belzutifan film-coated tablets (Welireg®)

Merck Sharp & Dohme (UK) Limited

08 September 2023

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

belzutifan (Welireg®) is accepted for use within NHSScotland.

Indication under review: 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.

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.

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.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Belzutifan is an inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α). HIF-mediated expression of genes associated with cellular proliferation, angiogenesis and tumour growth occurs in VHL disease due to a lack of functioning VHL protein, which usually acts to reduce HIF activity. The recommended dose of belzutifan is 120mg, swallowed whole, once daily, with or without food. Treatment should continue until disease progression or unacceptable toxicity.[1, 2]

1.2. Disease background

Von Hippel-Lindau (VHL) disease is a rare autosomal dominant hereditary disorder where there are pathogenic alterations of the VHL gene. The VHL protein acts, in an oxygen-dependent way, to lyse HIF and thereby limit its activity. However, pathogenic VHL proteins have reduced activity, which leads to constitutive activation of HIF-mediated pathways (independent of oxygen concentration) including expression of genes for factors associated with angiogenesis, cellular proliferation and tumour growth. Patients with VHL develop benign and malignant tumours, including clear-cell RCC (in approximately 70% of patients), pNET and hemangioblastomas in the CNS and retina.[1, 2]

1.3. Treatment pathway and relevant comparators

Management of VHL comprises regular surveillance to detect and manage complications at an early stage and thereby reduce morbidity and mortality. It allows RCC and pNET to be monitored until a diameter of 2cm to 3cm is reached and then surgery can be undertaken, with minimal risk of metastasis. Surgery is indicated when CNS hemangioblastomas become symptomatic. Over their lifetime, patients usually have several surgical procedures to resect VHL-associated tumours and prevent metastasis or manage symptoms. As there is a risk of further tumours, organ-sparing surgery, such as subtotal nephrectomy (or localised ablation or cryosurgery), is recommended if feasible. The surgeries and procedures may lead to morbidity including renal insufficiency (requiring dialysis), pancreatic insufficiency (requiring insulin and enzyme supplements) and neurological deficits. After tumours have metastasized, standard therapies for advanced malignancies are used. Management of VHL is a complex balance of symptom control, prevention of metastasis and preservation of organ function.[2-4] There are no medicines licensed for VHL and there is an unmet need for therapies to preserve quality of life, control the disease and spare patients from surgeries or procedures that may compromise organ function.

1.4. Category for decision-making process

Eligibility for interim acceptance decision option

Belzutifan received an Innovation Passport allowing entry into the Medicines and Healthcare Products Regulatory Agency (MHRA) Innovative Licensing and Access Pathway (ILAP) and has conditional marketing authorisation from the MHRA.

Eligibility for a PACE meeting

Belzutifan meets SMC orphan criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence is from the MK-6482-004 (LITESPARK-004) study detailed below.

Table 2.1. Overview of relevant studies

Criteria	MK-6482-004; LITESPARK-004.[2]
Study design	Open-label, multicentre, single-arm, phase II study.
Eligible patients	Adults with VHL and RCC with ≥1 lesion measurable on RECIST v1.1 (≥1cm in longest diameter) and no lesions ≥3cm that require immediate surgical intervention. No evidence of metastasis and ECOG performance status 0 or 1.
Treatments	Belzutifan 120mg once daily until disease progression or unacceptable toxicity.
Randomisation	Not applicable.
Primary outcome	Objective response rate in patients with RCC assessed by ICR on RECIST v1.1
Secondary outcomes	Duration of response, time to response, time to surgery and progression-free survival in patients with RCC; efficacy in non-RCC neoplasms associated; safety.
Statistical analysis	Descriptive.

ECOG = Eastern Cooperative Oncology Group; ICR = independent central review; RCC = renal cell carcinoma; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; VHL = von Hippel-Lindau.

