Belzutifan (WELIREG)
National Drug Monograph
February 2025

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. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION		
	Description / MOA	An inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α)
	Indication Under Review[1]	1. Adults with von Hippel Lindau (VHL) disease for associated renal cell carcinoma (RCC), CNS hemangioblastoma, or pancreatic neuroendocrine tumors not requiring immediate surgery 2. Advanced Renal Cell Carcinoma following PD-1 or PD-L1 inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI)
	Dosage Regimen	120mg (3 x 40mg tablets) once daily with or without food
	Dosage Forms Under Review	40 mg film-coated tablets

EFFICACY CONSIDERATIONS	**Trial**	**LITESPARK-004**[1]	**LITESPARK-005**[2]
	Design	Open-label, phase 2, VHL disease and at least 1 RCC tumor plus other VHL-associated tumors in other organs allowed	Open-label, phase 3, randomized, active control (everolimus) in advanced clear cell RCC; Primary outcome (dual): PFS and OS
	Population	Germline VHL alteration, at least 1 measurable RCC (no metastatic disease), ECOG 0 or 1; N=61	Locally advanced/metastatic clear cell RCC, prior tx with a PD-1/L1 inhibitor and VEGF TKI alone or in combination (NMT 3 prior systemic therapies), with progression, KPS ≥70% N=746 (n=374 B, n=372 E)
	Demographic	Med age: 41; Male-52%;, ECOG 0 82%; pancreatic-100%; pancreatic neuroendocrine tumors (Pan NET)-36%; CNS hemangioblastomas-82%; retinal hemangioblastoma-20%	Med age: 62; Male 74%, KPS 90-100: 64%; White 79.4%; IMDC* favorable: 21.1%; IMDC* Intermed: 66.6%; Prev Tx: 1-12.3%, 2-42%, 3-45.2%
	Intervention	Belzutifan 120mg (3 x 40mg) tablets daily	Belzutifan 120mg daily
	Comparator	None	Everolimus 10mg daily
	Results	Primary Outcome: ORR in VHL-associated RCC RCC ORR: 49% (PR 49%; SD 49%); Med DOR: NR Pancreatic: 77% (CR-10%); PanNET: 91% (CR 14%) CNS: 30% (CR 6%) <u>2-year update</u> RCC ORR: 59% (CR 3%); Med DOR: NR PanNETS: 90% CNS: 38%	Med PFS: 5.6 mos in both groups HR for death or progression: 0.75 (95%CI 0.63-0.90) Restricted mean PFS at 8.2 mos vs 6.7 mos at 18 mos OS: HR for death 0.88 (95%CI 0.73-1.07) NSS
	Notes	• **NCCN guidelines** o Nothing specific to VHL • **VA Oncology Clinical Pathways:** o Nothing specific to VHL	• **NCCN guidelines** o No preferred therapies for subsequent therapy o Belzutifan is one choice out of 5 for subsequent therapy if patient had prior PD-1/L-1 therapy (2A); (axitinib, belzutifan [prior PD-1 + VEGF TKI], cabozantinib, everolimus plus lenvatinib, tivozanib) o If only VEGF-TKI prior therapy, use belzutifan under certain circumstances (2B) • **VA Oncology Clinical Pathways:** o Nothing specific to VHL treatment; recurrent clear cell RCC currently recommends either of 2 combination therapies and then single-agent cabozantinib

*IMDC=**I**nternational **M**etastatic Renal-Cell Carcinoma **D**atabase **C**onsortium

SAFETY CONSIDERATIONS		
	Boxed Warnings	Embryo-fetal Toxicity
	Contraindications	None
	Other Warnings	Anemia (gr 3 in 7% in VHL and 29% in advanced RCC), Hypoxia, Embryo-Fetal Toxicity
	Top 5 AEs	VHL: anemia, fatigue, headache, dizziness, nausea RCC: anemia, fatigue, musculoskeletal pain, edema, nausea
	Drug Interactions	UGT2B17 inhibitors and CYP2C19 inhibitors-increased exposure of belzutifan

VHA PLACE IN THERAPY		
	Potential Use in VHA	1. VHL is an inherited, autosomal dominant disease characterized by benign and malignant tumors (e.g. renal cell carcinoma, hemangioblastoma, pheochromocytoma and other rare tumors). Normal VHL gene product targets certain proteins for degradation. 2. Hypoxia-inducible factor 1 alpha (HIF 1α) and 2 alpha (HIF 2α) are transcription proteins regulated by VHL. Variations in the VHL gene causing loss of function of one or two alleles creates a hypoxia-like condition and rising levels HIF 1α and 2α, resulting in increased levels of erythropoietin, VEGF, and other growth factors that can stimulate tumor growth. 3. There is no standard of care for patients with tumors from VHL, and Belzutifan is a reasonable choice in this population. 4. For previously treated clear cell RCC, there are several options for treatment depending on prior therapies. Belzutifan was studied in patients who received a prior PD-1/PD-L1 inhibitor and a VEGF TKI either alone or in combination. While the combination produced a modest increase in progression-free survival (PFS) and objective response rate (ORR), it did not have an overall survival (OS) advantage. In addition, the curves for PFS crossed over after 6 months due to an unknown early PFS advantage for everolimus. The use of everolimus as a comparator in this setting is also problematic as everolimus alone is not considered standard treatment in this pre-treated population. Combination therapy, cabozantinib, or tivozanib would have been better comparators.

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References

[1]Jonasch E, Donskov F, Iliopoulos O, et al. Belzutifan for renal cell carcinoma in von-Hippel Lindau disease. New Eng J Med 2021; 385: 2036-46.

[2]Choueiri TK, Powles T, Peltola K, et al. Belzutifan versus everolimus for advanced renal-cell carcinoma. New Eng J Med 2024; 391: 710-21.