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Belzutifan

Updated: July 20, 2023.

OVERVIEW

Introduction

Belzutifan is a small molecule inhibitor of hypoxia-inducible factor 2 alpha used to treat solid tumors in patients with von Hippel-Lindau disease. Belzutifan is associated with a low rate of minor serum enzyme elevations during therapy, but has not been linked to cases of clinically apparent liver injury.

Background

Belzutifan (bel zue' ti fan) is an oral small molecule inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α) which is elevated in tumors of patients with von Hippel-Lindau (VHL) disease. HIF is a regulator of oxygen homeostasis that has an oxygen-sensitive subunit (2α) and a constitutively expressed subunit (1β). With normal oxygen levels, HIF-2α is hydroxylated and binds to the VHL tumor suppressor protein which promotes its ubiquitin-targeted proteasomal degradation. With low levels of oxygen, HIF-2α binds to HIF-1β creating a transcription complex that stimulates hypoxia-inducible gene transcription, including genes for erythropoiesis, angiogenesis and cellular proliferation which can promote cancer cell growth. Patients with VHL disease have a defective protein that does not bind HIF-2α, leaving it free to bind HIF-1β and increase transcriptions of genes of angiogenesis and tumor cell growth. As a result, patients with VHL disease are at high risk of developing tumors including clear cell renal cell carcinoma, hemangioblastomas of the central nervous system (CNS) and retina, cystadenomas, and pancreatic neuroendocrine tumors. These tumors are generally slow growing and metastasize late, so that surgery is recommended only when they achieve a certain size or are symptomatic. In open label studies in patients with VHL disease and clear cell renal cell cancer, CNS hemangioblastomas or pancreatic neuroendocrine tumors, treatment with belzutifan resulted in a decrease in the size or retardation of growth (stable disease) of tumors in a high proportion of patients. Belzutifan was approved in the United States in 2021 for treatment of patients with tumors related to VHL disease not requiring immediate surgery. It is still being evaluated as therapy of patients with VHL disease who have cancers with acquired defects in the VHL gene. Belzutifan is available in tablets of 40 mg under the brand name Welireg. The recommended dose is 120 mg daily until disease progression or unacceptable toxicity. Side effects are common but usually do not require dose modification. The most common adverse events are anemia, fatigue, headache, dizziness, nausea, dyspnea, arthralgia, myalgia and increases in creatinine and glucose levels. Patients treated with belzutifan should be monitored for oxygen saturation and with blood tests for hemoglobin, creatinine, and glucose. Uncommon, but potentially severe adverse events include life-threatening anemia, severe hypoxia, and embryo-fetal toxicity.

Hepatotoxicity

In the preregistration trials of belzutifan, serum aminotransferase elevations occurred in up to 20% of patients, but were invariably transient and mild (less than 3 times ULN) and were not accompanied by symptoms or jaundice. No patient required dose modification or discontinuation because of liver test abnormalities. Furthermore, since its more widespread use after its approval, there have been no published reports of clinically apparent liver injury attributed to belzutifan.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The reason why belzutifan might cause serum enzyme elevations is not known, but it is metabolized in the liver by the cytochrome P450 system (predominantly CYP 2C19 and to a lesser extend 3A4) and liver injury may be the result of production of a toxic or immunogenic metabolic intermediate. Belzutifan is potentially susceptible to drug-drug interactions with agents that are substrates of CYP 3A4 or inhibit CYP 2C19.

Outcome and Management

Serum enzyme elevations are not uncommon during belzutifan therapy but rarely require dose modification or drug discontinuation. As with any drug, belzutifan should be held if ALT or AST values rise above 5 times the ULN and discontinued if elevations are more than 20 times the ULN or jaundice or symptoms of liver injury arise.

Drug Class: Antineoplastic Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Belzutifan – Welireg®

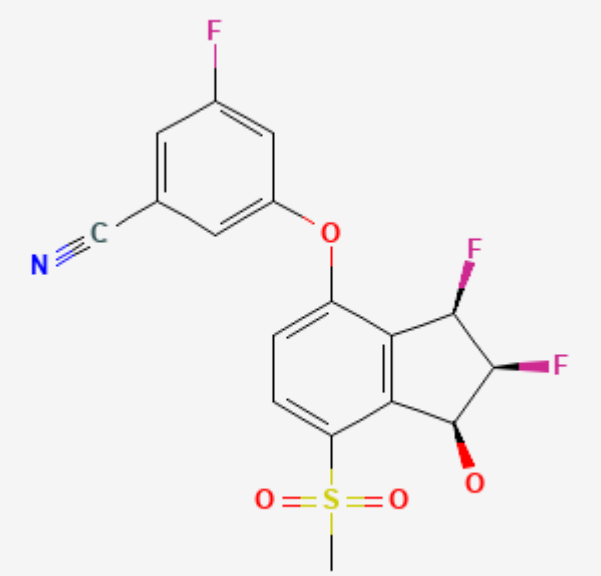
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Belzutifan	1672668-24-4	C17-H12-F3-NO4-S	

ANNOTATED BIBLIOGRAPHY

References updated: 20 July 2023

Abbreviations used: HIF, hypoxia inducible factor; VHL, von Hippel-Lindau.

