REZUROCK- belumosudil tablet
Kadmon Pharmaceuticals, LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use REZUROCK safely and effectively. See full prescribing information for REZUROCK.

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

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

DOSAGE FORMS AND STRENGTHS

Tablet: 200 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.1, 8.1, 8.3)

ADVERSE REACTIONS

The most common (≥20%) adverse reactions, including laboratory abnormalities, are infections, asthenia, nausea, diarrhea, dyspnea, cough, edema, hemorrhage, abdominal pain, musculoskeletal pain, headache, phosphate decreased, gamma glutamyl transferase increased, lymphocytes decreased, and hypertension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Kadmon Pharmaceuticals, LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A Inducers: Increase REZUROCK dosage to 200 mg twice daily. (7.1, 2.3)
- Proton Pump Inhibitors: Increase REZUROCK dosage to 200 mg twice daily. (7.1, 2.3)
- BCRP Substrates: Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions and decrease the substrates dosage(s) in accordance with the respective Prescribing Information. (7.2)
- OATP1B1 Substrates: If used together, monitor patients more frequently for adverse reactions and decrease the substrates dosage(s) in accordance with the respective Prescribing Information. (7.2)
- Certain CYP1A2, CYP3A, P-gp or UGT1A1 Substrates: Avoid concomitant use with these substrates for which minimal concentration changes may lead to serious toxicities. If concomitant use cannot be avoided, decrease the substrates dosage(s) in accordance with the respective Prescribing Information. (7.2)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)
- Moderate or Severe Hepatic Impairment: Avoid use of REZUROCK in patients with moderate or severe hepatic impairment. (2.4, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2026

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

REZUROCK is 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of REZUROCK is 200 mg given orally once daily until progression of chronic GVHD that requires new systemic therapy.

Instruct the patient on the following:

- Swallow REZUROCK tablets whole. Do not cut, crush, or chew tablets.
- Take REZUROCK with a meal at approximately the same time each day *[see Clinical Pharmacology (12.3)]*.
- If a dose of REZUROCK is missed, instruct the patient to not take extra doses to make up the missed dose.

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 potential benefits before initiating treatment with REZUROCK *[see Clinical Pharmacology (12.3)]*.

2.2 Dosage Modifications for Adverse Reactions

Monitor total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) at least monthly.

Modify the REZUROCK dosage for adverse reactions as per Table 1.

Table 1: Recommended Dosage Modifications for REZUROCK for Adverse Reactions

Adverse Reaction	**Severity***	**REZUROCK Dosage Modifications**
Hepatotoxicity *[see Adverse Reactions (6.1)]*	Grade 3 AST or ALT (5× to 20× ULN) or Grade 2 bilirubin (1.5× to 3× ULN)	Hold REZUROCK until recovery of bilirubin, AST and ALT to Grade 0–1, then resume REZUROCK at the recommended dose.
	Grade 4 AST or ALT (more than 20× ULN) or Grade ≥3 bilirubin (more than 3× ULN)	Discontinue REZUROCK permanently.
Other adverse reactions *[see Adverse Reactions (6.1)]*	Grade 3	Hold REZUROCK until recovery to Grade 0–1, then resume REZUROCK at the recommended dose level.
	Grade 4	Discontinue REZUROCK permanently.

* 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 of belumosudil to pregnant rats and rabbits during the period of 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 (≥20%) 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

	REZUROCK 200 mg once daily (N=83)	
Adverse Reaction	**All Grades (%)**	**Grades 3–4 (%)**
Infections and infestations		
Infection (pathogen not specified)*	53	16
Viral infection†	19	4
Bacterial infection‡	16	4
General disorders and administration site conditions		
Asthenia§	46	4
Edema¶	27	1
Pyrexia	18	1
Gastrointestinal		
Nausea#	42	4
Diarrhea	35	5
Abdominal painÞ	22	1
Dysphagia	16	0
Respiratory, thoracic and mediastinal		
Dyspneaß	33	5
Coughà	30	0
Nasal congestion	12	0
Vascular		

