BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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WELIREG™ (belzutifan)

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy:** Welireg (belzutifan) 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 is 18 years of age or older

  3. A confirmed diagnosis of **ONE** of the following:
     a. von Hippel-Lindau disease in an individual who requires therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery

     b. 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

  4. **ALL** of the following **baseline tests** have been completed before initiation of treatment with 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

  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

  7. There are no significant interacting drugs

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Welireg (belzutifan) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

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

  2. Individual's condition has responded/worsened while on therapy
     a. Response is defined as:
        i. No evidence of disease progression

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ii. No evidence individual has developed any significant unacceptable adverse drug reactions that may exclude continued use
iii. Documented evidence of efficacy, disease stability and/or improvement

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
   a. Significant adverse effect such as:
      i. Anemia that is life-threatening or requires urgent intervention
      ii. Hypoxia that is life-threatening or recurrent or requires intervention
      iii. Other severe adverse reaction that recurs after dose reduction or a life-threatening adverse reaction

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

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

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

8. There are no significant interacting drugs

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 a Non-cancer Medications**

2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

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.

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.

von Hippel-Lindau (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.

Resources:

Welireg (belzutifan) product information, revised by Merck Sharp & Dohme Corp. 08-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed October 05, 2021.

Plon SE, Jonasch E. Clinical features, diagnosis, 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. Accessed October 05, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Kidney Cancer Version 2.2022 – Updated September 08, 2021. Available at https://www.nccn.org. Accessed October 05, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Central Nervous System Cancers Version 2.2021 – Updated September 08, 2021. Available at https://www.nccn.org. Accessed October 05, 2021.

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.