BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

WELIREG™ (belzutifan)
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Welireg (belzutifan) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Adult (18 years or older) with von Hippel-Lindau (VHL) disease who requires therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery

    b. Adult (18 years or older) with advanced renal cell carcinoma (RCC) with a clear cell component following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor

and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI) (see Definitions section)

c. Individual 12 years or older with locally advanced, unresectable, or metastatic pheochromocytoma or paraganglioma (PPGL)

d. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

3. Individual has completed **ALL** the following **baseline tests** before initiation of treatment and will have continued monitoring as clinically appropriate:
   a. Hemoglobin
   b. Oxygen saturation
   c. Negative pregnancy test in a woman of childbearing potential
   d. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2
   e. Diagnosis of VHL disease is confirmed by a germline alteration in the *VHL* gene

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual does not have severe renal impairment (estimated glomerular filtration rate 15-29 mL/min/1.73 m^2)

6. Individual does not have severe hepatic impairment (total bilirubin greater than 1.5 times the upper limit of normal and any aspartate aminotransferase)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Welireg (belzutifan) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual has documentation of positive clinical response to therapy defined as there is documented evidence of efficacy, disease stability and/or improvement

3. Individual has been adherent with the medication

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
    a. Anemia that is life-threatening or requires urgent intervention
    b. Hypoxia that is life-threatening or recurrent or requires intervention
    c. Other severe adverse reaction that recurs after dose reduction or a life-threatening adverse reaction

6. The dose has not been reduced more than two times to avoid adverse reactions

7. Individual does not have severe renal impairment (estimated glomerular filtration rate 15-29 mL/min/1.73 m^2)

8. Individual does not have severe hepatic impairment (total bilirubin greater than 1.5 times the upper limit of normal and any aspartate aminotransferase

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Welireg (belzutifan) is a hypoxia-inducible factor-2 alpha (HIF-2 alpha) inhibitor indicated for treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery. Welireg (belzutifan) is also indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).

HIF-2 alpha is a transcription factor that plays a role in oxygen sensing by regulating genes that promote adaptation to hypoxia. Under normal oxygen levels, HIF-2 alpha is targeted for ubiquitin-proteasomal degradation by VHL protein. Lack of functional VHL protein results in stabilization and accumulation of HIF-2 alpha. Upon stabilization, HIF-2 alpha translocates into the nucleus and interacts with hypoxia-inducible factor 1 beta (HIF-1 beta) to form a transcriptional complex that induces expression of downstream genes, including genes associated with cellular proliferation, angiogenesis, and tumor growth. Belzutifan binds to HIF-2 alpha, and in conditions of hypoxia or impairment of VHL protein function, blocks the HIF-2 alpha-HIF-1 beta interaction, leading to reduced transcription and expression of HIF-2 alpha target genes.

VHL disease is an inherited, autosomal dominant syndrome manifested by a variety of benign and malignant tumors. Tumors and cysts can form in the brain, and spinal cord, kidneys, pancreas, adrenal gland, and reproductive tract. The tumors are usually benign but those in the kidney and pancreas can become malignant. A

pathogenic variant in the *VHL* gene diagnostic for VHL disease is present in approximately 1 in 36,000 individuals. Disease manifestation can appear in childhood, adolescence, or adulthood. Mean age at initial presentation is said to be approximately 26 years of age.
The spectrum of VHL-associated tumors includes: hemangioblastomas of the brain (cerebellum) and spine; retinal capillary hemangioblastomas (retinal angiomas); clear cell renal cell carcinomas (RCCs); pheochromocytomas; endolymphatic sac tumors of the middle ear; serous cystadenomas and neuroendocrine tumors of the pancreas; and papillary cystadenomas of the epididymis and broad ligament.

VHL is divided into types 1 and 2, based upon the likelihood of developing pheochromocytoma. The types are further divided into “A” and “B” and “C” categories. Type 1A patients have a lower risk of developing pheochromocytoma. Type 1B patients have a lower risk of both pheochromocytomas and renal cell carcinoma (RCC), Type 2 patients are at high risk for developing pheochromocytoma. Type 2A and 2B have a low and high incidence of RCC while Type 2C patients develop pheochromocytoma only, without RCC or hemangioblastoma.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Programmed death receptor-1 (PD-1) inhibitor or Programmed death-ligand 1 (PD-L1) inhibitor
- Keytruda (pembrolizumab)
- Opdivo (nivolumab)
- Bavencio (avelumab)
- Jemperli (dostarlimab)

Vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI)
- Cabometyx (cabozantinib)
- Lenvima (lenvatinib)
- Inlyta (axitinib)
- Fotivda (tivozanib)
- Pazopanib
- Sunitinib
- Sorafenib

Resources:

Welireg (belzutifan) product information, revised by Merck Sharp & Dohme LLC. 05-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 25, 2025.

Plon SE, Jonasch E. Clinical presentation, diagnosis, and surveillance of von Hippel-Lindau disease. In: UpToDate, Atkins MB, Firth HV, Perrone RD, Gajjar A, Geffner ME, Shah S (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through September 2025. Topic last updated March 31, 2025. Accessed October 09, 2025.

Plon SE, Jonasch E. Surveillance and management of von Hippel-Lindau disease. In: UpToDate, Atkins MB, Firth HV, Perrone RD, Gajjar A, Geffner ME, Shah S (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through September 2025. Topic last updated August 08, 2025. Accessed October 09, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Kidney Cancer Version 1.2026 – Updated July 24, 2025. Available at https://www.nccn.org. Accessed October 09, 2025.

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National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Central Nervous System Cancers Version 2.2025 – Updated August 28, 2025. Available at https://www.nccn.org. Accessed October 09, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Neuroendocrine and Adrenal Tumors Version 3.2025 – Updated October 01, 2025. Available at https://www.nccn.org. Accessed October 09, 2025.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.