WELIREG® (belzutifan)

Formulary application support pack

Purpose of this document

This document is to support healthcare professionals within the NHS in the completion of a formulary application for WELIREG for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for VHL associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumours (pNET), and for whom localised procedures are unsuitable or undesirable.[(MSD (UK) Ltd, 2024)]

This document is intended for digital viewing only.

Intended for UK Healthcare Professionals only.

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By clicking the above link you will be taken to the MHRA website (a third-party website).

Prescribing Information and adverse event reporting can be found here

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MSD

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How to use this document

Each local area will have their own formulary application form.

Some of the information in this pack can be copied and pasted into your local area's form. You will need to ensure that the copied information contains the required information requested by the formulary application.

Other areas will require customisation to your local area.

You must check that all information included in the formulary pack is up to date, relevant, and consistent with the expected format of the local formulary application

Referencing

Referencing within this pack is in a modified Harvard style, e.g. (Author A, 2023). This is to ensure that references remain clear should you copy and paste sections out of order. Please ensure that you include all relevant full citations in your application, or it may be rejected.

Abbreviations

Abbreviations have been avoided wherever possible, so that sections of this document can be used in isolation without confusion. Please ensure that the format of abbreviations is consistent throughout your application.

You must declare conflicts of interest appropriately where required.

Part 1: Medicine details

Non-proprietary name	Belzutifan[MSD (UK) Ltd, 2024]
Brand name	WELIREG[MSD (UK) Ltd, 2024]
Dosage form	Film-coated tablet[MSD (UK) Ltd, 2024]
Manufacturer	Merck Sharp & Dohme (UK) Ltd
Licensed indication	The treatment of adult patients with von Hippel-Lindau disease who require therapy for von-Hippel-Lindau associated renal cell carcinoma, central nervous system hemangioblastomas, or pancreatic neuroendocrine tumours, and for whom localised procedures are unsuitable or undesirable.[MSD (UK) Ltd, 2024]
Proposed formulary indication	The treatment of adult patients with von Hippel-Lindau disease who require therapy for von-Hippel-Lindau associated renal cell carcinoma, central nervous system hemangioblastomas, or pancreatic neuroendocrine tumours, and for whom localised procedures are unsuitable or undesirable.[MSD (UK) Ltd, 2024]
Dosing	120 mg (three 40 mg tablets) administered orally once daily, with or without food. Tablets should be swallowed whole.[MSD (UK) Ltd, 2024] If a dose is missed, it can be taken as soon as possible on the same day. The regular daily dose should be resumed the next day. Extra tablets should not be taken to make up for the missed dose. If vomiting occurs any time after taking belzutifan, the dose should not be retaken. The next dose should be taken the next day.[MSD (UK) Ltd, 2024] Dose modifications for adverse reactions are available. See the Summary of Product Characteristics for full details.[MSD (UK) Ltd, 2024]
Stopping criteria	Treatment should continue until disease progression or unacceptable toxicity occurs.[MSD (UK) Ltd, 2024]
Special populations	Elderly (≥ 65 years old): No dose adjustment is recommended for elderly patients. There are limited data available in patients aged 65 years and over.[MSD (UK) Ltd, 2024] Renal impairment: No dose adjustment is recommended in patients with mild or moderate renal impairment (eGFR ≥30 mL/minute/1.73 m^2). Belzutifan has not been studied in patients with severe renal impairment.[MSD (UK) Ltd, 2024] Hepatic impairment: No dose adjustment is recommended in patients with mild hepatic impairment. Belzutifan has not been studied in patients with moderate or severe hepatic impairment. Children <18 years: No data are available. The safety and efficacy has not yet been established. Belzutifan is licensed for the treatment of adult patients with von Hippel-Lindau disease who require therapy for von-Hippel-Lindau associated renal cell carcinoma, central nervous system hemangioblastomas, or pancreatic neuroendocrine tumours, and for whom localised procedures are unsuitable or undesirable.[MSD (UK) Ltd, 2024]

For further medicine details, please see Appendix 4: Prescribing details, including contra-indications, special warnings, and interactions, as well as the Summary of Product Characteristics.