Results, at the latest data cut-off (1 April 2022), for primary analysis in patients with RCC and on the key tumour types, CNS hemangioblastomas and pNET are detailed in Table 2.2 below.[5]

Table 2.2: Results from MK-6482-004 at 1 April 2022 data cut-off.[5]

	Renal Cell Carcinoma	CNS hemangioblastomas	Pancreatic NET
Number of patients	61	50	22
Overall response rate (ORR) by Independent Central Review on RECIST v.1.1			
Overall response rate, n (%)	39 (64%)	22 (44%)	20 (91%)
Overall response rate, 95% CI	51% to 76%	30% to 59%	71% to 99%
Complete response, n (%)	4 (6.6%)	4 (8.0%)	7 (32%)
Partial response, n (%)	35 (57%)	18 (36%)	13 (59%)
Stable disease, n (%)	21 (34%)	23 (46%)	2 (9.1%)
Progressive disease, n (%)	0	3 (6.0%)	0
Not evaluable, n (%)	1 (1.6%)	2 (4.0%)	0
Median time to ORR, months	11.1	*	*

CNS = central nervous system; NET = neuroendocrine tumour; ORR = overall response rate, defined as complete or partial response; RECIST v 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

*Results considered confidential by the company

At 1 April 2022 data cut-off, median follow-up was 37.7 months. However, it was not possible to estimate duration of response as the number of responding patients who subsequently progressed or died was too low: 5, 4 and 0 for RCC, CNS hemaglioblastoma and pNET, respectively. Median progression-free survival (PFS) could only be estimated for RCC. It was not possible to estimate median time to surgery as the number of patients having surgery was small: 7, 1 and 0 in the respective RCC, CNS hemaglioblastoma and pNET populations.[5] All 12 patients (16 eyes) with retinal hemangioglioblastoma had an 'improved' response with belzutifan.

2.2. Supportive Studies

The VHL Natural History Study[4, 6, 7] provided evidence that VHL tumours do not spontaneously regress, thereby supporting the clinical relevance of ORR with belzutifan in MK-6482-004.

The VHL Natural History Study was a retrospective observational study that included patients with VHL and at least one measurable (on Response Evaluation Criteria in Solid Tumors [RECIST v1.1]) renal tumour who had ≥3 measurements (initial plus two subsequent) of renal tumour diameter. Within the primary study population (n=131) and a subgroup who met additional criteria that matched MK-6482-004, the trial subgroup (n=114), there were 201 and 173 tumours, respectively, with ≥3 measurements. Data were collected by the National Cancer Institute's (NCI's) Urologic Oncology Branch from patients at the National Institutes of Health (NIH) Clinical Center in Bethesda, Maryland for the study period: 31 July 2004 to 30 June 2020. The primary outcome, median linear growth rate was 3.9mm/year in patients and 3.84mm/year in tumours in the primary study population, with an increase in maximal diameter of all tumours. In the trial subgroup, median linear growth rate was 3.84mm/year in patients and 3.69mm/year in tumours, with 99% of tumours having an increase in maximal diameter. These data indicate that spontaneous regression of VHL RCC is unlikely.[4, 6, 7]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing belzutifan with standard of care, the submitting company presented a matched adjusted indirect comparison (MAIC). This has informed the economic analysis.

Table 2.2: Summary of indirect treatment comparison

Criteria	Overview
Design	Matched adjusted indirect comparison.
Population	Adults with VHL-associated RCC, CNS hemangioblastoma or pNET without metastasis or prior systemic oncologic treatment.
Comparators	Standard of care.
Studies included	Belzutifan: open-label, phase II, MK-6482-004 study.[2, 5] Standard of care: retrospective observational VHL Natural History study.[4, 6, 7]
Outcomes	Exponential rate parameter for the cause-specific hazards of pre-surgery to first surgery. Incidence of non-RCC VHL-related surgeries with therapeutic intent.
Results	Belzutifan, compared with standard of care, was associated with a lower exponential rate parameter for RCC cause-specific hazards of pre-surgery to first surgery: 0.03692 versus 0.25324 events/person-year; and a lower incidence of non-RCC VHL-related surgeries with therapeutic intent: 0.02119 versus 0.178984 events/person-year.

