Welireg™ (belzutifan)
(Oral)

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I. Length of Authorization

Coverage will be provided for 6 months and may be renewed.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Welireg 40 mg tablets: 3 tablets per day

B. Max Units (per dose and over time) [HCPCS Unit]:

- 120 mg daily

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; **AND**
- Women of reproductive potential must have a confirmed negative pregnancy test prior to therapy; **AND**

Universal Criteria [1]

- Women of reproductive potential must use effective NON-hormonal contraception during treatment OR men with female partners of reproductive potential must use effective contraception during treatment; **AND**
- Patient has a serum hemoglobin level of at least 8 g/dl: **AND**
- Patient oxygen saturation will be monitored prior to initiation of therapy and periodically throughout therapy; **AND**
- Patient will avoid coadministration with UGT2B17-inhibitors (e.g., green teas, quercetin, red wine, etc.) or CYP2C19 inhibitors (e.g., fluconazole, fluvoxamine, ticlopidine, etc.), or if therapy is unavoidable, the patient will be monitored closely for adverse reaction and/or dose modifications will be implemented; **AND**
- Patient has not received prior treatment with another HIF-2α inhibitor; **AND**

- Used as a single agent *(Note: This does not apply when used as alternative front-line therapy concurrently with octreotide LAR or lanreotide for Neuroendocrine Tumors of the Pancreas)*; **AND**

Von Hippel-Lindau Disease (VHL) † ‡ Φ [1-4]

- Patient has a diagnosis of VHL based on a germline VHL-alteration; **AND**
  - Patient does not have an immediate need for surgical intervention for tumor treatment; **AND**
    - Patient has one or more of the following associated tumors:
      - Renal cell carcinoma (RCC) *[Note: Diagnosis may be confirmed radiologically only; histologic diagnosis is not required]*
      - Central Nervous System (CNS) hemangioblastomas
      - Pancreatic neuroendocrine tumors (pNET); **OR**
  - Patient has Neuroendocrine Tumors of the Pancreas (Well-Differentiated Grade 1/2); **AND**
    - Patient has resectable locoregional nonfunctioning pancreatic tumors; **OR**
    - Patient has one of the following tumor sub-types:
      - Gastrinoma
      - Glucagonoma
      - Insulinoma
      - Nonfunctioning pancreatic tumors
      - VIPoma; **AND**
    - Used for the management of symptomatic, clinically significant tumor burden and/or progressive recurrent, locoregional advanced disease and/or distant metastatic tumors; **AND**
      - Used alternative front-line therapy prior to or concurrently with octreotide LAR or lanreotide; **OR**
      - Used as subsequent therapy

Renal Cell Carcinoma (RCC) † [1,5]

- Used as subsequent therapy for advanced disease; **AND**
- Patient has clear cell histology; **AND**
- Used following prior treatment with both of the following either in sequence or in combination:
  - Programmed death receptor-1 (PD-1) (e.g., pembrolizumab, nivolumab, cemiplimab, dostarlimab, retifanlimab, etc.) or programmed death-ligand 1 (PD-L1) inhibitor (e.g., atezolizumab, avelumab, durvalumab, toripalimab, etc.); **AND**

- Vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI) (e.g., axitinib, pazopanib, sunitinib, etc.)

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Φ Orphan Drug

IV. Renewal Criteria [1]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet the universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe anemia, severe hypoxia, etc.; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread

V. Dosage/Administration [1]

Indication	Dose
Von Hippel-Lindau Disease and Renal Cell Carcinoma	The recommended dosage is 120 mg administered orally once daily until disease progression or unacceptable toxicity. ***Note:*** *Welireg should be taken at the same time each day and may be taken with or without food.*

VI. Billing Code/Availability Information

HCPCS:

- J8999 – Prescription drug, oral, chemotherapeutic, Not Otherwise Specified
- C9399 – Unclassified drugs or biological *(Hospital Outpatient Use ONLY)*

NDC:

- Welireg 40 mg tablet: 00006-5331-xx

VII. References

1. Welireg [package insert]. Rahway, NJ; Merck & Co., Inc.; December 2023. Accessed December 2023.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) belzutifan. National Comprehensive Cancer Network, 2023. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most

recent and complete version of the Compendium, go online to NCCN.org. Accessed December 2023.

3. Iliopoulos O, Jonasch E, Donskov F, et al. Phase II study of the oral hypoxia-inducible factor 2α (HIF-2α) inhibitor MK-6482 for Von Hippel-Lindau (VHL) disease-associated clear cell renal cell carcinoma (ccRCC). Journal of Clinical Oncology 2021 39:6_suppl, 333-333.
4. Jonasch E, Donskov F, Iliopoulos O, et al; MK-6482-004 Investigators. Belzutifan for Renal Cell Carcinoma in von Hippel-Lindau Disease. N Engl J Med. 2021 Nov 25;385(22):2036-2046. Doi: 10.1056/NEJMoa2103425.
5. Choueiri TK, Albiges L, Fan L, et al. Phase III study of the hypoxia-inducible factor 2α (HIF-2α) inhibitor MK-6482 versus everolimus in previously treated patients with advanced clear cell renal cell carcinoma (ccRCC). Journal of Clinical Oncology 38, no. 15_suppl. DOI: 10.1200/JCO.2020.38.15_suppl.TPS5094.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C64.1	Malignant neoplasm of right kidney, except renal pelvis
C64.2	Malignant neoplasm of left kidney, except renal pelvis
C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
C65.1	Malignant neoplasm of right renal pelvis
C65.2	Malignant neoplasm of left renal pelvis
C65.9	Malignant neoplasm of unspecified renal pelvis
C7A.098	Malignant carcinoid tumors of other sites
C7A.8	Other malignant neuroendocrine tumors
C7B.00	Secondary carcinoid tumors, unspecified site
C7B.01	Secondary carcinoid tumors of distant lymph nodes
C7B.02	Secondary carcinoid tumors of liver
C7B.03	Secondary carcinoid tumors of bone
C7B.04	Secondary carcinoid tumors of peritoneum
C7B.09	Secondary carcinoid tumors of other sites
C7B.8	Other secondary neuroendocrine tumors
C71.6	Malignant neoplasm of cerebellum
C72.0	Malignant neoplasm of spinal cord
D33.1	Benign neoplasm of brain, infratentorial
D33.4	Benign neoplasm of spinal cord
D43.1	Neoplasm of uncertain behavior of brain, infratentorial
D43.4	Neoplasm of uncertain behavior of spinal cord
E16.1	Other hypoglycemia
E16.3	Increased secretion of glucagon

ICD-10	ICD-10 Description
E16.8	Other specified disorders of pancreatic internal secretion
Q85.8	Other phakomatoses, not elsewhere classified
Z85.07	Personal history of malignant neoplasm of pancreas
Z85.858	Personal history of malignant neoplasm of other endocrine glands

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications, including any preceding information, may be applied at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC