NEW DRUG APPROVAL

Brand Name	Welireg™
Generic Name	belzutifan
Drug Manufacturer	Merck Sharp Dohme Corp.

New Drug Approval

FDA Approval Date: August 13, 2021

Review Designation: Priority; Orphan

Type of Review: Type 1 - New Molecular Entity; New Drug Application (NDA): 215383

Dispensing Restrictions: Speciality only, Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Von Hippel-Lindau (VHL) disease is an autosomal-dominant genetic condition resulting from a deletion or mutation in the VHL gene. VHL disease affects 1 in 36,000 people (10,000 cases in the United States and 200,000 cases worldwide) and 20% of patients are first-in-family or de novo cases.

The mean age of onset is 26 years, and 97% of people with a VHL gene mutation display symptoms by 65 years of age. VHL disease affects males and females and all ethnic groups equally. People with this condition may experience tumors and/or cysts in different parts of the body, including the brain, spine, eyes, kidneys, pancreas, adrenal glands, inner ears, reproductive tract, liver, and lung.

Efficacy

The safety and efficacy of Welireg™ were evaluated in Study 004 (NCT03401788), a Phase 2, open-label clinical trial in 61 patients with VHL disease who had at least one measurable solid tumor localized to the kidney as defined by response evaluation criteria in solid tumors (RECIST). Participants who enrolled in the trial had other VHL-associated tumors including CNS hemangioblastomas and pNETs. CNS hemangioblastomas and pNETs were diagnosed in these patients based on the presence of at least one measurable solid tumor in brain/spine or pancreas, respectively, as defined by RECIST v1.1 and identified by independent review committee (IRC). The study excluded patients with metastatic disease. Details of the study are included in Table 1.

Table 1. Study 004 (NCT03401788): Study Design Summary	
Study Population	• 61 patients with VHL-associated RCC (diagnosed based on a *VHL* germline alteration) and at least 1 measurable solid tumor localized to the kidney as defined by RECIST v1.1. • Median age: 41 years (range, 19–66 years) • 53% male • 90% White, 3.3% Black/African-American, 1.6% Asian, 1.6% Native Hawaiian/other Pacific Islander • ECOG PS: 0 = 82%, 1 = 16%, 2 = 1.6% • 84% had VHL type 1 • Median diameter of RCC target lesions per central IRC: 2.2 cm (range, 1–6.1 cm) • Median time from initial radiographic diagnosis of VHL-associated RCC tumors that led to enrollment in Study 004 to the time of treatment with Welireg™ was 17.9 months (range, 2.8–96.7 months) • 77% had prior surgical procedures for RCC • Patients with metastatic disease were excluded from participation.
Interventions	All patients received Welireg™ 120 mg once daily until progression of disease or unacceptable toxicity.
Endpoints	• The major efficacy endpoint for the treatment of VHL-associated RCC was ORR as measured by radiology assessment using RECIST v1.1 as assessed by IRC. • Additional efficacy endpoints included DOR and TTR

Abbreviations: DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; ORR, overall response rate; RCC, renal cell carcinoma; RECIST, response evaluation criteria in solid tumors; TTR, time to response; VHL, von Hippel-Lindau disease.

Table 2 summarizes the efficacy and safety results of Study 004.

Table 2. Efficacy Results (IRC Assessment) for Welireg™ for VHL-Associated RCC	
Efficacy Outcome Measure	**Welireg™ (n = 61)**
Overall Response Rate, % (n) (95% CI)	49% (30) * (36, 62)
Complete Response	0%
Partial Response	49%
Duration of Response	
Median in months (range)	Not reached (2.8†, 22†)
Percentage (n) with DOR ≥12 months	56% (17/30)

Abbreviations: CI, confidence interval; DOR, duration of response; IRC, independent review committee; RCC, renal cell carcinoma; VHL, von Hippel-Lindau disease.

*All patients with a response were followed for a minimum of 18 months from the start of treatment.

†Denotes ongoing response.

For VHL-associated RCC, the median time to response (TTR) was 8 months (range, 2.7–19 months).