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Review of hepatotoxicity published in 1999 before the availability of belzutifan).

DeLeve LD. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, p. 549-68.

(Review of hepatotoxicity of cancer chemotherapeutic agents published in 2013 does not discuss belzutifan).

Wellstein A, Giaccone G, Atkins MB, Sausville EA. Inhibitors of histone deacetylase. Pathway targeted therapies: monoclonal antibodies, protein kinase inhibitors, and various small molecules. In, Brunton LL Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, p. 1203-36.

(Textbook of pharmacology and therapeutics).

Jonasch E, Donskov F, Iliopoulos O, Rathmell WK, Narayan VK, Maughan BL, Oudard S, et al.; MK-6482-004 Investigators. Belzutifan for renal cell carcinoma in von Hippel-Lindau disease. N Engl J Med. 2021;385:2036-2046. PubMed PMID: 34818478.

(Among 61 patients with VHL disease and renal cell cancer treated with belzutifan [120 mg daily] for 20-30 months, half had confirmed partial responses and the 24 month progression-free survival was 96%, while adverse event rate was 100%, the most common adverse events being anemia [90%], fatigue [66%], headache [41%], and dizziness [39%], nausea [34%], dyspnea [23%], arthralgia [20%], resulting in drug interruption in 43%, dose reduction in 15% and discontinuation in 12%; ALT elevations arose in 16%, all were transient, asymptomatic and less than 3 times ULN and none required drug discontinuation).

Deeks ED. Belzutifan: first approval. Drugs. 2021 Nov;81(16):1921-1927. PubMed PMID: 34613603.

(Review of the mechanism of action, history of development, pharmacokinetics, clinical efficacy, and safety of belzutifan soon after its approval by the FDA as therapy for solid tumors related to von Hippel-Lindau disease, mentions that 20% of patients developed ALT elevations, but there were no liver-related serious adverse events).

Dhawan A, Peereboom DM, Stevens GH. First clinical experience with belzutifan in von Hippel-Lindau disease associated CNS hemangioblastoma. CNS Oncol. 2022;11(3):CNS91. PubMed PMID: 35819008.

(Description of two patients with VHL disease and CNS hemangioblastoma who had clinical improvement and slight decrease in the size of the tumors with belzutifan therapy, with side effects of anemia but good tolerability; no mention of ALT elevations or hepatotoxicity).

Fallah J, Brave MH, Weinstock C, Mehta GU, Bradford D, Gittleman H, Bloomquist EW, et al. FDA Approval summary: belzutifan for von Hippel-Lindau disease-associated tumors. Clin Cancer Res. 2022;28:4843-4848. PubMed PMID: 35727604.

(Description of the basis for the FDA approval of belzutifan summarizing the clinical efficacy of treatment in reducing the size and rate of grown of renal cell carcinoma in patients with VHL disease and the safety assessment with no drug related deaths and frequent but acceptable adverse event rates; no mention of ALT elevations or hepatotoxicity).

Takamori H, Yamasaki T, Kitadai R, Minamishima YA, Nakamura E. Development of drugs targeting hypoxia-inducible factor against tumor cells with VHL mutation: Story of 127 years. Cancer Sci. 2023;114:1208-1217. PubMed PMID: 36650918.

(History of the development of belzutifan from the description of VHL disease by von Hippel [1904] and Lindau [1927] to the description of the gene mutated in VHL disease [1993], the association of HIF with VHL mutated protein [1999], the Nobel Prize award to scientists who discovered how cells adapt to oxygen availability [2019], and the approval of the first HIF inhibitor as effective therapy of VHL disease [2021]).

Shirole NH, Kaelin WG Jr. von-Hippel Lindau and hypoxia-inducible factor at the center of renal cell carcinoma biology. Hematol Oncol Clin North Am. 2023;37(5):809-825. PubMed PMID: 37270382.

(Review of the molecular role of HIF-α2 in tumorigenesis and development of inhibitors as therapy of tumors associated with von Hippel-Lindau disease).

Neth BJ, Webb MJ, White J, Uhm JH, Pichurin PN, Sener U. Belzutifan in adults with VHL-associated central nervous system hemangioblastoma: a single-center experience. J Neurooncol. 2023;164(1):239-247. PubMed PMID: 37450072.

(Among 4 women with VHL disease and craniospinal hemangioblastoma not amenable to surgery were treated with belzutifan for 6-17 months, all had a radiographic response, while adverse events included anemia, dizziness, nausea, and fatigue, none requiring dose modification; no mention of ALT elevations).