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Section:	Prescription Drugs	**Effective Date:**	April 1, 2024
Subsection:	Antineoplastic Agents	**Original Policy Date:**	September 3, 2021
Subject:	Welireg	**Page:**	1 of 5

Last Review Date: March 8, 2024

Welireg

Description

Welireg (belzutifan)

Background
Welireg (belzutifan) is an inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α). HIF-2α is a transcription factor that plays a role in the body's adaptation response to low oxygen levels. Under normal oxygen levels, HIF-2α is degraded by the von Hippel-Lindau (VHL) protein. Without functional VHL protein, the HIF-2α transcription factor accumulates, interacts with hypoxia-inducible factor 1 beta (HIF-1β) and leads to the expression of genes associated with cellular proliferation, angiogenesis, and tumor growth. Welireg inhibits the formation of the HIF-2α- HIF-1β complex, leading to reduced expression of downstream oncogenes (1).

Regulatory Status
FDA-approved indications: Welireg is a hypoxia-inducible factor inhibitor indicated: (1)

- 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.
- For 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).

Welireg has a boxed warning regarding embryo-fetal toxicity. Exposure to Welireg during pregnancy can cause embryo-fetal harm and pregnancy status should be verified before initiation of treatment. Welireg can render some hormonal contraceptives ineffective. Female

patients of reproductive potential and male patients with partners of reproductive potential should be advised to use effective non-hormonal contraception during treatment with Welireg and for 1 week after the last dose (1).

Welireg has warnings regarding anemia and hypoxia. Patients should be monitored for anemia before initiation and periodically throughout treatment. Welireg should be withheld until hemoglobin ≥8g/dL, and then resumed at reduced dose or discontinued. Oxygen saturation should be monitored before initiating treatment and then periodically throughout treatment. If patient becomes hypoxic at rest, withhold Welireg until resolved, and then resume at reduced dose or discontinue permanently. In cases of life-threatening hypoxia, discontinue Welireg permanently (1).

The safety and effectiveness of Welireg in pediatric patients less than 18 years of age have not been established (1).

Related policies

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Welireg may be considered **medically necessary** if the conditions indicated below are met.

Welireg may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 18 years of age and older

Diagnoses

Patient must have **ONE** of the following:

1. Von Hippel-Lindau (VHL) disease
    a. Patient has **ONE** of the following:

i. Renal cell carcinoma (RCC)
ii. Central nervous system (CNS) hemangioblastomas
iii. Pancreatic neuroendocrine tumors (pNET)

b. Patient does not require immediate surgery

2. Advanced renal cell carcinoma (RCC)
   a. Previous treatment with **AL**L of the following:
      i. PD-1 inhibitor **OR** PD-L1 inhibitor
      ii. VEGF-TKI

AND ALL of the following:

1. Hemoglobin ≥8 g/dL
2. Prescriber agrees to monitor for anemia and hypoxia before initiation of treatment and periodically throughout treatment
3. Females of reproductive potential **only**: pregnancy will be excluded before start of treatment, and patient will be advised to use effective non-hormonal contraception during treatment with Welireg and for 1 week after the last dose
4. Males with female partners of reproductive potential **only**: pregnancy will be excluded before start of treatment and patient will be advised to use effective non-hormonal contraception during treatment with Welireg and for 1 week after the last dose

Prior–Approval *Renewal* Requirements

Age 18 years of age and older

Diagnoses

Patient must have **ONE** of the following:

1. Von Hippel-Lindau (VHL) disease
   a. Patient has **ONE** of the following:
      i. Renal cell carcinoma (RCC)
      ii. Central nervous system (CNS) hemangioblastomas
      iii. Pancreatic neuroendocrine tumors (pNET)
   b. Patient does not require immediate surgery
2. Advanced renal cell carcinoma (RCC)

AND ALL of the following:

1. **NO** disease progression or unacceptable toxicity
2. Hemoglobin ≥8 g/dL
3. Prescriber agrees to monitor for anemia and hypoxia periodically throughout treatment
4. Females of reproductive potential **only**: patient will be advised to use effective non-hormonal contraception during treatment with Welireg and for 1 week after the last dose
5. Males with female partners of reproductive potential **only**: patient will be advised to use effective non-hormonal contraception during treatment with Welireg and for 1 week after the last dose

Policy Guidelines

Pre–PA Allowance

None

Prior–Approval Limits

Quantity 120 mg per day

Duration 12 months

Prior–Approval *Renewal* Limits

Same as above

Rationale

Summary

Welireg (belzutifan) is an inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α) and is indicated for von Hippel-Lindau (VHL) disease and advanced renal cell carcinoma. Welireg carries a boxed warning regarding embryo-fetal toxicity and patients should be advised to use to effective non-hormonal contraception. Welireg has also been shown to cause hypoxemia and anemia. Patients should be monitored for these conditions and dosage adjusted, or treatment

discontinued as appropriate. The safety and efficacy of Welireg in pediatric patients less than 18 years of age have not been established (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Welireg while maintaining optimal therapeutic outcomes.

References

1. Welireg [package insert]. Whitehouse Station, NJ: Merck Sharpe & Dohme Corp.; December 2023.
2. NCCN Drugs & Biologics Compendium® Belzutifan 2024. National Comprehensive Cancer Network, Inc. Accessed on January 24, 2024.

Policy History

Date	Action
September 2021	Addition to PA
December 2021	Annual review and reference update
December 2022	Annual review and reference update
March 2023	Annual review and reference update
January 2024	Per PI update, added indication of advanced renal cell carcinoma (RCC). Changed hemoglobin requirement to ≥8 g/dL. Changed quantity limit to 120 mg per day
March 2024	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 8, 2024 and is effective on April 1, 2024.