Part 2: Proposed place in therapy

Proposed formulary indication	The treatment of adult patients with von Hippel-Lindau disease who require therapy for von-Hippel-Lindau associated renal cell carcinoma, central nervous system haemangioblastomas, or pancreatic neuroendocrine tumours, and for whom localised procedures are unsuitable or undesirable.[(MSD (UK) Ltd, 2024)]
Place in therapy recommended by National/Professional guidance	**NICE (TA1011):** Belzutifan is recommended with managed access as an option for treating VHL disease in adults:[(NICE, 2024)] • Who need treatment for VHL-associated renal cell carcinomas, central nervous system hemangioblastomas or pancreatic neuroendocrine tumours, and • When localised procedures are unsuitable or undesirable It is only recommended if the conditions in the managed access agreement for belzutifan are followed. **SMC (SMC2587):** Wording as per the SMC recommendation: "Accepted for use within NHSScotland for the treatment of adult patients with von Hippel-Lindau disease who require therapy for von Hippel-Lindau associated renal cell carcinoma, central nervous system haemangioblastomas, or pancreatic neuroendocrine tumours, and for whom localised procedures are unsuitable or undesirable.[(SMC, 2023)] • In a single-arm, phase II study, belzutifan was associated with overall response rates of at least 64%, 44% and 91% in RCC, CNS and pNET, respectively[(SMC, 2023)] • This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower[(SMC, 2023)] • This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting[(SMC, 2023)]" **AWMSG:** Excluded from AWMSG evaluation due to NICE appraisal[(AWMSG, 2023)]
Place in therapy proposed in this application	In line with NICE/SMC recommendation as appropriate.
Proposed prescribing restrictions	Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer.[(MSD (UK) Ltd, 2024)]
Proposed RAG rating NOTE: Adjust wording according to local needs	Red Drugs considered to be specialist medicines and prescribing responsibility for these medicines should normally remain with the consultant or specialist clinician. These drugs should not be initiated or prescribed in primary care. It is recommended that the supply of these specialist medicines should be organised via the

	hospital pharmacy or specialist service. This may include arranging for supply via a home care company.
Currently available alternative treatments	None – there are no other licensed effective systemic treatment options for von Hippel-Lindau disease in the UK currently.[Shepherd et al., 2023]

Part 3: Disease information and reason for request

About VHL

VHL is a rare, life-limiting, potentially life-threatening genetic disease which causes tumour growth in multiple organ systems[(NORD, 2021, Varshney et al., 2017)]

- Tumours can grow in several different sites at the same time. They are often heavily vascularised[(Gläsker et al., 2020)]
- Tumours can predominantly affect the brain, spine, eyes, kidneys, pancreas, adrenal glands and inner ears[(NORD, 2021)]
- Tumours are often benign, but they have the potential to cause pressure on the brain, nerves, and spinal tissue. They can lead to permanent damage, disability, or death in some cases[(VHL Alliance, 2023, Rednam et al., 2017)]
- Some tumours can become cancerous, such as those found in the kidneys and pancreas[(VHL Alliance, 2023)]
- Patients diagnosed with VHL face a daunting journey marked by constant surveillance and multiple surgeries throughout their lifetime[(NORD, 2021, Kasparian et al., 2015)]

The hereditary nature of VHL means it has wide-ranging impacts for families[(Kasparian et al., 2015)]

- Coping mechanisms, emotional response, and engagement with behaviours that promote health and wellbeing may be affected by witnessing the effects of the disease on other family members[(Kasparian et al., 2015)]
- Complex family planning decisions may be influenced by the presence of VHL[(Kasparian et al., 2015)]
- Other consequences of the presence of VHL in a family can include: sustained uncertainty about future tumour development, frustration regarding the need for lifelong screening, strained family relationships, perceived isolation from peers and colleagues, limited career opportunities, concerns about financial security, and difficulties gaining access to appropriate and timely support[(Kasparian et al., 2015)]

Based on 23 individual telephone interviews (15 patients, 8 carers) recruited via the Hereditary Cancer Clinic (Prince of Wales Hospital, Sydney, Australia).[(Kasparian et al., 2015)]

VHL is a highly variable disease: No two patients are alike, and their care is inherently complex[(Maher et al., 2022)]

- Incidence of cyst or tumour development varies depending on factors such as age, underlying genotypic variant, and organ(s) involved[(Binderup et al., 2016)]
- Within the same family, individual family members may show one or several features of the disease[(Kasparian et al., 2015)]

Renal cell carcinoma develops in up to 70% of people with VHL by 60 years of age[(Varshney et al., 2017)]

- Renal manifestations of VHL include benign renal cysts and clear cell carcinoma[(VHL Alliance, 2023)]
- VHL-related cysts are usually multiple and present in both kidneys. Each cyst may contain a tumor, which has the potential to become a renal cell carcinoma[(VHL Alliance, 2023)]