CNS = central nervous system; pNET = pancreatic neuroendocrine tumour; RCC = renal cell carcinoma; VHL = von Hippel-Lindau.

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

In the MK-6482-004 study at data cut-off 1 April 2022, all 61 patients reported treatment-related adverse events with belzutifan. Adverse events of grade 3 or higher were noted by 44% of patients. Serious adverse events were reported by 30% of patients and were treatment-related in

6.6% of patients. Adverse events lead to dose reduction in 16% of patients, treatment discontinuation in 6.6% of patients and death in 3.3% of patients.[5]

Belzutifan, via HIF-2α inhibition, reduces erythropoietin levels leading to decrease in haemoglobin levels.[4] In the MK-6482-004 study, all patients had a reduction in haemoglobin levels from baseline of at least 1.9g/dL during the first 13 weeks of treatment and thereafter, the haemoglobin levels stabilised. At 1 December 2020 data cut-off, four patients (6.6%) had received blood transfusions to treat their anaemia and 12 patients (20%) had received erythropoietin-stimulating agents, with a median of 2.5 administrations (range 1 to 17). One patient (1.6%) had grade 3 transient hypoxia, which resolved with one week of dose interruption followed by dose reduction to 80mg. Anaemia was an adverse event for almost all patients (90%; 55/61), with substantial proportions reporting fatigue (66%), headache (41%) and dizziness (39%). Other common adverse events included nausea (34%), dyspnoea (23%), myalgia (20%), constipation (20%) and arthralgia (20%).[2]

At the latest data cut-off, 1 April 2022, there was a similar profile of adverse events but increased incidences: anaemia was reported as an adverse event for almost all patients, with many patients experiencing fatigue, headache and dizziness. Other common adverse events included nausea, dyspnoea, myalgia, constipation, arthralgia, blurred vision, abdominal pain and alanine aminotransferase increase.[5]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In MK-6428-004, at the latest data cut-off (April 2022), belzutifan was associated with an ORR of 64% for RCC. That is 64% of patients had a reduction of at least 30% in the sum of diameters of target lesion (partial response [PR]), with 6.6% of patients having complete disappearance of lesions (CR). An additional 34% of patients had stable disease. For CNS hemangioblastomas, the ORR was 44%, with 8.0% achieving a CR and a further 46% of patients having stable disease. For pNET, the ORR was 91%, with 32% achieving a CR and a further 9.1% of patients having stable disease.[5]
- Reductions in tumours of the magnitude observed in MK-6428-004 could be considered clinically relevant as the VHL Natural History Study found that spontaneous remission is unlikely.[2, 4-7]
- Belzutifan is the first medicine licensed for treatment of VHL.

4.2. Key uncertainties

- The MK-6482-004 study is ongoing, with ORR appearing to continue to increase: 49% and 64% at data cut-off 1 December 2020 and 1 April 2022, respectively.[2, 5] It is possible that ORR may increase further and additional follow-up may be required to fully characterise the benefits of belzutifan. The optimum duration of treatment is unclear and long-term efficacy and safety data are limited.
- The study is limited by its open-label, uncontrolled design. However, the primary outcome ORR was assessed by ICR using RECIST.

