NCPE Assessment Summary

Belzutifan (Welireg®)

HTA ID: 25020

May 2026

Applicant: MSD HH Ireland

Belzutifan (Welireg®) for the treatment of adult patients with von Hippel-Lindau disease who require therapy for associated, localised renal cell carcinoma, central nervous system haemangioblastomas or pancreatic neuroendocrine tumours, and for whom localised procedures are unsuitable

Conditional Marketing Authorisation

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of belzutifan (Welireg®).

Following assessment of the Applicant's submission, the NCPE recommends that belzutifan (Welireg®) not be considered for reimbursement, for this indication, unless cost-effectiveness can be improved relative to existing treatments*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (MSD HH Ireland) Health Technology Assessment of belzutifan (Welireg®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In November 2025, MSD HH Ireland submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of belzutifan (Welireg®) for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated, localised renal cell carcinomas (VHL-RCCs), central nervous system haemangioblastomas (VHL-CNS-Hbs) or pancreatic neuroendocrine tumours (VHL-pNETs), and for whom localised procedures are unsuitable. MSD HH Ireland is seeking reimbursement of belzutifan on the High Tech Drug Arrangement.

VHL disease is a rare, autosomal dominant genetic disorder which causes the development of benign and malignant neoplasms . The disease typically arises from a single, mutated germline variant of the *VHL* tumour suppressor gene, although spontaneous manifestations do occur. The mean age of initial tumour manifestation in patients with VHL disease is 26 years, with over 90% of patients developing symptoms before 65 years. The most recent Irish prevalence of VHL disease (1 in 80,000) was recorded by the Economic and Social Research Institute in 2000.

Patients with VHL disease are at risk of developing highly vascularised Hbs involving various organ systems, including, VHL-RCCs (kidney), VHL-CNS-Hbs (brain and spinal cord), VHL-pNETs (endocrine), retinal Hbs (eye), pancreatic cysts, endolymphatic sac tumours, among others. VHL-RCCs are the leading cause of death in patients with the disease and have high recurrence rates. VHL-CNS-Hbs tend to occur at a younger age in patients with the disease and often present as multiple lesions, contributing to their propensity for recurrence. VHL-pNETs manifestations are somewhat rarer, however, these tumours can behave malignantly and are a major contributor to the morbidity and mortality linked to VHL disease. Consequences of VHL disease-associated tumours include cerebellar ataxia, vision loss, severe headaches, hearing loss, spinal cord dysfunction and potential paralysis.

In VHL disease there is an accumulation of HIF-2α protein which leads to abnormal cell growth and potential tumour formations. Belzutifan binds to HIF-2α in conditions of VHL protein impairment and blocks HIF-2α to HIF-1β interactions, leading to a reduction in uncontrolled transcription and expression of target genes. Belzutifan is an oral drug and the

recommended dose is 120mg (three 40mg tablets) once daily. The product licence recommends that belzutifan is continued life-long until unacceptable toxicity or disease progression.

The current standard of care (SoC) for individuals with VHL disease-associated tumour manifestations includes surgical resection, radiation therapy and ablation. Many patients require multiple surgical procedures throughout their lifetime, which may ultimately result in loss to organ function in cases of locoregional recurrences. Surgical resections are generally successful and reduce the tumour burden for patients, however, some patients may be deemed unsuitable for surgical resections due to the location and risks associated with their tumour(s). The current conditional licence states that any patient considered for belzutifan must be deemed "unsuitable" for localised procedures (i.e., surgical resection, radiation or ablation).

1. Comparative effectiveness of belzutifan

The clinical trial programme for belzutifan includes a suite of multi-centre, international studies known as the LITESPARK trials. This includes the LITESPARK-004, LITESPARK-005 and LITESPARK-015 trials, among others. All trials in the LITESPARK programme are open-label studies and none of these trials evaluated belzutifan versus an active control or placebo in patients with VHL disease. Many of the LITESPARK trials are Phase II or Phase III and currently remain in progress.

LITESPARK-004 is an ongoing, phase II, single-arm, open-label study and is the only study designed to assess the clinical effectiveness of belzutifan 120mg once daily in adults with VHL disease. Data supporting this assessment were presented from the April 2024 data-cut. The study began in May 2018 and remains active with an estimated completion date of April 2027, but is not recruiting (n=61 at initiation). The single-arm nature of the LITESPARK-004 study has the potential to introduce immeasurable bias and confounding in the trial results and the computed treatment effect estimates.

