PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Welireg Prior Authorization Policy
- Welireg® (belzutifan tablets – Merck)

REVIEW DATE: 05/07/2025; selected revision 05/21/2025

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Welireg, a hypoxia-inducible factor inhibitor, is indicated for the treatment of:
- **Pheochromocytoma or paraganglioma**, locally advanced, unresectable, or metastatic disease in patients ≥ 12 years of age.
- **Renal cell carcinoma**, **advanced** 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) in adults.
- **von Hippel-Lindau (VHL) disease,** in adults who require therapy for associated renal cell carcinoma, central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors, not requiring immediate surgery.[1]

The pivotal trial for VHL disease included patients with VHL disease-associated renal cell carcinoma, CNS hemangioblastomas, pancreatic neuroendocrine tumor, and retinal hemangioblastoma.[2]

Guidelines

Welireg is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):

- **CNS Cancers:** NCCN guidelines (version 5.2024 – March 18, 2025) recommend Welireg for VHL-associated CNS hemangioblastoma not requiring immediate surgery or those for whom surgery is contraindicated due to location or prior surgery or comorbidities, growing or symptomatic as "useful in certain circumstances" (category 2A).[3] Welireg is used as a single-agent treatment for brain metastases in VHL-associated renal cell carcinoma (category 2B).
- **Kidney Cancer:** NCCN guidelines (version 3.2025 – January 9, 2025) recommend Welireg as a "preferred" regimen for VHL-associated renal cell carcinoma (category 2A). Welireg is also recommended as a single-agent therapy for relapse or stage IV disease as subsequent therapy for clear cell histology if prior history includes immuno-oncology therapy (PD-1 or PD-L1 inhibitor and a VEGF-TKI) as "other recommended regimens" (category 2A) and as immuno-oncology therapy naive as "useful in certain circumstances" (category 2B).[4]
- **Neuroendocrine and Adrenal Tumors:** NCCN guidelines (version 1.2025 – March 27, 2025) list VHL disease as a hereditary endocrine neoplasia. Welireg is recommended in a variety of settings for pancreatic neuroendocrine tumors with germline VHL alteration (category 2A).[5] Welireg is not addressed in the guidelines for the treatment of pheochromocytoma or paraganglioma.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Welireg. All approvals are provided for the duration noted below.

- **Welireg® (belzutifan tablets - Merck)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indications

1. **Pheochromocytoma or Paraganglioma**. Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 12 years of age; AND
   B) Patient has locally advanced, unresectable, or metastatic disease.

2. **Renal Cell Carcinoma**. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has advanced disease; AND
   C) The cancer has a clear cell histology; AND
   D) Patient has tried at least one programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor; AND
   Note: Examples of PD-1 inhibitor or PD-L1 inhibitor include: Keytruda (pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), and Bavencio (avelumab intravenous infusion).
   E) Patient has tried at least one vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).

Note: Examples of VEGF-TKI include Cabometyx (cabozantinib tablets), Lenvima (lenvatinib capsules), Inlyta (axitinib tablets), Fotivda (tivozanib capsules), pazopanib, sunitinib, and sorafenib.

3. **Von Hippel-Lindau Disease.** Approve for 1 year if the patient meets ALL of the following (A, B, C and D):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has a von Hippel-Lindau (VHL) germline alteration as detected by genetic testing; AND
   C) Patient does not require immediate surgery; AND
   D) Patient requires therapy for ONE of the following conditions (i, ii, iii, or iv):
      i. Central nervous system hemangioblastomas; OR
      ii. Pancreatic neuroendocrine tumors; OR
      iii. Renal cell carcinoma; OR
      iv. Retinal hemangioblastoma.

CONDITIONS NOT COVERED

- **Welireg® (belzutifan tablets - Merck)**

is(are) considered not medically necessary for ANY other use(s).

REFERENCES

1. Welireg® tablets [prescribing information]. Whitehouse Station, NJ: Merck; May 2025.
2. Jonasch E, Donskov F, Iliopoulos O, et al. Belzutifan for renal cell carcinoma in von Hippel-Lindau disease. *N Eng J Med*. 2021; 385(22):2036-2046.
3. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 5.2024 – March 18, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 1, 2025.
4. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (version 3.2025 – January 9, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 1, 2025.
5. The NCCN Neuroendocrine and Adrenal Tumors Clinical Practice Guidelines in Oncology (version 1.2025 – March 27, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 1, 2025.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	09/13/2023
Selected Revision	**Renal Cell Carcinoma**: Indication and criteria were added to the FDA-Approved Indications section due to new indication in advanced renal cell carcinoma 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) in adults.	12/20/2023
Annual Revision	No criteria changes.	06/19/2024
Annual Revision	**Renal Cell Carcinoma**: The requirement that the cancer has a clear cell histology was added.	05/07/2025
Selected Revision	**Pheochromocytoma or Paraganglioma:** Condition of approval and criteria was added to FDA approved indications section.	05/21/2025