	• Renal cell carcinoma is the leading cause of death in patients with VHL[(Varshney et al., 2017)] CNS haemangioblastomas are the most common tumours in VHL[(Varshney et al., 2017)] • 60-80% of VHL patients are affected by CNS haemangioblastomas in their lifetime[(Varshney et al., 2017)] • The risks associated with them vary according to location and size[(Lonser et al., 2014)] • Growth can be unpredictable,[(Klingler et al., 2020)] complicating decision-making regarding timing of surgical interventions Pancreatic neuroendocrine tumours affect 5-18% of people with VHL disease[(Coco et al., 2023, Binderup ML et al., 2022)] • The average age of diagnosis of pancreatic neuroendocrine tumour is between 30 and 39 years[(Binderup ML et al., 2022)] • Because pancreatic neuroendocrine tumours in vHL most often are non-functioning and have a malignant potential, early diagnosis is crucial[(Binderup ML et al., 2022)]
Incidence, prevalence, and heritability	• VHL affects ~1 in 69,000 people in the UK[(Maher et al., 2022, NORD, 2021)] • A national audit identified 842 people with VHL in the UK[(Maher et al., 2022)] • Males, females, and all ethnic groups are affected equally[(NORD, 2021)] • 80% of cases present with a known family history of VHL[(Varshney et al., 2017)] • 20% of cases are due to *de novo* mutations, i.e. there is no positive family history of VHL[(Varshney et al., 2017)] • VHL is inherited in an autosomal dominant manner. Children of a parent affected by VHL have a 50% risk of inheriting the VHL pathogenic variant[(van Leeuwaarde RS et al., 2023)]
Unmet needs and reason for request	There are currently no licensed effective systemic treatment options for von Hippel-Lindau disease in the UK[(NICE, 2024)] Along with regular surveillance, surgery is the mainstay of treatment for active tumours. Repeat surgeries are common.[(Shepherd et al., 2023)] • Some patients have inoperable tumours, or operable tumours that would result in catastrophic injury due to surgery[(NICE, 2024)] • Surgical removal of pancreatic neuroendocrine tumours can cause severe adverse effects – e.g. pancreatectomy can result in loss of pancreatic function, resulting in type 3c diabetes requiring lifelong insulin therapy[(NICE, 2024)] • Surgical resection of tumours may lead to impairment of the affected organ functions, or may require removal of the entire organ[(Binderup ML et al., 2022, Wang et al., 2023, NICE, 2024)]

Repeated surgeries are common in VHL, causing a negative impact on health and quality of life[Sundaram et al., 2023]

- Surgery negatively impacts the lives of people with von Hippel-Lindau disease, resulting in fatigue, mental health issues, and impairing their daily life[Sundaram et al., 2023]
- Over three quarters (78%) of people with VHL with renal cell carcinoma, pancreatic neuroendocrine tumours, or CNS haemangioblastomas had experienced multiple surgeries in a international, cross-sectional survey of 220 people with VHL in the United States, Canada, United Kingdom, France, and Germany[Sundaram et al., 2023]

Delaying or reducing the number of surgeries required is a high priority for people with VHL[Sundaram et al., 2023]

- In people with VHL with renal cell carcinoma, pancreatic neuroendocrine tumours, or CNS haemangioblastomas, almost half would like a treatment that reduces the number of surgeries[Sundaram et al., 2023]
- Over a third would like a treatment that delays the need for surgery[Sundaram et al., 2023]

Belzutifan is the first-in-class hypoxia-inducible factor 2 alpha (HIF-2α) inhibitor and the first systemic treatment licensed for people with VHL disease-associated tumours providing a novel therapy in an area of high unmet need[Fallah et al., 2022]

Part 4: Cost and budget impact

Customise this section with information on number of potential patients in your local area.

