NEW DRUG APPROVAL

Brand Name	Rezurock™
Generic Name	belumosudil
Drug Manufacturer	Kadmon Pharmaceuticals, LLC

New Drug Approval

FDA Approval Date: July 16, 2021

Review Designation: Priority; Orphan

Type of Review: Type 1 - New Molecular Entity; New Drug Application (NDA): 214783

Dispensing Restriction: N/A

Dispensing Restrictions: Open Distribution Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Acute and chronic graft-versus-host disease (GVHD) are multisystem disorders that are common complications of allogeneic hematopoietic cell transplant (HCT). GVHD occurs when immune cells transplanted from a non-identical donor (the graft) recognize the transplant recipient (the host) as foreign, thereby initiating an immune reaction that causes disease in the transplant recipient.

Clinical manifestations of acute GVHD include a classic maculopapular rash; persistent nausea and/or emesis; abdominal cramps with diarrhea; and a rising serum bilirubin concentration. In contrast, patients with chronic GVHD commonly demonstrate skin involvement resembling lichen planus or the cutaneous manifestations of scleroderma; dry oral mucosa with ulcerations and sclerosis of the gastrointestinal tract; and a rising serum bilirubin concentration.

While risk factors for the development of acute GVHD have been identified, reliable estimates of GVHD incidence in various cohorts are not available due to variability in the identification, measurement, and documentation of acute GVHD.

Clinically significant acute GVHD occurs in patients who receive an allogeneic hematopoietic cell transplant (HCT) despite intensive prophylaxis with immunosuppressive agents. The exact incidence of acute GVHD after allogeneic HCT is unknown. Reported incidence rates range from 9 to 50 percent in patients who receive an allogeneic HCT from a genotypically human leukocyte antigen (HLA)-identical sibling. Acute GVHD is also common in matched unrelated donors and in haploidentical related donors.

Efficacy

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 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.

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.

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

[a] Estimated using Clopper-Pearson method

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Safety

ADVERSE EVENTS

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.

WARNINGS & 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.

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Belumosudil is an inhibitor of rho-associated, coiled-coil containing protein kinase (ROCK) which inhibits ROCK2 and ROCK1 with IC50 values of approximately 100 nM and 3 µM, respectively. Belumosudil downregulated 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.

Dose & Administration

ADULTS

200 mg orally once daily until progression of chronic GVHD that requires new systemic therapy. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary.

PEDIATRICS

Pediatric patients 12 years and older: 200 mg orally once daily until progression of chronic GVHD that requires new systemic therapy. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

Specific guidelines for dosage adjustments in baseline renal impairment are not available; it appears that no dosage adjustments are needed.

HEPATIC IMPAIRMENT

Specific guidelines for dosage adjustments in baseline hepatic impairment are not available; it appears that no dosage adjustments are needed.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablet: 200 mg.