody>
</table>

ORR results were supported by exploratory analyses of patient-reported symptom bother which showed at least a 7-point decrease in the Lee Symptom Scale summary score through Cycle 7 Day 1 in 52% (95% CI: 40, 65) of patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

REZUROCK 200 mg tablets are supplied as pale yellow film-coated 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 in 30 count bottle; NDC 79802-200-30

Store at room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Dispense to patient in original container only. Store in original container to protect from moisture. Replace cap securely each time after opening. Do not discard desiccant.
17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

• Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.1), Use in Specific Populations (8.1, 8.3)].
• Advise females of reproductive potential to use effective contraceptive during treatment with REZUROCK and for one week after the last dose [see Warnings and Precautions (5.1)].
• Advise males with female partners of reproductive potential to use effective contraceptive during treatment with REZUROCK and for one week after the last dose [see Use in Specific Populations (8.3)].

Lactation
• Advise women not to breastfeed during treatment with REZUROCK and for one week after the last dose [see Use in Specific Populations (8.2)].

Infertility
• Advise males and females of reproductive potential that REZUROCK may impair fertility [see Use in Specific Populations (8.3)].

Administration
• Inform patients to take REZUROCK orally once daily with food according to their physician’s instructions and that the oral dosage (tablets) should be swallowed whole with a glass of water, without cutting, crushing or chewing the tablets approximately the same time each day [see Dosage and Administration (2.1)].
• Advise patients that in the event of a missed daily dose of REZUROCK, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra doses to make up the missed dose [see Dosage and Administration (2.1)].

Drug Interactions
• Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions (7)].

Distributed and marketed by:
Kadmon Pharmaceuticals, LLC
Bridgewater, NJ 08807
A SANOFI COMPANY
1-800-633-1610

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For patent information: https://www.sanofi.us/en/products-and-resources/patents

PATIENT INFORMATION
REZUROCK (REZ-ur-ok)
(belumosudil)
tablets

What is REZUROCK?
REZUROCK is a prescription medicine used to treat adults and children 12 years of age and older with chronic graft-versus-host disease (chronic GVHD) after you have received at least 2 prior treatments (systemic therapy) and they did not work. It is not known if REZUROCK is safe and effective in children less than 12 years old.

Before taking REZUROCK, tell your healthcare provider about all of your medical conditions, including if you:
• have kidney or liver problems.
• are pregnant or plan to become pregnant. REZUROCK can harm your unborn baby. If you are able to become pregnant, your healthcare provider will do a pregnancy test before starting treatment with REZUROCK. Tell your healthcare provider if you become pregnant or think you may be pregnant during treatment with REZUROCK.
  o Females who can become pregnant should use effective birth control during treatment with REZUROCK and for at least 1 week after the last dose.
  o Males with female partners who can become pregnant should use effective birth control during treatment with REZUROCK and for at least 1 week after the last dose.
• are breastfeeding or plan to breastfeed. It is not known if REZUROCK passes into breast milk. Do not breastfeed during treatment with REZUROCK.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. REZUROCK may affect the way other medicines work, and other medicines may affect the way REZUROCK works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take REZUROCK?
• Take REZUROCK exactly as your healthcare provider tells you to take it.
• Do not change your dose or stop taking REZUROCK without first talking to your healthcare provider.
• Take REZUROCK 1 time a day with a meal.
• Take REZUROCK at about the same time each day.
• Swallow REZUROCK tablets whole with a glass of water.
• Do not cut, crush, or chew REZUROCK tablets.
• Your healthcare provider will do blood tests to check your liver at least 1 time a month during treatment with REZUROCK.
• If you miss a dose of REZUROCK, take it as soon as you remember on the same day. Take your next dose of REZUROCK at your regular time on the next day. Do not take extra doses of REZUROCK to make up for a missed dose.
• If you take too much REZUROCK, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of REZUROCK?
The most common side effects of REZUROCK include:
• infections
• tiredness or weakness
• nausea
• diarrhea
• shortness of breath
• cough
• swelling
• bleeding
• stomach (abdominal) pain
• muscle or bone pain
• headache
• high blood pressure

Your healthcare provider may change your dose of REZUROCK, temporarily stop, or permanently stop treatment with REZUROCK if you have certain side effects. REZUROCK may affect fertility in males and females. Talk to your healthcare provider if this is a concern for you. These are not all the possible side effects of REZUROCK. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Kadmon Pharmaceuticals, LLC at 1-800-633-1610.
How should I store REZUROCK?

- Store REZUROCK at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep REZUROCK in its original container. The REZUROCK bottle contains a desiccant packet to help keep your tablets dry (protect from moisture). Keep the desiccant in the bottle.
- Tightly close the REZUROCK bottle after you take your dose. Keep REZUROCK and all medicines out of the reach of children.

General information about the safe and effective use of REZUROCK.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use REZUROCK for a condition for which it was not prescribed. Do not give REZUROCK to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about REZUROCK that is written for health professionals.

What are the ingredients in REZUROCK?

Active ingredient: belumosudil mesylate

Inactive ingredients:
- Tablet core: microcrystalline cellulose, hypromellose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.
- Tablet coating: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, and yellow iron oxide.

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For more information, call 1-800-633-1610 or go to www.REZUROCK.com.

This Patient Information has been approved by the U.S. Food and Drug Administration

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