Drug Monograph

Drug Name:	**Rezurock™ (belumosudil) tablets**
Drug Class:	**Immunologic: Rho-Associated, Coiled-Coil Containing Protein Kinase (ROCK) Inhibitor**
Prepared For:	MO HealthNet
Prepared By:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Rezurock is available in a 200 mg oral tablet.
Manufacturer:	Distributed by: Kadmon Pharmaceuticals, LLC, Warrendale, PA 15086.
Summary of Findings:	Rezurock was approved based on the results of a Phase 2 randomized, open-label multicenter clinical trial (N=66) in patients ≥12 years with chronic graft-versus-host disease who had received 2 to 5 previous lines of systemic therapy. The primary endpoint of overall response rate (ORR) was met by 75% of patients taking Rezurock 200 mg daily and was consistent across all organ systems; 69% of patients displayed a partial response and 6% displayed a complete response. The median time to first response was 1.8 months.

Status Recommendation:	☐ Clinical Edit ☒ Open Access	☐ PA Required ☐ PDL
Type of PA Criteria:	☐ Appropriate Indications ☒ No PA Required	☐ Non-Preferred ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2,3]

Graft-versus-host disease (GVHD) is a common complication following allogeneic hematopoietic stem cell transplantation (allo-HSCT) and occurs when immunocompetent T lymphocyte cells transplanted from a non-identical donor (graft) attack the immunodeficient tissue of the transplant recipient (host) as foreign due to histocompatibility differences causing tissue damage. An estimated 10,000 allo-HSCTs are performed each year in the United States. There is distinct pathophysiology and presentation of acute GVHD and chronic GVHD (cGVHD). About 50% of patients are found to have cGVHD within 3 years post-allogeneic HSCT. Chronic GVHD is the leading cause of death and complication in patients following allo-HSCT. More than 10% of patients will die from this complication. The high mortality rate in cGVHD is likely due to current immunosuppressive treatment modalities in which recurrent infections are common. Typically, cGVHD presents like many autoimmune disorders and affects a variety of organs and tissues, including the mouth, skin and nails, gastrointestinal (GI) system, lungs and genitalia. Due to the multiorgan involvement, cGVHD severity is measured using the National Institutes of Health (NIH) GVHD scoring system, which assigns a number to each organ's severity of disease. Mild disease (involves 1 to 2 organs) can be treated using targeted adjunct therapies, whereas severe cGVHD (affects ≥3 organs with severity scores >2) will require systemic therapy. Prednisone is usually chosen as the initial therapy; some patients will use prednisone for 2 to 3 years, but many will require lifelong treatment. Unfortunately, approximately 50% of cGVHD patients will require at least 2 lines of therapy. Options for treating steroid-refractory cGVHD include: Imbruvica (ibrutinib), a tyrosine kinase inhibitor, and Jakafi (ruxolitinib), a Janus kinase inhibitor.

Dosage Form [3]

Rezurock is available in a 200 mg oral tablet.

Manufacturer [3]

Distributed by: Kadmon Pharmaceuticals, LLC, Warrendale, PA 15086.

Indication(s) [3]

Rezurock is a kinase inhibitor indicated for the treatment of adult and pediatric patients ≥12 years with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of therapy.

Clinical Efficacy [3,4] (mechanism of action/pharmacology, comparative efficacy)

Rezurock is an inhibitor of rho-associated, coiled-coil containing protein kinase (ROCK) which inhibits ROCK2 and ROCK1 with the half maximal inhibitory concentration (IC_{50}) values of

approximately 100 nM and 3 μM, respectively. Rezurock down-regulated proinflammatory responses via regulation of STAT3/STAT5 phosphorylation and shifting T helper 17 cells/regulator T cells (Th17/Treg) balance in ex-vivo or in vitro-human T cell assays. Rezurock also inhibited aberrant pro-fibrotic signaling, in vitro. In vivo, Rezurock demonstrated activity in animal models of chronic GVHD.

Pharmacokinetics:

Absorption	Mean bioavailability:64%
Metabolism	Hepatic CYP3A4, and to a lesser extent CYP2C8, CYP2D6, and UGT1A9 in vitro
Excretion	Fecal (85%); Renal (<5%)
Half-life	19 hours

Clinical Trials Experience

STUDY 1 DESIGN (NCT03640481)	Randomized, open-label, multicenter trial (N=65)
INCLUSION CRITERIA	• Patients ≥12 years with chronic GVHD who had received 2 to 5 prior lines of systemic therapy and required additional treatment • Concomitant treatment with supportive therapies for chronic GVHD • 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
EXCLUSION CRITERIA	• Platelet count <50 x 10^9/L • Absolute neutrophil count <1.5 x 10^9/L • Aspartate aminotransferase or alanine transaminase >3 x upper limit of normal (ULN) • Total bilirubin >1.5 x ULN • Corrected QT interval [QTc(F)] >480 ms • Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 • Forced expiratory volume in one second (FEV1) ≤39% • Initiation of new systemic chronic GVHD therapy while on study was not permitted
TREATMENT REGIMEN	Participants took 200 mg of Rezurock once daily in 28-day treatment cycles until clinically significant progression of disease. Patients who did not achieve a response after 12 cycles were withdrawn from the study.
RESULTS	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 National Institutes of Health (NIH) Response Criteria. Complete Response was the resolution of all manifestations in each organ/site. Partial response was improvement in at least 1 organ/site without progression in any other organ/site.