This study informed the EMA's appraisal of belzutifan for patients with VHL disease and led to a conditional marketing authorisation (MA) granted by the European Commission. The NCPE Review Group note that the conditional MA granted covers a broader population than

defined in the original LITESPARK-004 eligibility criteria. Specifically, the product licence was extended from the original trial population (patients with VHL-RCCs) to patients with VHL-RCCs, VHL-CNS-Hbs and VHL-pNETs, for whom localised procedures are unsuitable. All participants recruited to LITESPARK-004 had at least one diagnosed VHL-RCCs manifestation at baseline (n=61), additional tumour manifestations (i.e., VHL-CNS-Hbs [n=50] and VHL-pNETs [n=22]) were identified and analysed as part of post-hoc exploratory analyses.

The primary endpoint of the LITESPARK-004 study is the objective response rate (ORR) assessed by best overall response (BOR). This was defined as the percentage of participants in the analysis population who have a confirmed: complete response (CR: disappearance of all target lesions) or; partial response (PR: at least a 30% decrease in the sum of diameters of target lesions), per the RECIST v1.1 criteria. The NCPE Review Group note that achieving a BOR of CR could effectively eliminate the need for surgical resection in patients with VHL disease and that a BOR of PR may also reduce this need.

The primary endpoint of the trial was considered to be met as belzutifan demonstrated an ORR considered favourable in the VHL-RCCs cohort (CR and PR: 44/61) (ORR: 70.5% [95% CI: 57.4% to 81.5%]). ORR results in participants with VHL-CNS-Hbs (CR and PR: 25/48) (ORR: 50.0% [35.5% to 64.5%]) and VHL-pNETs (CR and PR: 18/20) (ORR: 90.9% [68.3% to 98.8%]) were considered secondary endpoints and were measured during post-hoc analyses. The NCPE Review Group note a very limited number of participants obtained a CR in the VHL-RCCs and VHL-CNS-Hbs groups (11.5% and 12.0%, respectively).

The median time to response (TTR) was measured as a secondary endpoint in each cohort. The median TTR was 11.1 months (range: 2.7 months to 54.7 months) in the VHL-RCCs cohort, 7.9 months (range: 2.3 months to 52.3 months) in the VHL-CNS-Hbs cohort and 8.2 months (range: 2.5 months to 16.4 months) in the VHL-pNETs cohort. These ranges span the amount of time it took for patients to progress to PR or CR after initiating belzutifan therapy. The Review Group note that the TTR measures span extensive durations in all cohorts and that, in the real-world setting, surgery might not be withheld for such extensive durations.

Other secondary endpoint measures such as overall survival, progression-free survival and duration of response could not be assessed due to trial data immaturity, which is a limitation of the assessment. No conclusions could be drawn regarding the effect of belzutifan on

patient health-related quality of life (HRQoL) as this data was not collected by the Applicant during the trial period.

Comparative trials were not available for belzutifan versus the comparators of relevance to the assessment (SoC), therefore, indirect comparisons (ITCs) using inverse-probability of treatment weighting (IPTW) methodologies were provided. Such propensity scoring type approaches attempt to match data from unconnected sources to estimate a treatment effect. In order to accurately implement such an approach, all prognostic and effect-modifying variables (i.e., all variables that influence treatment outcomes) must be included in the model, which is challenging to achieve in practice. The VHL Disease Natural History Study (VHL-NHS) was used to inform the comparator (SoC) arm (IPTW weighted to the LITESPARK-004 trial data using the average treatment effect among the treated (ATT) approach). The Review Group identified a number of potentially relevant confounders that were excluded. As the VHL-NHS included was conducted in a Centre of Excellence (National Institutes of Health Clinical Centre in Bethesda, Maryland, USA); transitions in the SoC arm of the model were adjusted using real-world data from another registry - the Optum Clinformatics Data Mart (where Optum could not be used to represent SoC in the model due to data limitations).

Due to concerns with the stability of the IPTW ATT approach, the Review Group requested both alternative approaches/estimands (IPTW ATC and IPTW ATE) and "before versus after" IPTW weightings for all transitions (where applicable). The Applicant failed to produce this analyses; and is regarded as a significant limitation of the assessment.**Error! Reference source not found.**

2. Safety of belzutifan

At the most recent data cut-off, all participants (n=61) in the LITESPARK-004 trial had experienced at least one adverse event (AE) and all participants had experienced AEs related to belzutifan use. Among the most frequently reported AEs were anaemia (93.4%), fatigue (77.0%), headache (49.2%), dizziness (45.9%), myalgia (31.1%) and dyspnoea (26.2%). Approximately half of participants experienced grade ≥ 3 AEs, most commonly anaemia (13.1%), hypertension (9.8%), fatigue (4.9%) and syncope (3.3%).

Serious AEs occurred in 20 participants (32.8%), including four cases considered treatment-related. Treatment discontinuation due to AEs occurred in 6.6% of participants, and AEs led to death in 3.3% (n=2). Treatment-related AEs resulted in dose interruptions in 24.6% of participants and dose reductions in 18.0%.