NHS list price	1 pack of 90 x 40 mg tablets = £11,936.70[(MIMS, 2024)] NICE and SMC have agreed a commercial arrangement which makes belzutifan available to the NHS with a discount. The size of the discount is commercial in confidence. Details of the patient access price can be found within the NHS Commercial Access and Pricing (CAP) portal, which can be accessed by the relevant NHS Pharmacists including your Chief Pharmacist at your local Trust.
Eligible population	In a service audit, there were 842 people with VHL in the UK[(Maher et al., 2022)] It is estimated that in England around 100 people may be eligible for treatment with belzutifan in the first year, and around 50 people per year thereafter.[(NHS England, 2024)] In Scotland, the submitting company estimated there would be 7 patients eligible for treatment with belzutifan each year. The estimated uptake rate was 100% per year, resulting in 7 patients estimated to receive treatment each year.[(SMC, 2023)]
Funding stream	In England, belzutifan is available through managed access, with funding provided through the Cancer Drugs Fund.[(NICE, 2024)] In Wales, the NHS must usually provide funding and resources within 2 months of the first publication of the final draft guidance or agreement of a managed access agreement by the NHS in Wales, whichever is the later.[(NICE, 2024)] In Scotland, belzutifan was approved by the SMC as an orphan drug[(SMC, 2023)], so will be the responsibility of Health Boards, who need to accept it onto formulary as part of their processes where relevant.
Service implications	Belzutifan must be initiated and supervised by specialist physicians experienced in the treatment of cancer[(MSD (UK) Ltd, 2024)] VHL services are multidisciplinary, including specialisms such as ophthalmology, endocrinology, urology, nephrology etc.[(Maher et al., 2022)] Oncology is not currently routinely represented, so specialist services will need to take steps to ensure pathways are in place to allow effective prescribing of belzutifan. The effects of belzutifan may mean suitable patients require fewer procedures and/or interventions compared with standard of care[(Schmidinger, 2021)] In the four years preceding a Phase 2 trial, 46 patients underwent a total of 86 tumour reduction procedures. Following initiation of belzutifan, at more than 4 years of follow up, 16 patients underwent 18 tumour reduction procedures.[(Srinivasan et al., 2024)]

Appendix 1: Evidence of clinical efficacy

Reason for inclusion of Phase 2 trial data:
Belzutifan is designated as an orphan drug by the MHRA.[(MHRA, 2024)] VHL is a rare disease, and randomised trials assessing time to event end points in each potential type of tumor are challenging to conduct.[(Hollasch M, 2023)]
Regulatory approval has therefore been made on the basis of a pivotal Phase 2 trial.[(Schmidinger, 2021, Jonasch et al., 2021, MHRA, 2022)]

Evidence summary:
Early use of belzutifan may spare people with VHL associated real cell carcinoma, CNS haemangioblastoma, or pancreatic neuroendocrine tumours from multiple surgeries and decrease their risk of loss of organ function (such as renal failure) compared with standard care.[(Jonasch et al., 2021, Schmidinger, 2021, Srinivasan et al., 2024)]

The NICE committee concluded that clinical evidence suggests that belzutifan reduces tumour size from baseline and increases the amount of time people have before their condition gets worse compared with standard of care, but by how much is uncertain.[(NICE, 2024)]

LITESPARK-004 (NCT03401788) is an ongoing Phase 2, open-label clinical trial which aimed to evaluate the efficacy and safety of belzutifan in adult patients with VHL-disease associated renal cell carcinoma.[(Jonasch et al., 2021)]

Included patients were adults ≥ 18 years with VHL disease diagnosed based on a germline VHL alteration, and at least one measurable renal cell carcinoma. Exclusion criteria included prior systemic anticancer therapy, metastatic disease, an Eastern Co-Operative Oncology Group Performance Status above 1, a major surgical procedure within 4 weeks of study enrolments, and a major cardiovascular event within 6 months of study drug administration.[(MSD (UK) Ltd, 2024, Jonasch et al., 2021)]

61 patients were enrolled, 97% of whom had previously undergone at least one tumour reduction procedure. Patients had a median of 2 renal cell carcinoma target tumours at baseline.[(Jonasch et al., 2021)]

Patients received oral belzutifan 120 mg once daily (as 3 x 40 mg tablets) unless unacceptable adverse events or disease progression occurred.[(Jonasch et al., 2021)]

Primary endpoint: Objective response rate of treatment with belzutifan (complete response or partial response), as defined according to Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, in patients with VHL-disease–associated renal cell carcinoma.[(Jonasch et al., 2021)]

Secondary end points: Duration of response, time to response, and progression-free survival.[(Jonasch et al., 2021)]

Other secondary end points: Efficacy in the treatment of non–renal cell carcinoma neoplasms associated with VHL disease (including retinal and central nervous system hemangioblastomas and pancreatic lesions [i.e., serous cystadenomas and pancreatic neuroendocrine tumours])[(Jonasch et al., 2021)]