Hemorrhage[è]	23	5
Hypertension	21	7
Musculoskeletal and connective tissue		
Musculoskeletal pain[ð]	22	4
Muscle spasm	17	0
Arthralgia	15	2
Nervous system		
Headache[ø]	21	0
Metabolism and nutrition		
Decreased appetite	17	1
Skin and subcutaneous		
Rash[ý]	12	0
Pruritus[£]	11	0

* infection with an unspecified pathogen includes acute sinusitis, device related infection, ear infection, folliculitis, gastroenteritis, gastrointestinal infection, hordeolum, 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 viremia, Epstein-Barr virus infection, parainfluenzae virus infection, Varicella zoster virus infection, viral infection.
‡ includes cellulitis, Helicobacter infection, Staphylococcal bacteremia, catheter site cellulitis, Clostridium 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.
Þ includes abdominal pain, abdominal pain upper, abdominal pain lower.
ß includes dyspnea, dyspnea exertional, apnea, orthopnea, sleep apnea syndrome.
à includes cough, productive cough.
è includes contusion, hematoma, epistaxis, increased tendency to bruise, conjunctival hemorrhage, hematochezia, mouth hemorrhage, catheter site hemorrhage, hematuria, hemothorax, purpura.
ð includes pain in extremity, back pain, flank pain, limb discomfort, musculoskeletal chest pain, neck pain, musculoskeletal pain.
ø includes headache, migraine.
ý includes rash, rash maculo-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

	REZUROCK 200 mg once daily		
	Grade 0–1 Baseline	**Grade 2–4 Max Post**	**Grade 3–4 Max Post**

Parameter	(N)	(%)	(%)
Chemistry			
Phosphate decreased	76	28	7
Gamma Glutamyl Transferase increased	47	21	11
Calcium decreased	82	12	1
Alkaline Phosphatase increased	80	9	0
Potassium increased	82	7	1
Alanine Aminotransferase increased	83	7	2
Creatinine increased	83	4	0
Hematology			
Lymphocytes decreased	62	29	13
Hemoglobin decreased	79	11	1
Platelets decreased	82	10	5
Neutrophil Count decreased	83	8	4

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on REZUROCK

Proton Pump Inhibitors

Belumosudil exhibits pH-dependent solubility. Concomitant use 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 used concomitantly with proton pump inhibitors *[see Dosage and Administration (2.3)].*

Strong CYP3A Inducers

Belumosudil is a CYP3A substrate. Concomitant use of REZUROCK with strong CYP3A inducers decreases belumosudil exposure *[see Clinical Pharmacology (12.3)]*, which may reduce the efficacy of REZUROCK. Increase the dosage of REZUROCK when used concomitantly with strong CYP3A inducers *[see Dosage and Administration (2.3)].*

7.2 Effect of REZUROCK on Other Drugs

BCRP and OATP1B1 Substrates

Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions and decrease the BCRP substrates dosage(s) in accordance with the respective Prescribing Information.

Belumosudil is a BCRP inhibitor. Concomitant use of REZUROCK with BCRP substrates increases their plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions related to these substrates.

Belumosudil is an OATP1B1 inhibitor. Concomitant use of REZUROCK with OATP1B1 substrates may increase their plasma concentrations. Monitor patients more frequently for adverse reactions of these substrates and decrease the OATP1B1 substrates dosage(s) in accordance with the respective Prescribing Information *[see Clinical*

Pharmacology (12.3)].

Certain CYP1A2 Substrates

Avoid concomitant use of REZUROCK with drugs that are sensitive CYP1A2 substrates, for which minimal concentration changes may lead to serious toxicities. If concomitant use cannot be avoided, decrease the CYP1A2 substrate dosage(s) in accordance with the respective Prescribing Information.

Belumosudil is a CYP1A2 inhibitor. Concomitant use of REZUROCK with sensitive CYP1A2 substrates (e.g., caffeine) is predicted to increase CYP1A2 substrate exposure *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions related to these substrates.

Certain CYP3A Substrates

Avoid concomitant use of REZUROCK with drugs that are sensitive CYP3A substrates, for which minimal concentration changes may lead to serious toxicities. If concomitant use cannot be avoided, decrease the CYP3A substrate dosage(s) in accordance with the respective Prescribing Information.

