Pharmacy Policy Bulletin: J-1118 Welireg (belzutifan) – Commercial and Healthcare Reform	
Number: J-1118	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial:** **Prior Authorization (1.):** **1.** Miscellaneous Specialty Drugs Oral = Yes w/ Prior Authorization **Healthcare Reform:** Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** None
Version: J-1118-006	**Original Date:** 10/06/2021
Effective Date: 07/18/2025	**Review Date:** 06/25/2025

Drugs Product(s):	• Welireg (belzutifan)
FDA-Approved Indication(s):	• 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. • Treatment of adult patients with advanced RCC with a clear cell component following a programmed death receptor-1 (PD-1) or programmed death-ligand (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI). • Treatment of adult and pediatric patients 12 years and older with locally advanced, unresectable, or metastatic pheochromocytoma or paraganglioma (PPGL).

Background:	• Welireg is an inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α). HIF-2α regulates genes that promote adaptation to hypoxia and is a transcription factor that induces genes associated with cellular proliferation, angiogenesis, and tumor growth. In conditions of hypoxia or impairment of VHL protein function, Welireg reduces transcription and expression of HIF-2α target genes. • VHL syndrome is an inherited disorder characterized by the formation of tumors made of newly formed blood vessels called hemangioblastomas and fluid-filled cysts in many different parts of the body. This is a rare genetic disease with an estimated incidence of 10,000 people in the US. Patients with VHL syndrome are at risk for benign blood vessel tumors as well as some cancerous ones including RCC. Surgery may be appropriate for patients when the largest tumor reaches 3 cm to prevent metastasis. • RCC is the most common type of kidney cancer; an estimated 85% of kidney tumors are RCC. Systemic treatment of advanced RCC generally includes a VEGF inhibitor (for example, axitinib, cabozantinib, lenvatinib) in combination

	with a PD-1 (for example, pembrolizumab, nivolumab) or PD-L1 inhibitor (for example, avelumab). • Pheochromocytomas and paragangliomas are rare tumors that originate from the same type of tissue; however, pheochromocytomas form in nerve tissue in the adrenal medulla (the center of the adrenal gland), while paragangliomas form in nerve tissue outside of the adrenal gland. Symptoms may include high blood pressure, heavy sweating, headache, tachycardia, pallor, and dyspnea. Surgical resection is generally the mainstay of treatment for benign and malignant PPGL. • ICD-10 Code Information: o ICD-10: Q85.8 "Other phakomatoses, not elsewhere classified" may apply to VHL syndrome; however, the prescriber must confirm that the member has a specific diagnosis of VHL syndrome. o ICD-10: D3A.8 "Other benign neuroendocrine tumors" or C25.4 "Malignant neoplasm of endocrine pancreas" may apply to pNET; however, the prescriber must confirm that the member has a specific diagnosis of pancreatic neuroendocrine tumor. • Prescribing Considerations: o Welireg can cause embryo-fetal harm when administered during pregnancy. o Welireg may impair fertility in males and females. o The patient should be tested for anemia and hypoxia prior to initiation of Welireg and monitored throughout treatment. Welireg dose should be withheld if anemic (hemoglobin < 9 g/dL) or hypoxic at rest (pulse oximeter < 88%, or $PaO_2 \leq 55$ mm Hg) and resumed at a lower dose when resolved or discontinued.

Approval Criteria

I. Initial Authorization

A. Von Hippel-Lindau (VHL) Disease
When a benefit, coverage of Welireg may be approved when all of the following criteria are met **(1., 2., and 3.)**:
1. The member is 18 years of age or older.
2. The member has a diagnosis of VHL disease (no ICD-10 code).
3. The member has a diagnosis of one (1) of the following not requiring immediate surgery **(a., b., or c.)**:
a. Renal cell carcinoma (ICD-10: C64.9)
b. CNS hemangioblastoma (ICD-10: D18.02, D33)
c. Pancreatic neuroendocrine tumor (no ICD-10 code)

B. Advanced Renal Cell Carcinoma (RCC)
When a benefit, coverage of Welireg may be approved when all of the following criteria are met **(1. through 4.)**:
1. The member is 18 years of age or older.
2. The member has a diagnosis of advanced RCC (ICD-10: C64) with a clear cell component.
3. The member has received prior treatment with one (1) of the following **(a. or b)**:
a. PD-1 inhibitor (for example, pembrolizumab, nivolumab)
b. PD-L1 inhibitor (for example, avelumab)
4. The member has received prior treatment with a VEGF-TKI (for example, axitinib, cabozantinib, lenvatinib).

C. Pheochromocytoma or Paraganglioma (PPGL)
When a benefit, coverage of Welireg may be approved when all of the following criteria are met **(1. and 2.)**:

1. The member is 12 years of age or older.
2. The member has a diagnosis of one (1) of the following **(a. or b.)**:
   a. Locally advanced, unresectable, or metastatic pheochromocytoma.
   b. Locally advanced, unresectable, or metastatic paraganglioma.

II. Reauthorization

When a benefit, reauthorization of Welireg may be approved when the following criterion is met **(A.)**:

A. The prescriber attests that the member is tolerating therapy and has experienced a therapeutic response defined as one (1) of the following **(1. or 2.)**:
   1. Disease improvement
   2. Delayed disease progression.

III. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

IV. Coverage of oncology drug(s) listed in this policy may be approved on a case-by-case basis per indications supported in the most current NCCN guidelines.

Limitations of Coverage

I. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.

II. For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

- Commercial and HCR Plans: If approved, up to a 12 month authorization may be granted.

Automatic Approval Criteria

None

References:

1. Welireg (belzutifan) [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme; May 2025.
2. Medlineplus.gov. VHL gene von Hippel-Lindau tumor suppressor. Available at: https://medlineplus.gov/genetics/gene/vhl/. Accessed August 26, 2021.
3. NCCN. Kidney Cancer version 3.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed April 28, 2025.
4. NCCN. Central Nervous System Cancers version 5.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed April 28, 2025.
5. NCCN. Neuroendocrine and Adrenal Tumors version 1.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed May 19, 2025.
6. National Cancer Institute. Pheochromocytoma and Paraganglioma Treatment (PDQ®)–Patient Version. Available at: https://www.cancer.gov/types/pheochromocytoma/patient/pheochromocytoma-treatment-pdq. Accessed May 19, 2025.