Evolent Clinical Guideline 3052 for Welireg™ (belzutifan)

Guideline Number: Evolent_CG_3052	**Applicable Codes**	
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STATEMENT

Purpose

To define and describe the accepted indications for Welireg (belzutifan) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

Evolent is responsible for processing all medication requests from network ordering providers. Medications not authorized by Evolent may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

INDICATIONS

Continuation requests for a not-approvable medication shall be exempt from this Evolent policy provided

- The member has not experienced disease progression on the requested medication AND
- The requested medication was used within the last year without a lapse of more than 30 days of having an active authorization AND
- Additional medication(s) are not being added to the continuation request.

Pheochromocytoma or Paraganglioma (PPGL)

- Welireg (belzutifan) may be used for the treatment of adult and pediatric members 12 years and older with locally advanced, unresectable, or metastatic pheochromocytoma or paraganglioma (PPGL).

Renal Cell Carcinoma (RCC)

- Welireg (belzutifan) may be used in adult members with unresectable, locally advanced or metastatic renal cell carcinoma with a clear cell component (ccRCC) following an immune checkpoint inhibitor (i.e. avelumab, pembrolizumab, nivolumab, ipilimumab) and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI) (i.e. axitinib, pazopanib).
- Welireg (belzutifan) may be used in combination with Keytruda (pembrolizumab) as adjuvant treatment for adult members with renal cell carcinoma with a clear cell component (ccRCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.
    - Intermediate-high risk of recurrence includes:

        - pT2, Grade 4 only
        - pT3, any Grade without nodal involvement (N0) or distant metastases (M0)
    - High risk of recurrence includes:
        - pT4, any Grade N0 and M0
        - Any pT, any Grade with nodal involvement and M0

Von-Hippel Lindau (VHL) Associated Renal Cell Carcinoma (RCC) or Solid Tumors of the Brain/Spine or Pancreas

- Welireg (belzutifan) may be used as monotherapy in a member with VHL associated non-metastatic RCC, central nervous system hemangioblastomas, or pancreatic neuroendocrine tumors (pNET) that do not require immediate surgical intervention.

CONTRAINDICATIONS/WARNINGS

- US Boxed Warning
    - Exposure to belzutifan during pregnancy can cause embryo-fetal harm. Verify pregnancy status prior to the initiation of belzutifan. Advise patients of these risks and the need for effective nonhormonal contraception. Belzutifan can render some hormonal contraceptives ineffective.

EXCLUSION CRITERIA

- Disease progression while taking Welireg (belzutifan).
- The member has metastatic disease if being used for VHL associated non-metastatic RCC, central nervous system hemangioblastomas, or pancreatic neuroendocrine tumors (pNET) that do not require immediate surgical intervention.
- Dosing exceeds single dose limit of Welireg (belzutifan) 120 mg.
- Treatment exceeds the maximum limit of 90 (40 mg) tablets/month.
- Investigational use of Welireg (belzutifan) with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:
    - Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
    - Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
    - Whether the reported study outcomes represent clinically meaningful outcomes

experienced by patients. Generally, the definitions of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.

- Whether the experimental design, the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).
- That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
- That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
- That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

CODING AND STANDARDS

Codes

- J8999 - belzutifan

Applicable Lines of Business

☐	CHIP (Children's Health Insurance Program)
☒	Commercial
☒	Exchange/Marketplace
☒	Medicaid
☐	Medicare Advantage

POLICY HISTORY

Date	Summary
July 2026	• Updated Renal Cell Carcinoma indication • Updated contraindications/warnings section • Updated exclusion criteria • Updated references
July 2025	• Added new indication for pheochromocytoma or paraganglioma • Updated indication section • Updated references
March 2025	• Converted to new Evolent guideline template • This guideline replaces UM ONC_1446 Welireg (belzutifan) • Updated verbiage in Renal Cell Carcinoma indication • Updated exclusion criteria • Updated references
March 2024	• Added Renal Cell Carcinoma indication • Added new reference • Updated NCH verbiage to Evolent

LEGAL AND COMPLIANCE

Guideline Approval

Committee

Reviewed / Approved by Evolent Specialty Services Clinical Guideline Review Committee

Disclaimer

Evolent Clinical Guidelines do not constitute medical advice. Treating health care professionals are solely responsible for diagnosis, treatment, and medical advice. Evolent uses Clinical Guidelines in accordance with its contractual obligations to provide utilization management. Coverage for services varies for individual members according to the terms of their health care coverage or government program. Individual members' health care coverage may not utilize some Evolent Clinical Guidelines. Evolent clinical guidelines contain guidance that requires prior authorization and service limitations. A list of procedure codes, services or

drugs may not be all inclusive and does not imply that a service or drug is a covered or non-covered service or drug. Evolent reserves the right to review and update this Clinical Guideline in its sole discretion. Notice of any changes shall be provided as required by applicable provider agreements and laws or regulations. Members should contact their Plan customer service representative for specific coverage information.

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