Results at 29.2 months median follow-up

Note: Information provided from the Summary of Product Characteristics

Renal cell carcinoma response

Partial renal cell carcinoma response was observed in 59.0% (n=36/61) of patients treated with belzutifan over the follow-up period[(MSD (UK) Ltd, 2024)]

Primary efficacy endpoint

Objective response (complete or partial response; the primary end point) was observed in 59.0% (95% CI: 45.7 to 71.4, n=36/61) of patients treated with belzutifan, and disease control in 98.4%. The percentage of patients with progression-free survival was not estimated.[(MSD (UK) Ltd, 2024)]

- 3.3% (2/61) had complete response in their renal cell carcinoma(s)[(MSD (UK) Ltd, 2024)]
- 55.7% (34/61) had a partial response in their renal cell carcinoma(s)[(MSD (UK) Ltd, 2024)]
- 39.3% (24/61) maintained stable disease[(MSD (UK) Ltd, 2024)]
- No patients experienced disease progression[(MSD (UK) Ltd, 2024)]

Secondary efficacy endpoints

- Response was ongoing at the time of data cutoff (median duration not reached, range (36.1 weeks ongoing to 119.9 weeks ongoing)[(MSD (UK) Ltd, 2024)]
- The median time to response was 46.7 weeks (range 11.6 to 96.6)[(MSD (UK) Ltd, 2024)]
- Median progression-free survival was not estimated (24-month PFS rate 94.6%)[(MSD (UK) Ltd, 2024)]

Non-renal cell carcinoma neoplasm response (other efficacy endpoints)

Pancreatic neuroendocrine tumours

90% of patients had an objective response in pancreatic neuroendocrine tumours (95% CI: 68.3 to 98.8, n=18/20)[(MSD (UK) Ltd, 2024)]

CNS haemangioblastomas

38% of patients had an objective response in CNS haemangioblastomas 95% CI: 24.7 to 52.8, (n=19/50)[(MSD (UK) Ltd, 2024)]

Results at 49.9 months median follow-up

Note: Include this information if your local formulary group accepts conference abstracts or posters in their applications

At a median follow-up of 49.9 months (48.2 to 58.1), the majority of patients (59%, n=36/61) continued to receive belzutifan following trial completion.(Srinivasan R et al., 2024)

Renal cell carcinoma response

Objective response (complete or partial response; the primary end point) was observed in 67% (95% CI: 54.0 to 78.7) of patients treated with belzutifan.(Srinivasan R et al., 2024)

- 7 (n=11/61) experienced complete response(Srinivasan R et al., 2024)
- 56% (n=34/61) had a partial response(Srinivasan R et al., 2024)
- 31% (n=19/61) maintained stable disease(Srinivasan R et al., 2024)
- No patients experienced disease progression(Srinivasan R et al., 2024)
- One patient (2%) was non-evaluable due to insufficient data being available for assessment of response per RECIST v1.1(Srinivasan R et al., 2024)
- The median time to response was 11.1 months (range 2.7 to 41.2)(Srinivasan R et al., 2024)
- Response was ongoing at the time of data cutoff (median duration not reached, range (8.6 ongoing to 44.4 ongoing)(Srinivasan R et al., 2024)

Non-renal cell carcinoma neoplasm response

Pancreatic neuroendocrine tumours

91% of patients had an objective response in pancreatic neuroendocrine tumours (95% CI: 70.8 to 98.9, N=22*)(Srinivasan R et al., 2024)

- 50% (n=11/22) had complete response(Srinivasan R et al., 2024)
- 41% (n=9/22) had partial response(Srinivasan R et al., 2024)
- 9% (n=2/22) had stable disease(Srinivasan R et al., 2024)
- No patients experienced disease progression(Srinivasan R et al., 2024)
- The median time to response was 8.2 months (range 2.5 to 16.4 months)(Srinivasan R et al., 2024)
- Response was ongoing at the time of data cutoff (median duration not reached, range (11.0 ongoing to 48.3 ongoing)(Srinivasan R et al., 2024)

CNS haemangioblastomas

48% of patients had an objective response in CNS haemangioblastomas (95% CI: 33.7 to 62.6, N=50)(Srinivasan R et al., 2024)

- 8% (n=4/50) had complete response(Srinivasan R et al., 2024)
- 40% (n=20/50) had partial response(Srinivasan R et al., 2024)
- 42% (n=21/50) had stable disease(Srinivasan R et al., 2024)
- 6% (n=3) experienced disease progression(Srinivasan R et al., 2024)
- 2 patients were non-evaluable (4%)(Srinivasan R et al., 2024)
- The median time to response was 5.5 months (range 2.3 to 38.7)(Srinivasan R et al., 2024)
- Response was ongoing at the time of data cutoff (median duration not reached, range (0.0 ongoing to 47.5 ongoing)(Srinivasan R et al., 2024)

* The number of people with pNET in this data at 49.9 months follow up (n=22)(Srinivasan R et al., 2024) differs to that in the SmPC at 29.2 month of follow up (n=20).(MSD (UK) Ltd, 2024) This is due to difference in reader acceptance.