Belumosudil is a CYP3A inhibitor. Concomitant use of REZUROCK with sensitive CYP3A substrates (e.g., midazolam) is predicted to increase CYP3A substrate exposure *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions related to these substrates.

Certain UGT1A1 Substrates

Avoid concomitant use of REZUROCK with drugs that are UGT1A1 substrates, for which minimal concentration changes may lead to serious toxicities. If concomitant use cannot be avoided, decrease the UGT1A1 substrates dosage(s) in accordance with the respective Prescribing Information.

Belumosudil is a UGT1A1 inhibitor. Concomitant use of REZUROCK with a UGT1A1 substrate decreased plasma concentrations of the glucuronide metabolite of the UGT1A1 substrate *[see Clinical Pharmacology (12.3)].* Concomitant use of belumosudil with other UGT1A1 substrates may increase their plasma concentrations, which may increase the risk of adverse reactions related to these substrates.

Certain P-gp Substrates

Avoid concomitant use of REZUROCK with drugs that are P-gp substrates, for which minimal concentration changes may lead to serious toxicities. If concomitant use cannot be avoided, decrease the P-gp substrates dosage(s) in accordance with the respective Prescribing Information.

Belumosudil is a P-gp inhibitor. Concomitant use of REZUROCK with P-gp substrates increased their plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions related to these substrates.

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 ≥1.4 (rat) and ≥0.08 (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 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 1.4 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 0.08 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. If 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 *[see Nonclinical Toxicology (13.1)].*

Males

Based on findings from rats and dogs, REZUROCK may impair male fertility *[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 drug substance, that 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 potential benefits before initiating treatment with REZUROCK *[see Dosage and*

Administration (2.1) and Clinical Pharmacology (12.3)].

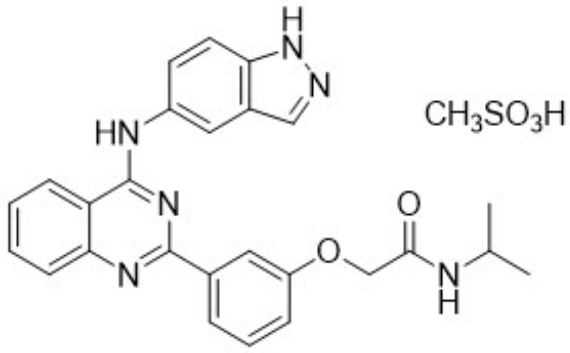
8.7 Hepatic Impairment

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 $C_{27}H_{28}N_6O_5S$ and the molecular weight is 548.62 g/mol. The chemical name for belumosudil mesylate is 2-{3-[4-(1*H*-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-*N*-(propan-2-yl) acetamide methanesulfonate (1:1). The chemical structure is as follows:



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: colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, and microcrystalline cellulose.

The tablet film consists of polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide and yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Belumosudil is an inhibitor of rho-associated, coiled-coil containing protein kinase (ROCK) which inhibits ROCK2 and ROCK1 with IC_{50} values of approximately 100 nM and 3 µM, 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 (% coefficient of variation, %CV) steady-state AUC and C_{max} of belumosudil was 22,700 (48%) h•ng/mL and 2390 (44%) ng/mL, respectively. Belumosudil C_{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 T_{max} 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_{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 T_{max} 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 α_1-acid glycoprotein was 99.9% and 98.6%, respectively, *in vitro*.

Elimination

The mean (%CV) elimination half-life of belumosudil was 19 hours (39%), and clearance was 9.83 L/hours (46%) in patients.

Metabolism

Belumosudil is primarily metabolized by CYP3A 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 impairment (eGFR ≥60 and <90 mL/min/1.72m^2 to eGFR ≥30 and <60 mL/min/1.72m^2). 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 of belumosudil, changes in belumosudil exposure in subjects with varying 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 4: Effect of Varying Degrees of Hepatic Impairment on Belumosudil Exposure

Hepatic Impairment Category	**Changes in Belumosudil Exposure in Subjects with Hepatic Impairment Compared to Subjects with Normal Hepatic Function**			
	Total (Free + Bound) Concentrations		**Free Concentrations**	
	C_{max}	**AUC**	**C_{max}**	**AUC**
Mild (Child-Pugh A)	1.2-fold increase	1.4-fold increase	14% decrease	19% decrease
Moderate (Child-Pugh B)	6% decrease	1.5-fold increase	12% decrease	1.4-fold increase
Severe (Child-Pugh C)	1.3-fold increase	4.2-fold increase	5.4-fold increase	16-fold increase

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Proton Pump Inhibitors: Concomitant use of rabeprazole decreased belumosudil C_{max} by 87% and AUC by 80%, and omeprazole decreased belumosudil C_{max} by 68% and AUC by 47% in healthy subjects.

