Belumosudil (REZUROCK) In Chronic GVHD
National Drug Mini-monograph
April 2024

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION

Description / MOA	Inhibitor of rho-associated, coiled-coil containing protein kinase (ROCK), that inhibits ROCK1 and ROCK2, down-regulating proinflammatory responses
Indication Under Review[1]	Treatment of chronic graft vs. host disease (GVHD) after failure of at least 2 prior lines of therapy
Dosage Regimen	200 mg PO once daily with food
Dosage Forms Under Review	200 mg tablet

DISEASE BASICS 101

Chronic Graft versus Host Disease (cGVHD)	**NIH Consensus Criteria for organ scoring**. Score 0-3 (least to most impactful) Grading classified by symptoms, affected organ systems and extent of disease involvement **Mild** ≤ 2 affected organs; no clinically significant functional dysfunction **Moderate** ≥ 3 organs with no dysfunction or ≥ 1 organ with dysfunction but no major disability **Severe** Major disability **Treatment for mild**. Localized therapy (i.e. PUVA, ECP) **Moderate.** Prednisone **Severe.** Prednisone + ruxolitinib

EFFICACY CONSIDERATIONS

Trial	**ROCKstar Study**
Design	Phase 2, randomized, multicenter trial in 28 U.S centers
Population	s/p AlloHCT; age ≥ 12 yrs; persistent cGVHD; s/p 2-5 prior lines of therapy; on stable CS x2 weeks; KPS ≥ 60
Demographics	N = 132; mAge 56 yrs (range 21-77), 31% moderate cGVHD; 67% severe cGVHD; 52% ≥ 4 involved organs; median 3 prior lines; 34% prior ibrutinib; 29% prior ruxolitinib; 72% ≥ 3 prior lines
Intervention	Belumosudil 200 mg once daily
Comparator	Belumosudil 200 mg twice daily; stratified by (1) cGVHD severity (2) prior ibrutinib
Results	Primary: ORR (defined as CR or PR) per NIH Consensus Criteria for clinical trials in cGVHD Secondary: DOR, TTR, changes in LSS summary score, FFS, CS dose-reduction, OS Belumosudil daily vs. twice daily ORR 74 vs. 77%; prior ibrutinib (n=46) ORR 74%; prior ruxolitinib (n=38) ORR 68%; Best ORR joints/fascia 71%; lower GI 69%; upper GI 52%; mouth 55%; esophagus 45%; eyes 42%; skin 37%; liver 39%; lungs 26% ORR observed in all subgroups regardless of severity or prior therapy; mDOR 54 weeks; TTR 5 wks (range, 4-66); FFS 75% @6 mos, 56% @ 12 mos, 2-yr OS 89%; improvement in LSS score 59 vs. 62%; mean CS dose-reduction 45% in mITT pop'n, 54% in responders
Summary	In a heavily pre-treated population of patients with moderate to severe cGVHD, belumosudil offered response rates of 74 and 77% (QD vs. BID) Responses were noted in all affected organ systems QoL was not a measured outcome; a reduction in the LSS was clinically meaningful (≥ 7-point reduction) in both treatment arms Belumosudil therapy allowed the reduction of CS dose with 21% discontinuing CS Preferred regimen is belumosudil 200 mg PO once daily as the differences in response were not significant Responses noted in heavily pre-treated patients; lasted ~54 weeks; 44% remain on therapy ≥ 1 yr

	KEY	alloHCT allogeneic hematopoietic stem cell transplant; cGVHD chronic graft vs. host disease; ORR overall response rate; CR complete response; PR partial response; DOR duration of response, TTR time to response; LSS Lee symptom scale; FFS failure free survival; CS corticosteroid; OS overall survival; mITT median intent to treat; NIH National Institutes of Health; KPS Karnofsky Performance Scale; LOT lines of therapy; SR steroid-refractory

SAFETY CONSIDERATIONS	**Boxed Warnings**	None
	Contraindications	None listed; avoid use in moderate or severe hepatic impairment
	Other Warnings	Embryo-fetal toxicity
	Top AEs (all/3-4)	Infection (53/16%); asthenia (46/4%); nausea (42/4%); diarrhea (35/5%); dyspnea (33/5%); HTN (21/7%)
	Top lab abnl	↓phos, ↑ggtp, ↓lymphocytes
	Drug Interactions	Strong CYP3A inducers. Increase belumosudil dose to 200 mg twice daily Proton pump inhibitors. Increase belumosudil dose to 200 mg twice daily
	DC due to AE	18%
	Interruption	29%

	DRUG	VANF	CFU	FDA	GUIDELINES
PLACE IN THERAPY	Belumosudil 200 mg PO daily	TBD	TBD	cGVHD s/p ≥ 2 prior LOT	EBMT 2024 recs mgmt gvhd after hsct: • Potential option in SR-cGVHD UpToDate. No recommendation; await long-term data NCCN v3.2023. Recommended after ≥ 2 prior lines of therapy (Cat 2A)
	Ruxolitinib 10 mg PO twice daily	PA-F	CFU	cGVHD s/p 1-2 prior LOT	P3 open-label, randomized; n=329; Rux vs. BAT, @ 24 wks: ORR 50 vs. 26%; LSS 24 vs. 11%; CR 7 vs. 3%; FFS 19 vs. 6% EBMT 2024 recs mgmt gvhd after hsct: • Preferred option in SR-cGVHD NCCN v3.2023. Preferred after 1-2 lines (Cat 1)
	Ibrutinib 420 mg PO daily	PA-F	CFU	cGVHD s/p ≥ 1 prior LOT	P2; n=42; in SR-cGVHD; s/p 1-3 LOT; @13.9 months, best ORR 67%; CS dose reduced; 71% sustained response ≥ 20 weeks EBMT 2024 recs mgmt gvhd after hsct: • Potential option in SR-cGVHD NCCN v3.2023. Included after ≥ 1 line (Cat 2A)

VHA PLACE IN THERAPY	**Potential Use in VHA**	1. Heavily pre-treated patients with cGVHD achieved ORR 74% with once daily therapy 2. Responses ranged from 26-72% in the following organ systems: skin, eyes, mouth, liver, lungs, joints/fascia, upper and lower GI track and esophagus 3. Responses were noted following prior ibrutinib and prior ruxolitinib (ORR 74 and 68%, respectively) 4. Reduction in corticosteroid dose was also notable in 65% of patients 5. Belumosudil is an effective therapeutic option for the treatment of cGVHD in patients who have progressive disease or contraindication to ibrutinib or ruxolitinib

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References

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