- The interpretation of the belzutifan indication is partially subjective in relation to two criteria: 'requires therapy' and 'for whom localised procedures are unsuitable or undesirable'.[1] This creates challenges in defining the patient population, the disease stage for treatment initiation and relevant comparator.
- The company suggest that 'requires therapy' could be interpreted needing a surgical or related procedure for RCC tumours >3cm in diameter, pNET tumours >2cm in diameter or CNS tumours causing unbearable symptoms. However, MK-6482-004 excluded patients with RCC >3cm who required immediate surgery. Also, median time to ORR for RCC was 11 months. In practice, belzutifan may be used at an earlier stage of tumour growth, that is, prior to the immediate need for surgery (and before metastasis). Clinical experts consulted by SMC advise that belzutifan may be particularly useful for patients with tumours that are difficult to access or would require surgery that is complex or associated with increased risks of morbidity and mortality.
- The second subjective part of the indication, 'for whom localised procedures are unsuitable or undesirable' has been interpreted by the company as patients who would not be able to have a successful local procedure without negative consequences such as the loss of organ function. The company suggest that the current clinical standard of care for patients with VHL RCC or pNETs for whom localised procedures are unsuitable or undesirable are still localised procedures. However, in these patients the localised procedures would result in loss of organ function with sequelae that would not allow patients to live a healthy life.
- It might be expected that the ORR observed with belzutifan in a condition that does not spontaneously regress, would reduce the frequency of surgery. However, the quantitative comparative evidence for avoidance of surgery is limited to a MAIC with historical controls.
- The MAIC of belzutifan versus historical controls was limited by heterogeneity across the groups in number of prior VHL-associated procedures. Adjustment for this substantially reduced the effective sample size (ESS) in the VHL Natural History Study group and the sample size of MK-6482-004 was small. In MK-6482-004, compared with the VHL Natural History Study group, there was much shorter follow-up and very few surgeries. Follow-up in MK-6482-004 began later (median 17.9 months) than first detection of tumour, as was the case in the VHL natural history study. There were no objective criteria indicating when surgery should be performed in either group, creating comparability issues. Some potential treatment-effect modifiers could not be matched due to lack of data. The primary outcome of the VHL Natural History Study, tumour linear growth rate, was not included in the MAIC. Similar to the comparison of RECIST responses with belzutifan in MK-6482-004 versus the relentless tumour growth in the VHL Natural History Study, the MAIC appears to support in principal the potential surgery sparing benefits of belzutifan. However, due to these limitations of the MAIC, there is uncertainty around the estimate of the magnitude of the surgery sparing benefits.[5, 7]

4.3. GB/EMA conditional marketing authorisation specific obligations

Belzutifan has a conditional marketing authorisation in Great Britain (GB) with the obligations to perform further studies and provide additional measures to minimise risk, including the final study report of MK-6482-004 and results from a prospective patient registry.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that belzutifan fills an unmet need in this therapeutic area, as it is the first medicine for this condition and can be used to treat patients for whom surgical and ablative procedures are not possible. They note that it is a therapeutic advance as it is the first medicine licensed for this condition. The clinical experts advise that its place in therapy would for patients for with VHL tumours for whom surgery could be problematic as it would negate or delay the time to surgery.

4.5. Service implications

Clinical experts consulted by SMC considered that the introduction of this medicine would have limited impact on service delivery as patient numbers are small and it is administered orally.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of belzutifan, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- VHL is a devastating, rare, life-long, life-limiting inherited disorder that causes tumours and cysts to grow in certain parts of the body, including the brain, pancreas, kidney, spinal cord, eyes, inner ear, adrenal glands, and reproductive system. It can affect all ages, including adolescents and young adults. More than two thirds of people with VHL disease develop clear cell renal cell carcinoma (RCC). Patients can suffer from a wide range of debilitating symptoms, including constant pain, loss of balance and motor skills, loss of vision, breathlessness, coughing, headaches, confusion, and severe nausea and fatigue. VHL is a variable and unpredictable condition; some patients may only develop a few or a single tumour in a single organ while other patients may develop multiple tumours across multiple organs throughout their life.
- VHL greatly impacts the daily living activities and mental health of patients, family members and carers. As a hereditary condition, it can affect many members of a family; people with VHL may be carers for other family members with VHL, and these roles can evolve over time as the condition develops.
- There are no licensed medicines available for the treatment of VHL. Surgery is the primary option for patients, who can receive numerous surgeries throughout their life. Surgeries can be associated with ongoing, long-term complications and may not be an option for some patients, for example due to repeated surgery in the same part of the body. There is a large unmet need in this area, to prevent tumours from growing, to potentially reduce the use of anti-cancer medicines, and to delay surgeries if considered appropriate.
- Belzutifan is a first in class treatment and felt to be a true paradigm shift that could have a number of benefits for patients. Treatment with belzutifan may reduce the need for risky, invasive, life changing surgeries and help prevent patients from developing a range of complications due to tumours located throughout the body. VHL tumours do not regress naturally.