Appendix 2: Evidence of safety and tolerability

The safety of belzutifan was evaluated in an open-label Phase 2 clinical study, in 61 patients with von-Hippel Lindau disease-associated renal cell carcinoma and who did not require immediate nephrectomy or partial nephrectomy.(MSD (UK) Ltd, 2024)

- Patients were treated with 120 mg belzutifan once daily(MSD (UK) Ltd, 2024)

The median duration of exposure to belzutifan was 28.9 months (range: 1.9 to 37.5)(MSD (UK) Ltd, 2024)

The most common adverse reactions with belzutifan were anaemia (90%), fatigue (71%), dizziness (44%) and nausea (36%)(MSD (UK) Ltd, 2024)

- The most common Grade 3 or 4 adverse reactions were anaemia (10%), and fatigue (5%)(MSD (UK) Ltd, 2024)
- Serious adverse reactions occurred in 5% of patients who received belzutifan, including anaemia, dyspnoea and hypoxia (1 patient each)(MSD (UK) Ltd, 2024)
- Dose interruption of belzutifan due to adverse reactions occurred in about 23% of patients. The most common adverse reactions resulting in dose interruption of belzutifan were fatigue (13.1%), nausea (8.2%), and anaemia (4.9%)(MSD (UK) Ltd, 2024)
- Dose reduction of belzutifan due to adverse reactions occurred in about 11.5% of patients. The adverse reactions resulting in dose reduction of belzutifan were fatigue (8.2%), anaemia, and hypoxia (one patient each 1.6%)(MSD (UK) Ltd, 2024)

List of adverse events reported in the Summary of Product Characteristics:(MSD (UK) Ltd, 2024)

- Very common adverse events (occurring in ≥1/10 patients) included anaemia (all grades), dizziness (all grades), dyspnoea (all grades), nausea (all grades), fatigue (all grades), and weight increased (all grades)(MSD (UK) Ltd, 2024)
- Common adverse events (occurring in ≥1/100 to <1/10 patients) included anaemia (grades 3-4), dyspnoea (grades 3-4), hypoxia (all grades), fatigue (grades 3-4), and weight increased (grades 3-4) (MSD (UK) Ltd, 2024)
- Very rare adverse events (occurring in <1/10,000 patients) included dizziness (grades 3-4) and nausea (grades 3-4)(MSD (UK) Ltd, 2024)

Description of selected adverse reactions

Anaemia due to decreased erythropoietin	• In a phase 2 study anaemia was reported in 90.2% of all patients, with Grade 3 anaemia occurring in 9.8%. Median time to onset of all Grade anaemia events was 31 days (range: 1 day to 8.38 months). Most of the anaemia occurred in the first 3 months of treatment initiation and was not progressive(MSD (UK) Ltd, 2024) • Three (4.9%) participants had anaemia events leading to study drug interruption and 1 participant (1.6%) had a dose reduction due to anaemia. No participant discontinued treatment due to anaemia(MSD (UK) Ltd, 2024) • Of the 13 participants that were treated with an erythropoietin stimulating agent, 4 received treatment with both an erythropoietin stimulating agent and blood transfusions, while 9 received treatment with an erythropoietin stimulating agent alone. Patients received an erythropoietin stimulating agent

	based on haemoglobin levels and physician discretion[MSD (UK) Ltd, 2024] • Anaemia was reported as resolved in 13 (21.3%) of participants and resolving or not yet resolved in 40 (65.6%) participants[MSD (UK) Ltd, 2024]
Hypoxia	• In a Phase 2 study, Grade 3 hypoxia occurred in 1 patient (1.6%). This case of hypoxia occurred within 2 months of treatment initiation in a patient with previously undiagnosed restrictive lung disease and was asymptomatic. This patient did not receive supplemental oxygen and was managed with dose reduction to 80 mg once daily with no recurrence of hypoxia[MSD (UK) Ltd, 2024]