Strong Cytochrome P450 (CYP) 3A Inhibitors: There was no clinically meaningful effect on belumosudil exposure when used concomitantly with itraconazole (strong CYP3A inhibitor) in healthy subjects.

Strong CYP3A Inducers: Concomitant use of rifampin (strong CYP3A inducer) decreased belumosudil C_{max} by 59% and AUC by 72% in healthy subjects.

Moderate CYP3A Inducers: Concomitant use of efavirenz (moderate CYP3A inducer) is predicted to decrease belumosudil C_{max} by 19% and AUC by 35% in healthy subjects.

CYP1A2 Substrates: Concomitant use of belumosudil is predicted to increase caffeine (sensitive CYP1A2 substrate) C_{max} and AUC approximately 1.1- and 1.6-fold, respectively.

CYP3A Substrates: Concomitant use of belumosudil is predicted to increase midazolam (sensitive CYP3A substrate) C_{max} and AUC approximately 1.3- and 1.7-fold, respectively.

UGT1A1 Substrates: Concomitant use of belumosudil did not have clinically significant effect on the exposure of raltegravir (UGT1A1 substrate), but decreased raltegravir glucuronide (metabolite formed via the UGT1A1 pathway) C_{max} by 42% and AUC by 40%.

BCRP/OATP1B1 Substrates: Concomitant use of belumosudil increased rosuvastatin (BCRP and OATP1B1 substrate) C_{max} and AUC by 3.6- and 4.6-fold, respectively.

P-glycoprotein (P-gp) Substrates: Concomitant use of belumosudil increased dabigatran (P-gp substrate) C_{max} and AUC by 2-fold.

Other drugs: Concomitant use of belumosudil is not predicted to have clinically significant effects on the exposure of (*S*)-warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), and CYP2C8 substrates that are not an OATP1B1 substrate.

In Vitro Studies

UDP-Glucuronosyltransferase (UGT): Belumosudil is an inhibitor of UGT1A9.

Transporter Systems: Belumosudil is a substrate of P-gp.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Belumosudil did not result in any carcinogenic effect in a 6-month CByB6F1-Tg (HRAS)2Jic hemizygous mouse study at oral doses up to 15 mg/kg/day in female and 30 mg/kg/day in male mice.

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 and early embryonic development 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) regarding early embryonic development 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 3-month and 6-month toxicology studies. In males, findings included spermatozoa degeneration at a

belumosudil dose of 50 mg/kg/day in rats and 35 mg/kg/day in dogs. The exposure (AUC) at the doses of 50 mg/kg/day in male rats and 35 mg/kg/day in male dogs is approximately equivalent to the clinical exposure at the recommended dose of 200 mg/day. Changes were reversible in dogs but not fully reversible in rats. In female rats, changes included decreased follicular development in ovaries and lower uterine weights that correlated with uterine/cervical hypoplasia at 275 mg/kg/day [corresponding to 9 times exposure in patients at the recommended dose of 200 mg/day]. Changes were fully reversed during the 4-week recovery period.