- Belzutifan gives family members and carers hope of a better future. In patients whose disease is controlled by belzutifan there are expected to be improvements in wellbeing that will enable patients to contribute socially and economically to society. It is also expected to contribute positively to a patient's social/ leisure activities, independence, relationships, work/ career/ education, and ability to travel. The availability of belzutifan could improve mental health, reducing stress and anxiety for patients who worry about the future. Belzutifan can be taken at home, and over time may reduce the number of hospital visits. It is an oral treatment which is expected to be well tolerated.

Additional Patient and Carer Involvement

We received patient group submissions from Action Kidney Cancer and VHL UK/Ireland, both organisations are registered charities. Action Kidney Cancer has received 59% pharmaceutical company funding in the past two years, including from the submitting company. VHL UK/Ireland has not received any pharmaceutical company funding in the past two years. Representatives from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The economic submission is summarised below.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost utility analysis
Time horizon	Life time (59 years based on an assumed starting age of 41)
Population	Patients with VHL-associated RCC, CNS Haemangioblastoma (CNS Hb) or pNET tumours who require treatment, and for whom surgery is unsuitable or undesirable. The economics focused on three subgroups defined by the site of their primary tumour: RCC, CNS Hb and pNET. The results for each group were presented separately.
Comparators	The comparator was defined as standard of care (SOC). SOC could comprise of immediate surgery or active surveillance. In the RCC and pNET cohorts, 50% of patients were assumed to receive immediate surgery. The remaining 50% received active monitoring and symptom management, but could undergo surgery later in the model. In the CNS Hb cohort, 25% of patients were assumed to receive immediate surgery. A further 50% were treated with active monitoring and symptom management, with the possibility of subsequent surgery. The final 25% of CNS Hb patients were assumed to have inoperable tumours and so received active monitoring and symptom management, but without the subsequent possibility of surgery.
Model description	The company used a 5 state Markov model within their submission. The 5 mutually exclusive states were – pre-surgery, surgery, event free after surgery, metastatic disease and death. The surgery state was a tunnel state, lasting 1 week. All patients started in the pre-surgery state. Patients in the SOC arm who received immediate surgery moved to the surgery state in the first model cycle. The surgery state was assumed to relate to surgery for the patients primary tumour site. More widely patients could suffer from non-primary site tumours. Surgery on non-primary tumours was captured through background event rates. CNS Hb tumours did not metastasise in the model in line with observations in the VHL Natural History Study.[4, 6, 7] However, all patients were at risk of metastatic disease, as all patients could experience RCC or pNET, regardless of the site of their primary tumour.