49.9 month median cut-off

Note: Include this information if your local formulary group accepts conference abstracts in their applications

No new safety signals were observed with additional follow-up[Srinavasan R et al., 2022, Srinivasan R et al., 2024]

At a median follow up of 49.9 months, all people treated had experienced any grade of treatment-related adverse event but a substantial proportion (59%, n=36) remained on treatment as of the data cutoff date.[Srinivasan R et al., 2024]

- 18% (n=11/61) experienced a grade 3 (serious but not immediately life-threatening) treatment-related adverse event[Srinivasan R et al., 2024]
- Anaemia was the most common treatment-emergent adverse event, occurring in 89% (n=54) of people. 11% (n=7) of anaemia cases were considered serious[Srinivasan R et al., 2024]
- Two thirds (66%, n=40) experienced fatigue, which was considered serious in 5% (n=3)[Srinivasan R et al., 2024]
- Other grade 3 events in 1 patient each were blister, hypoxia, and urinary tract infection[Srinivasan R et al., 2024]
- No grade 4 or 5 treatment-related AEs occurred[Srinivasan R et al., 2024]

Appendix 3: Mechanism of action

Belzutifan is an inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α)[MSD (UK) Ltd, 2024]

- HIF-2α is a transcription factor that plays a role in oxygen sensing by regulating genes that promote adaptation to hypoxia[MSD (UK) Ltd, 2024]
    - Under normal oxygen levels, HIF-2α is targeted for ubiquitin-proteasomal degradation by VHL protein[MSD (UK) Ltd, 2024]
    - Lack of functional VHL protein results in stabilisation and accumulation of HIF-2α[MSD (UK) Ltd, 2024]
    - Upon stabilisation, HIF-2α translocates into the nucleus and interacts with hypoxia-inducible factor 1 beta (HIF-1b) to form a transcriptional complex that regulates expression of downstream genes, including genes associated with cellular proliferation, angiogenesis, and tumour growth (including CCND1, VEGFA, SLC2A1 (GLUT1), IGFBP3, TGFa, AXL, CXCR4, IL6)[MSD (UK) Ltd, 2024]
- Belzutifan binds to HIF-2α, and in conditions of hypoxia or impairment of VHL protein function, belzutifan blocks the HIF-2α-HIF-1b interaction, leading to reduced transcription and expression of HIF-2α target genes[MSD (UK) Ltd, 2024]

Appendix 4: Prescribing details, including contra-indications, special warnings, and interactions

For full prescribing information, please refer to the Summary of Product Characteristics.

Contra-indications[MSD (UK) Ltd, 2024]	Hypersensitivity to the active substance(s) or to any of the excipients listed in the Summary of Product Characteristics
Special warnings and precautions for use[MSD (UK) Ltd, 2024]	**Anaemia due to decreased erythropoietin** Anaemia occurred very commonly in patients receiving belzutifan. • Patients should be monitored for anaemia before initiation of and periodically throughout treatment with belzutifan with more frequent monitoring within the first 6 months of treatment • For patients who develop Grade 3 anaemia (Hb <8 g/dL), belzutifan should be withheld and patients should be treated according to standard medical practice, including erythropoiesis-stimulating agent administration until resolved to ≤ Grade 2 (Hb ≥8 g/dL) • For recurrent Grade 3 anaemia, belzutifan should be discontinued • For patients who develop Grade 4 anaemia, the dose of belzutifan should be reduced or permanently discontinued **Hypoxia** Belzutifan can cause severe hypoxia that may require discontinuation, supplemental oxygen, or hospitalisation • Patients should be monitored for oxygen saturation with pulse oximetry before initiation of and periodically throughout treatment with belzutifan with more frequent monitoring within the first 6 months of treatment • Smoking cessation is recommended • For Grade 2 hypoxia, providing supplemental oxygen and continuing or withholding treatment should be considered. If withheld, belzutifan should be resumed at a reduced dose • For patients who have Grade 3 hypoxia, belzutifan should be withheld, hypoxia treated, and dose reduction should be considered. If Grade 3 hypoxia continues to recur, treatment should be discontinued • For Grade 4 hypoxia, treatment should be permanently discontinued. Patients treated with belzutifan must be given the patient alert card **Embryo-foetal toxicity** • Based on findings in animals, belzutifan may cause foetal harm, including foetal loss, in humans • In a rat study, belzutifan caused embryo-foetal toxicity when administered during the period of organogenesis at maternal exposures that were lower than the human exposures at the recommended dose of 120 mg daily