The most common significant toxicities from belzutifan treatment are anaemia and hypoxia, which can be explained by the mechanism of action. These AEs led to treatment modifications in a small percentage of patients. Individuals taking the medication should be screened for anaemia prior to initiation of treatment and monitored periodically throughout treatment. Patients should also be assessed for hypoxia prior to starting belzutifan and monitored throughout therapy. In the event that grade ≥ 3 anaemia or hypoxia develops, dose withholding or drug discontinuation should be considered.

Belzutifan should not be prescribed to patients of childbearing potential or in receipt of oral contraceptives without prior consultation and verification of pregnancy status as coadministration may lead to contraceptive failure. Belzutifan may also cause embryo-foetal harm including foetal loss. CNS haemorrhaging has been observed in patients with VHL-CNS-Hbs. The SmPC notes that physicians should be cautious of the symptoms or signs of CNS haemorrhaging in patients with VHL-CNS-Hbs who receive belzutifan. Further, long-term safety data is limited, which is a relevant concern given the anticipated long-term use of belzutifan in patients with VHL disease.

3. Cost effectiveness of belzutifan

The Applicant developed a *de-novo* cost-effectiveness model (CEM) using a Markov cohort structure in Microsoft Excel® to estimate the health outcomes, clinical events and costs associated with the use of belzutifan from the perspective of the publicly-funded health service in Ireland. The caregiver perspective was explored in a scenario analyses.

Methods

The model distinguishes cohorts of patients with VHL disease and provides individual and aggregate results for the following cohorts: VHL-RCCs cohort, VHL-CNS-Hbs cohort, VHL-pNETs cohort; and a weighted cohort (supported by clinical opinion on tumour distribution

in Ireland). Each cohort was categorised by the Applicant based on the "primary tumour". Primary tumour(s) were defined as tumours that "drove treatment decisions". These cohorts were not mutually exclusive, which raises generalisability concerns (e.g., the same patient who suffered from all three tumour types, would exist in all three cohorts regardless of which tumour was "driving treatment decisions"). Additional cost and quality-of-life burdens of having multiple simultaneous tumour manifestations were also not accounted for in the model.

The CEM consisted of five distinct health states: 'pre-surgery' (model entry); 'surgery' (a one-week tunnel state); 'event-free after surgery'; 'metastatic disease' and; 'death' (an absorbing health state). In line with the licence restriction to those "for whom localised procedures are unsuitable", it is assumed that only one surgery was possible as a "last resort" intervention. On- and off-treatment health states exist, in the CEM, for patients who have or have not discontinued belzutifan treatment. Patients who discontinue are assumed to require surgery after a period of treatment effect waning (2.75 years). While patients who receive SoC are assumed to require surgery after eight weeks. The Review Group had concerns regarding the representativeness of these assumptions toclinical practice.

In addition to the limitations described previously, there was inconsistent methodology in calculating pivotal health outcomes, use of immature trial data to extrapolate these long-term health outcomes, and use of alternative costs for treatments where Irish sources were available. Due to a paucity of evidence, the Review Group were unable to address all of these limitations. However, to address the inappropriate sources of costs used in the submission, an NCPE exploratory base case was conducted with these costs updated per the HSE-ABF document (Table 2). Key scenarios were also explored.

Results

An incremental analysis of the costs and benefits of belzutifan versus the established SoC was presented by the Applicant (Table 1). Several significant limitations have already been highlighted by the Review Group pertaining to these results. Due to these limitations, caution is advised when interpreting the results. Results of the probabilistic analysis, which were estimated for 1,000 simulations, are stable and similar to the results of the deterministic

analysis.

Table 1: Applicant base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
SoC	553,963	1.18	-	-	-
Belzutifan	1,185,429	6.22	631,466	5.05	125,154[b]

ICER: Incremental cost effectiveness ratio; **QALY**: Quality adjusted life year; **SoC:** Standard of care

[a] Corresponding probabilistic ICER using 1,000 iterations = €127,239/QALY. Figures in the table are rounded. Annual discount rate of 4% is applied

[b] Weighted ICER based on VHL tumour incidence assumptions (obtained from clinical opinion). ICER VHL-RCCs €121,482/QALY (15% incidence); ICER VHL-CNS-Hbs €125,093/QALY (80% incidence); ICER VHL-pNETs €136,044/QALY (5% incidence)

Table 2: NCPE exploratory base case incremental cost-effectiveness results

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
SoC	516,635	1.18	-	-	-
Belzutifan	1,164,320	6.22	647,685	5.05	128,368

ICER: Incremental cost-effectiveness ratio; **QALY**: Quality-adjusted life year; **SoC**: Standard of care