Table 3 provides details about the efficacy results for Welireg™ for VHL-associated subgroups with CNS hemangioblastomas or pNETs.

Table 3. Efficacy Results (IRC Assessment) for Welireg™ for VHL-Associated Subgroups with CNS Hemangioblastomas or pNETs

Endpoint	Patients with CNS Hemangioblastomas (n = 24) *	Patients with pNETs (n = 12) *
Overall Response Rate, % (n) (95% CI)	63%, (15) (41, 81)	83% (10) (52, 98)
Complete Response	4% (1)	17% (2)
Partial Response	58% (14)	67% (8)
Duration of Response		
Median in months (range)	Not reached (3.7†, 22†)	Not reached (11†, 19†)
Percentage (n) with DOR ≥12 months	73% (11/15)	50% (5/10)

Abbreviations: CNS, central nervous system; IRC, independent review committee; pNET, pancreatic neuroendocrine tumor; VHL, von Hippel-Lindau disease

*Number of patients with measurable solid lesions, based on IRC assessment.

†Denotes ongoing response.

For VHL-associated CNS hemangioblastomas, the median TTR was 3.1 months (range, 2.5–11 months). For VHL-associated pNETs, the median TTR was 8.1 months (range 2.7–11 months). Decreases in the size of CNS hemangioblastoma-associated peritumoral cysts and syringes were also observed.

Safety

ADVERSE EVENTS

Most common (≥ 25%) adverse reactions, including laboratory abnormalities, were decreased hemoglobin, anemia, fatigue, increased creatinine, headache, dizziness, increased glucose, and nausea.

WARNINGS & PRECAUTIONS

- **Anemia**: Monitor for anemia before initiation of and periodically throughout treatment with Welireg™. Withhold Welireg™ until hemoglobin ≥9g/dL, then resume at reduced dose or discontinue. For life threatening anemia, or for anemia requiring urgent intervention, withhold Welireg™ until hemoglobin ≥9g/dL and resume at a reduced dose or permanently discontinue Welireg™.
- **Hypoxia**: Monitor oxygen saturation before initiation of, and periodically throughout, treatment with Welireg™. For hypoxia at rest, withhold until resolved, resume at reduced dose, or discontinue depending on severity. For life-threatening hypoxia, permanently discontinue Welireg™.

CONTRAINDICATIONS

None.

NEW DRUG APPROVAL

Clinical Pharmacology

MECHANISMS OF ACTION

Belzutifan is an inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α). HIF-2α is a transcription factor that plays a role in oxygen sensing by regulating genes that promote adaptation to hypoxia. Under normal oxygen levels, HIF-2α is targeted for ubiquitin-proteasomal degradation by VHL protein. Lack of functional VHL protein results in stabilization and accumulation of HIF-2α. Upon stabilization, HIF-2α translocates into the nucleus and interacts with hypoxia-inducible factor 1 beta (HIF-1β) to form a transcriptional complex that induces expression of downstream genes, including genes associated with cellular proliferation, angiogenesis, and tumor growth. Belzutifan binds to HIF-2α, and in conditions of hypoxia or impairment of VHL protein function, belzutifan blocks the HIF-2α-HIF-1β interaction, leading to reduced transcription and expression of HIF-2α target genes. In vivo, belzutifan demonstrated anti-tumor activity in mouse xenograft models of renal cell carcinoma.

Dose & Administration

ADULTS

The recommended dosage of Welireg™ is 120 mg administered orally once daily with or without food.

PEDIATRICS

Safety and effectiveness of Welireg™ have not been established in pediatric patients.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No dosage modification of Welireg™ is recommended in patients with mild (eGFR 60-89 mL/min/1.73 m2 estimated by MDRD) and moderate (eGFR 30-59 mL/min/1.73 m2) renal. Welireg™ has not been studied in patients with severe (eGFR 15-29 mL/min/1.73 m2) renal impairment.

HEPATIC IMPAIRMENT

No dosage modification of Welireg™ is recommended in patients with mild [total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin >1 to 1.5 x ULN and any AST] hepatic impairment. Welireg™ has not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 x ULN and any AST).

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 40 mg