Clinical data	The main source of clinical data on belzutifan was the MK-6482-004 study.[2, 5] This informed many of the transition probabilities for patients receiving belzutifan who occupied the pre-surgery and event-free-after-surgery states. Those same transition probabilities in the SOC arm, were primarily informed by the MAIC, which matched and weighting data from the VHL Natural History Study to the MK-6482-004 study. Due to an inability to isolate patients with current CNS Hb and pNET in the VHL Natural History Study, several transitions in the SOC arm were informed by a retrospective case analysis of the participants of MK-6482-004. This used data on participants' disease history prior to receiving belzutifan as a proxy for a control arm.
Extrapolation	The transition probabilities from the pre-surgery state and the event-free-after-surgery state were estimated by fitting of exponential curves to data from the MK-6482-004 study, the matched VHL Natural History study and the retrospective analysis of the MK-6482-004 cohort. The company considered that the VHL Natural History Study and MK-6482-004 study were unlikely to represent clinical outcomes seen in Scottish practice, with patients having received more active monitoring and treatment that expected in Scotland. As a result several transition probabilities were adjusted based on the work of Jonasch et al. (2022) to reduce the probability of surgery and increase the chance of metastatic disease.[2] Death from metastasised RCC for patients receiving sunitinib, a treatment prescribed at that stage, was estimated by applying an exponential curve to digitised data from the KEYNOTE-426 study.[10] Survival for alternative treatments were estimated based on a network meta-analysis (NMA) of RCC treatments.[11] Those survival curves were weighted into a composite overall survival curve based on assumed treatment distributions for metastatic RCC. A similar approach was taken for pNET, using the no treatment arm of the E1281 study and a separate NMA.[12, 13]
Quality of life	No HRQoL data were collected as part of the MK-6482-004 or VHL Natural History studies. Utility values were estimated from various external sources. For the pre-metastatic states, rather than linking quality of life to health state occupancy, the company relied on utility estimates based on objective response levels – complete response, partial response, stable disease and progressive disease. Those values were extracted from external sources, including company data not in the public domain.[14, 15] For the belzutifan arm response values were weighted based on the observed levels in the MK-6482-004 study. For the SOC arm, the weighting was based on self-reported status in a VHL study conducted by the company, which is not in the public domain. This led to uniform utility values across the pre-metastatic states, but separate utility values across the model arms. Those utility values were 0.762 and 0.728 for belzutifan and SOC patients respectively in the RCC cohort, 0.751 and 0.695 for belzutifan and SOC patients respectively in the CNS Hb cohort, and 0.790 and 0.728 for belzutifan and SOC patients respectively in the pNET cohort. Utility values in metastatic disease were estimated at 0.525 (pre-progression) and 0.412 (post-progression), from the company study which is not publicly available. Utility values were age adjusted and additional disutilities were applied for adverse events, surgery and complications of surgery.
Costs and resource use	Medicine costs included drug acquisition costs (belzutifan and two lines of metastatic treatment), administration costs and adverse events costs. Wider health maintenance costs included clinical visits, scans and tests. Surgery costs were included as was terminal care and social care cost resulting from CNS surgery or progression.
PAS	Following the New Drugs Committee (NDC) review, the submitting company proposed a new Patient Access Scheme (PAS). That PAS was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount of was offered on the list price. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the list price results can be presented. The results presented below do not take into account various PAS discounts available upon treatments for metastatic RCC and pNET.

6.2. Results

Using list prices for all medicines, the incremental cost effectiveness ration (ICER) when comparing belzutifan against SOC was £73,592 in the RCC population, £57,214 in the CNS Hb population and £68,375 in the pNET population.

The main driver of the cost differences between belzutifan and SOC was the acquisition cost of belzutifan. The main differences in health outcomes was the result of greater occupancy of the pre-surgery state by belzutifan patients.

6.3. Sensitivity analyses

The company provided deterministic and probabilistic sensitivity analyses exploring areas of uncertainty. That analysis indicated that the model was most sensitive to the assumed proportions of patients undergoing immediate surgery in the SOC arm and the pre-metastatic utility values.

Additionally, the company provided scenario analysis. A selection of those scenarios is presented below. These results have been generated using list prices for all medicines.

Table 6.3 Scenario analysis results – List prices for all medicines

#	Scenario	Base case description	RCC cohort	CNS Hb cohort	pNET cohort
1	Time horizon: 20 years	Time horizon: 59 years	66,205	53,385	67,980
2	Time horizon: 30 years		70,841	55,668	67,844
3	Proportion of SOC patients receive immediate surgery (or sequelae in case of CNS Hb) – 60%	Proportion of SOC patients receive immediate surgery (or sequelae in case of CNS Hb) – 50%	67,897	52,629	63,730
4	Proportion of SOC patients receive immediate surgery (or sequelae in case of CNS Hb) – 40%		79,900	62,528	73,330
5	Distribution for pre-surgery→surgery in the belzutifan arm modelled through gamma distribution	Distribution for pre-surgery→surgery in the belzutifan arm modelled through exponential distribution	98,186	57,214	71,951
6	No transitions adjusted to account for real-world standard of care	Selected transitions adjusted to account for real-world standard of care	76,097	53,362	70,747
7	No treatment waning	Treatment waning starting at 7.68yrs following discontinuation and concluded at 10.39yrs following discontinuation	36,750	20,514	25,154
8	Treatment effect instantaneously lost at 7.68yrs following discontinuation		81,346	63,667	77,054
9	Assume same utility for CR as PR/SD	Separate utility values between CR, PR and SD	74,512	57,915	72,347