[a] Corresponding probabilistic ICER using 1,000 iterations = €126,794/QALY. Figures in the table are rounded. Annual discount rate of 4% is applied

[b] Weighted ICER based on VHL tumour incidence assumptions (obtained from clinical opinion). ICER VHL-RCCs €118,916/QALY (15% incidence); ICER VHL-CNS-Hbs €129,254/QALY (80% incidence); ICER VHL-pNETs €136,250/QALY (5% incidence)

Sensitivity analysis

Deterministic one-way sensitivity analysis provided by the Applicant indicated that the most influential parameters in the CEM related to belzutifan treatment effect waning (with immediate surgery assumption) and health state utility values (which reflects health related quality of life benefits of belzutifan).

While many limitations could not be explored in an NCPE exploratory base case, multiple assumptions of the model were tested as part of scenario analysis as described below.

Results of scenario analyses conducted by the Review Group indicate that assumptions included by the Applicant appear to either be conservative (relative to available alternative methodology) or non-influential to cost-effectiveness results.

Key scenarios explored included:

- Assuming immediate surgery in all patients who have discontinued belzutifan (Applicant base case assumed discontinued belzutifan surgery after a 2.75 year period): ICER €150,316/QALY
- Assume surgery for all patients who receive SoC in the model after 4 months (Applicant

base case assumed SoC surgery after 2 months): ICER €131,755/QALY.

- Assuming a relative dose intensity with belzutifan of 100% (Applicant base case assumed RDI of 91.2%): ICER €144,367/QALY.

A Price-ICER analysis was conducted to estimate the reductions in the price to wholesaler of belzutifan, which would be required for belzutifan to meet the €45,000/QALY and €20,000/QALY thresholds. A price-reduction of 51% and 63% was estimated for cost-effectiveness at each threshold, respectively. The NCPE Review Group note that there are inherent uncertainties, in the cost-effectiveness evaluation, that cannot be addressed. As such, it is possible that the discounts, presented here, are underestimated.

4. Budget impact of belzutifan

The price-to-wholesaler for one pack of belzutifan (90 x 40 mg tablets) is €14,474.42. VAT is not applicable to belzutifan as it is an oral medicine. The estimated cost of belzutifan per patient per year is €175,208. The Applicant presented an estimated cost per patient per treatment course of €1,077,905. The estimate is uncertain given the heterogeneous population and time to discontinuation uncertainties.

The Applicant's estimated gross and net drug budget impact estimates were considered very uncertain. They included a number of assumptions including uncertain market share estimates, the inclusion of a prevalence rate which could not be appropriately defined or verified, the inclusion of an excess mortality rate based on audit data from the UK, and an assumption that just 13.68% of all patients would be treated with belzutifan under the current licence. The Applicant's estimated cumulative net drug budget impact, for belzutifan, was €6,279,049 over five years. The Review Group conducted a scenario analysis to investigate the impact of the abovementioned uncertainties. The Applicant's market share estimates and proportion of patients treatable under the licence were increased per clinical opinion to the Review Group. This resulted in an estimated net budget impact of €14,371,284 over five years. However, the Review Group also noted the limitations with this approach, attributed to paucity of research data in this disease area.

5. Patient Organisation Submission

A patient organisation submission was received from VHL UK/Ireland and was shared with the HSE. This submission will form part of the information that the HSE considers when making their drug funding decision.

6. Conclusion

The NCPE recommends that belzutifan (Welireg®) not be considered for reimbursement, for this indication, unless cost effectiveness can be improved relative to existing treatments*.

The NCPE have appraised the clinical evidence and have determined that belzutifan (Welireg®) may cause the shrinkage or disappearance of tumours in patients with VHL-RCCs, VHL-CNS-Hbs and/or VHL-pNETs. The medicine may also delay the time until surgery is required in patients with VHL disease-associated tumours. However, this evidence is sourced from an ongoing, phase II single-arm trial (LITESPARK-004) in which the design did not allow for robust conclusions to be drawn regarding the drug's efficacy and safety.

Belzutifan currently holds a conditional marketing authorisation from the EMA. This was granted in the absence of trial evidence which would usually be required for a full marketing authorisation as the medicine has a potential to address an unmet need in patients with VHL disease.

Furthermore, the assumptions which underlie the cost-effectiveness and budget impact estimates for belzutifan remain very uncertain due to a lack of published data in this disease area and could not be fully interrogated as part of this assessment.

* Next steps: The NCPE Assessment Report and recommendation and Patient Organisation submission, will be considered by the HSE when making their decision on reimbursement, while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013. Further information on this process may be found here.

Please refer to the HSE website for updated information on the reimbursement status of this medicine.