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 $<50 \times 10^9$/L; absolute neutrophil count $<1.5 \times 10^9$/L; AST or ALT >3 × ULN; total bilirubin >1.5 × ULN; QTc(F) >480 ms; eGFR <30 mL/min/1.73 m^2; or FEV1 ≤39%. 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

	REZUROCK 200 mg once daily (N=65)
Age, Median, Years (minimum, maximum)	53 (21, 77)
Age ≥65 Years, n (%)	17 (26)
Male, n (%)	42 (65)
Race, n (%)	
White	54 (83)
Black	6 (9)
Other or Not Reported	5 (8)
Median (range) time (months) from Chronic GVHD Diagnosis	25.3 (1.9, 162.4)
≥4 Organs Involved, n (%)	31 (48)
Median (range) Number of Prior Lines of Therapy	3 (2, 6)
Number of Prior Lines of Therapy, n (%)	
2	23 (35)
3	12 (19)
4	15 (23)
≥5	15 (23)

Prior chronic GVHD treatment with ibrutinib, n (%)	21 (32)
Prior chronic GVHD treatment with ruxolitinib, n (%)	20 (31)
Refractory to Last Therapy, n (%*)	43/55 (78)
Severe chronic GVHD, n (%)	46 (71)
Median (range) Global Severity Rating	7 (2, 9)
Median (range) Lee Symptom Scale Score at baseline	27 (7, 56)
Median (range) Corticosteroid dose at baseline (PE/kg)†	0.19 (0.03, 0.95)

* Denominator excludes patients with unknown status
† Prednisone equivalents/kilogram

The efficacy of REZUROCK was based on 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 results are presented in Table 6. The ORR was 75% (95% CI: 63, 85). 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). The median time to first response was 1.8 months (95% CI: 1.0, 1.9). 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 since response.

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

	REZUROCK 200 mg once daily (N=65)
Overall Response Rate (ORR)	49 (75%)
95% Confidence Interval*	(63%, 85%)
Complete Response	4 (6%)
Partial Response	45 (69%)

* Estimated using Clopper-Pearson method

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).

Embryo-fetal Toxicity:

- 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

Morristown, NJ 07960
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.
  - **Females** who can become pregnant should use effective birth control during treatment with REZUROCK and for 1 week after the last dose.
  - **Males** with female partners who can become pregnant should use effective birth control during treatment with REZUROCK and for 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 and for 1 week after the last dose.

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: colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, and microcrystalline cellulose.
Tablet coating: polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide and yellow iron oxide.
Distributed and marketed by **Kadmon Pharmaceuticals, LLC,** Morristown, NJ 07960, A SANOFI COMPANY
REZUROCK® is a registered trademark of Kadmon Pharmaceuticals, LLC

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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