	• Females of reproductive potential should be advised to use highly effective non-hormonal contraceptive methods during treatment with belzutifan and for 1 week after the last dose, since belzutifan can render some hormonal contraceptives ineffective • Advise male patients and their female partners of reproductive potential to use highly effective contraception during treatment with belzutifan and for 1 week after the last dose • Advise male patients with female partners who are pregnant to use a barrier method of contraception during treatment with belzutifan and 1 week after the last dose **Information about some of the ingredients** • This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'
Interactions[(MSD (UK) Ltd, 2024)]	*In vitro* and pharmacogenomic studies indicate that belzutifan is metabolised by UGT2B17 and by CYP2C19. **Effects of belzutifan on other medicinal products** • Coadministration of belzutifan with CYP3A4 substrates, including hormonal contraceptives, decreases concentrations of CYP3A substrates, which may reduce the efficacy of these substrates. The magnitude of this reduction may be more pronounced in patients who are dual UGT2B17 and CYP2C19 poor metabolisers • Avoid coadministration of belzutifan with sensitive CYP3A4 substrates, for which minimal decrease in concentration may lead to therapeutic failures of the substrate. If coadministration cannot be avoided, increase the sensitive CYP3A4 substrate dosage in accordance with its summary of product characteristics. • Coadministration of belzutifan with hormonal contraceptives may lead to contraceptive failure or an increase in breakthrough bleeding **Effects of other medicinal products on belzutifan** • Co-administration of belzutifan with inhibitors of UGT2B17 or CYP2C19 increases plasma exposures of belzutifan, which may increase the incidence and severity of adverse reactions of belzutifan. Monitor for anaemia and hypoxia and reduce the dosage of belzutifan as recommended
Fertility, pregnancy, and lactation	**Pregnancy:** There are no data from the use of belzutifan in pregnant women. Studies in animals have shown reproductive toxicity. Belzutifan is not recommended during pregnancy and in women of childbearing potential not using contraception.[(MSD (UK) Ltd, 2024)] **Breast-feeding:** It is unknown whether belzutifan or its metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with belzutifan and for 1 week after the last dose.[(MSD (UK) Ltd, 2024)]

	Women of child-bearing potential/ contraception in males and females Pregnancy testing: The pregnancy status of females of reproductive potential should be verified prior to initiating treatment with belzutifan.(MSD (UK) Ltd, 2024) Contraception: Belzutifan may cause embryo-foetal harm, including foetal loss, when administered to a pregnant woman.(MSD (UK) Ltd, 2024) Females: Females of reproductive potential should be advised to use highly effective contraception during treatment with belzutifan and for at least 1 week after the last dose. Use of belzutifan may reduce the efficacy of hormonal contraceptives. Patients using hormonal contraceptives should be advised to use an alternative non-hormonal contraceptive method or have their male partner use a condom during treatment with belzutifan.(MSD (UK) Ltd, 2024) Males: Male patients and their female partner of reproductive potential should be advised to use highly effective contraception during male patient treatment with belzutifan and for at least 1 week after the last dose (see section 4.4). Advise male patients with female partners who are pregnant to use barrier method of contraception during treatment with belzutifan and 1 week after the last dose.(MSD (UK) Ltd, 2024) Fertility: Based on findings in animals, belzutifan may impair fertility in males and females of reproductive potential. Advise patients of this potential risk. The reversibility of the effect on fertility is unknown. Family planning should be discussed with patients as appropriate.(MSD (UK) Ltd, 2024)
Overdose	There is no specific treatment for belzutifan overdose. In cases of suspected overdose, withhold belzutifan and institute supportive care. The highest dose of belzutifan studied clinically was 240 mg daily (120 mg twice a day or 240 mg once a day). Adverse reactions observed in patients receiving more than 120 mg once a day were generally similar to those observed at other doses except for Grade 3 hypoxia observed at 120 mg twice a day and Grade 4 thrombocytopenia observed at 240 mg once daily.(MSD (UK) Ltd, 2024)
Effects on ability to drive and use machines	Belzutifan may have a minor influence on the ability to drive and use machines. Dizziness and fatigue may occur following administration of belzutifan.(MSD (UK) Ltd, 2024) Patients should be advised not to drive and use machines, until they are reasonably certain belzutifan therapy does not affect them adversely.(MSD (UK) Ltd, 2024)

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