CNS: central nervous system; CR: complete response; Hb: haemangioblastoma; ICER: incremental cost effectiveness ratio; PD: progressed disease; pNET: pancreatic neuroendocrine tumour; PR: partial response; RCC: renal cell carcinoma; SD: stable disease; SOC: standard of care

*Other data were also assessed but remain confidential.**

6.4. Key strengths

The key strengths of the economics were identified as:

- The economic analysis matched the product licence.
- Expert responses received by the SMC confirmed that the treatment strategies included in the comparator were appropriate.
- Scenario and sensitivity analyses showed that in several areas the base case could be considered conservative, for example the use of the Gompertz function to model time on treatment for belzutifan patients over more flexible functions, and some benefits of belzutifan treatment have not been fully captured. However, there remained significant uncertainty associated with other areas of the modelling which may increase the incremental cost-effectiveness ratio above the base case value.

6.5. Key uncertainties

The key uncertainties of the economic case were identified as:

- The model structure was relatively simplistic, while the disease area is complex, with patients capable of having multiple and recurrent tumours. However, there was likely insufficient data to produce a more granular model. The company reported that the omission of some disease and treatment characteristics would lead to the cost-effectiveness of belzutifan being underestimated, although that is uncertain.
- In the SOC arm, a proportion of patients were assumed to receive surgery immediately. Those proportions were not well grounded in evidence or clinical opinion. Given the ambiguity in the licence conditions, it is possible that belzutifan is integrated into the patient pathway in advance of the point at which immediate surgery is needed. A smaller proportion of patients needing surgery early in the model and an increase in the treatment duration of belzutifan may increase the incremental cost-effectiveness ratio (see Scenario 4 for a reduction in the immediate use of surgery in the SOC arm).
- There was no direct evidence comparing belzutifan with SOC in a randomised study, leading to a reliance upon an indirect treatment comparison and a retrospective control group. That indirect comparison was seen at high risk of bias, which translated into uncertainty in the economic results.
- The two main data sources, the MK-6482-004 study and the VHL Natural History Study only contained patients with RCC, although patients could also simultaneously have CNS Hb and pNET. This led to an imbalance in the evidence base, with the strongest clinical and economic evidence being for the RCC cohort. As a result, greater uncertainty was attached to the results in the CNS Hb and pNET cohorts.
- The results for the RCC cohort were highly volatile to changes in the survival distributions used in modelling transitions from the pre-surgery state. The exponential functions was used in the base case, but was assessed as having poor visual fit to the data from the MK-6482-004 study. The company identified the gamma distribution as the second best fitting curve. This showed better visual fit to the belzutifan data but led to a large increase in the incremental cost-effectiveness ratio (see scenario 5).

7. Conclusion

The Committee considered the benefits of belzutifan in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for the absence of other treatments of proven benefit was satisfied. In addition, as belzutifan is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted belzutifan for use in NHSScotland.

8. Guidelines and Protocols

There are no relevant guidelines.

9. Additional Information

9.1. Product availability date

October 2022

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Belzutifan	120mg orally once daily	144,832

Costs from BNF online on 19 April 2023. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 7 patients eligible for treatment with belzutifan each year. The estimated uptake rate was 100% per year. This resulted in 7 patients estimated to receive treatment each year. Using the list price for belzutifan, the gross impact on the medicines budget was estimated to be £311k in year 1 and £941k in year 5. No comparator medicines were assumed to be displaced, but with cost savings associated with a change in the treatment pathway and some savings associated with delaying disease progression to advanced cancer, the net medicines budget impact was estimated to be £228k in year 1 and £691k in year 5.

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This assessment is based on data submitted by the applicant company up to and including 13 July 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.