Revised: 4/2025

PRINCIPAL DISPLAY PANEL - 200 mg Tablet Bottle Carton

NDC 79802-200-30
Rx only

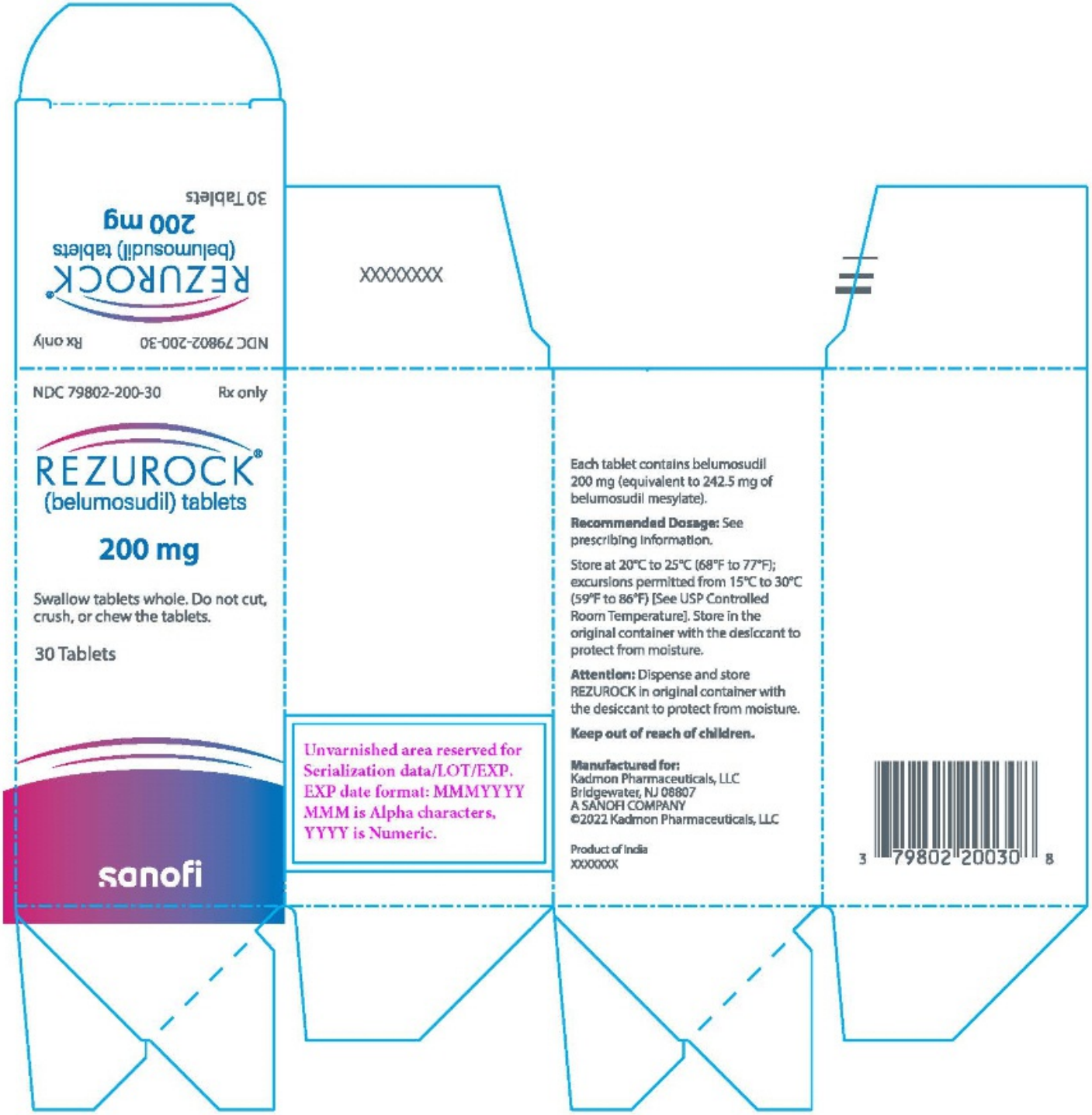
REZUROCK®
(belumosudil) tablets

200 mg

Swallow tablets whole. Do not cut, crush, or chew the tablets.

30 Tablets

sanofi



REZUROCK

belumosudil tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:79802-200
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
BELUMOSUDIL (UNII: 834YJF89WO) (BELUMOSUDIL - UNII:834YJF89WO)	BELUMOSUDIL	200 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
TALC (UNII: 7SEV7J4R1U)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	

Product Characteristics

Color	YELLOW (Pale Yellow to Yellow)	**Score**	no score
Shape	OVAL	**Size**	14mm
Flavor		**Imprint Code**	KDM;200
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:79802-200-30	1 in 1 CARTON	07/16/2021	
1		30 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA214783	07/16/2021	

Labeler - Kadmon Pharmaceuticals, LLC (119013632)

Establishment

Name	Address	ID/FEI	Business Operations
Dr. Reddy's Laboratories Limited, CTO Unit-V1		650443430	ANALYSIS(79802-200) , API MANUFACTURE(79802-200) , PACK(79802-200)

Establishment

Name	Address	ID/FEI	Business Operations
Catalent Micron		015966157	ANALYSIS(79802-200)

Establishment

Name	Address	ID/FEI	Business Operations
Gregory Pharmaceutical Holdings, Inc., dba UPM Pharmaceuticals		081301372	ANALYSIS(79802-200) , MANUFACTURE(79802-200) , PACK(79802-200) , LABEL(79802-200)

Establishment

Name	Address	ID/FEI	Business Operations
Daicel Chiral Technologies (I) Pvt. Ltd.		650645067	ANALYSIS(79802-200)

Establishment

Name	Address	ID/FEI	Business Operations
Carton Service Inc. (dba Pharma Packaging Solutions)		928861723	PACK(79802-200) , LABEL(79802-200)

Establishment

Name	Address	ID/FEI	Business Operations
Sanofi S.r.l.		543209212	ANALYSIS(79802-200) , MANUFACTURE(79802-200) , PACK(79802-200) , LABEL(79802-200)