	Rezurock 200 mg once daily (N=65) n (%)
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

	Key secondary endpoints were: the duration of response (DOR), change in Lee Symptom Scale score, failure-free survival, corticosteroid dose reductions and overall survival. 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.
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [3,4]

- None

Warnings and Precautions [3,4]

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

Adverse Effects [3,4]

Most common, ≥10%	Rezurock 200 mg once daily (N=83)	
	All Grades (%)	Grades 3-4 (%)
Infection (pathogen not specified)[a]	53	16
Viral infection[b]	19	4
Bacterial infection[c]	16	4
Asthenia[d]	46	4
Edema[e]	27	1
Pyrexia	18	1
Nausea[f]	42	4
Diarrhea	35	5
Abdominal pain[g]	22	1
Dysphagia	16	0
Dyspnea[h]	33	5
Cough[i]	30	0
Nasal congestion	12	0
Hemorrhage[j]	23	5
Hypertension	21	7
Musculoskeletal pain[k]	22	4
Muscle spasm	17	0
Arthralgia	15	2
Headache[l]	21	0
Decreased appetite	17	1
Rash[m]	12	0
Pruritus[n]	11	0

[a] 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.
[b] 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.
[c] 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.
[d] includes fatigue, asthenia, malaise.
[e] includes edema peripheral, generalized edema, face edema, localized edema, edema.
[f] includes nausea, vomiting.
[g] includes abdominal pain, abdominal pain upper, abdominal pain lower.
[h] includes dyspnea, dyspnea exertional, apnea, orthopnea, sleep apnea syndrome.
[i] includes cough, productive cough.
j includes contusion, hematoma, epistaxis, increased tendency to bruise, conjunctival hemorrhage, hematochezia, mouth hemorrhage, catheter site hemorrhage, hematuria, hemothorax, purpura.
[k] includes pain in extremity, back pain, flank pain, limb discomfort, musculoskeletal chest pain, neck pain, musculoskeletal pain.
l includes headache, migraine.
[m] includes rash, rash maculo-papular, rash erythematous, rash generalized, dermatitis exfoliative.
[n] includes pruritus, pruritus generalize

Drug Interactions (3,4)

- Strong CYP3A4 Inducers: Increase Rezurock dosage to 200 mg twice daily
- Proton Pump inhibitors: Increase Rezurock dosage to 200 mg twice daily

Dosage and Administration (3,4)

The recommended dosage of Rezurock is 200 mg taken orally once daily with food.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Month
Belumosudil	Rezurock™	Kadmon Pharmaceuticals	200 mg orally once daily with food	$15,500

** Wholesale Acquisition Cost

Conclusion

Rezurock is the first and only FDA-approved ROCK2 inhibitor. ROCK2 is a signaling pathway that modulates inflammatory response and fibrotic processes. By inhibiting ROCK2, Rezurock is thought to restore immune homeostasis and reduce fibrosis in affected organs. Rezurock was approved based on the results of a Phase 2 randomized, open-label multicenter clinical trial (N=66) in patients ≥12 years with chronic graft-versus-host disease who had received 2 to 5 previous lines of systemic therapy. The primary endpoint of overall response rate (ORR) was met by 75% of patients taking Rezurock 200 mg daily and was consistent across all organ systems; 69% of patients displayed a partial response and 6% displayed a complete response. The median time to first response was 1.8 months. Rezurock is considered an add-on therapy to steroids and was well-tolerated in clinical trials with adverse effects similar to corticosteroids and other immunosuppressants. Common adverse reactions included: infection, diarrhea, fatigue, nausea, cough, upper respiratory tract infection, dyspnea, headache, peripheral edema, vomiting, muscle spasms, and pneumonia. Rezurock will only be available through limited distribution at select specialty pharmacies.

Recommendation

MO HealthNet Division recommends Open Access status for this product.

References

1) Justiz Vailant AA, Modi P, Mohammadi O. Graft Versus Host Disease. National Center for Biotechnology Information. Available at: https://www.ncbi.nlm.nih.gov/books/NBK538235/. Accessed November 5, 2021.
2) Lee SJ, Wolff D, Kitko C, et. al. Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group report. Biol Blood Marrow Transplant. 2015 Jun;21(6):984-99. doi: 10.1016/j.bbmt.2015.02.025. Epub 2015 Mar 19. PMID: 25796139; PMCID: PMC4744804.
3) IPD Analytics. Rezurock New Drug Review. Available at: https://secure.ipdanalytics.com/. Accessed November 4, 2021.
4) Rezurock [package insert]. Warrendal, PA: Kadmon Pharmaceuticals; 2021

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