Technology Guidance

# Belzutifan

## for von Hippel-Lindau disease with associated non-metastatic renal cell carcinoma, central nervous system hemangioblastomas, or pancreatic neuroendocrine tumours

**Technology Guidance from the MOH Drug Advisory Committee**

## Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended belzutifan for inclusion on the MOH List of Subsidised Drugs for von Hippel-Lindau disease with associated non-metastatic renal cell carcinoma, central nervous system hemangioblastomas, or pancreatic neuroendocrine tumours, in patients not requiring immediate surgery. The decision was based on the uncertain extent of clinical benefit, unfavourable cost-effectiveness compared with active surveillance alone, and the unacceptable price-volume agreement proposed by the company.

***Clinical indication, subsidy class and MediShield Life claims eligibility for belzutifan are provided in the Annex.***

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## Technology evaluation

1.1. At the April 2026 meeting, the MOH Drug Advisory Committee ("the Committee") considered the technology evaluation of belzutifan for von Hippel-Lindau (VHL) disease with associated non-metastatic renal cell carcinoma (RCC), central nervous system hemangioblastomas (CNS Hb), or pancreatic neuroendocrine tumours (pNET), in patients not requiring immediate surgery. The evaluation considered the company's evidence submission for belzutifan by MSD Pharma, and a review conducted by one of ACE's evidence review centres.

1.2. Expert opinion from clinicians at public healthcare institutions, the MOH Cancer Drug Subcommittee, and patient experts from local patient and voluntary organisations helped ACE ascertain the clinical value of belzutifan

1.3. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.4. Additional factors, including social and value judgments, may also inform the Committee's funding considerations.

## Clinical need

2.1. VHL disease is a rare, autosomal dominant hereditary condition caused by mutations in the *VHL gene*. The disease predisposes patients to develop both benign and malignant tumours, including RCC, CNS Hb, and pNET, across many body locations. In Singapore, approximately 33 patients require treatment annually for VHL-associated non-metastatic RCC, CNS Hb and pNET.

2.2. In local practice, patients with VHL-associated tumours undergo lifelong active surveillance (AS), followed by surgical intervention when these tumours reach certain size thresholds or become symptomatic. Patients may undergo multiple surgeries over their lifetime, which may be associated with cumulative morbidity and decline in organ function, including renal impairment. The Committee heard that there is a clinical need for effective treatment options for VHL-associated tumours. Belzutifan is an oral treatment that inhibits hypoxia-inducible factor-2α (HIF-2α), a key driver of tumour growth in VHL disease. Thus, it may delay or reduce the need for surgeries in patients with VHL-associated non-metastatic RCC, CNS Hb, or pNET. Nonetheless, the Committee noted that patients on belzutifan would still require ongoing surveillance and monitoring, given the nature of VHL disease.

2.3. Local patient and voluntary organisations were invited to provide patient input to inform this evaluation, however, no responses were received. Patient insights from Australia, Canada and the United Kingdom provided by the company highlighted the high clinical need for non-surgical treatment options and the physical, mental and financial burden that VHL disease has on patients and their families. The Committee acknowledged the complexity of managing the condition, noting that it affects each patient differently, but considered that, without local input, it is uncertain whether experiences reported in other countries fully reflect the lived experiences of patients in Singapore.

## Clinical effectiveness and safety

3.1. The Committee reviewed the clinical evidence for belzutifan from an open-label, single-arm phase II study (LS-004) in 61 patients with at least one VHL-associated non-metastatic RCC, with or without concurrent CNS Hb or pNET, who did not require immediate surgery. The company's requested listing included patients with CNS Hb or pNET, without concurrent RCC, as well as those without genetically confirmed VHL disease, and patients earlier in the disease pathway. The Committee considered that the requested listing would extend beyond the population evaluated in the clinical evidence, and noted that even for the RCC population, the clinical evidence was limited.

3.2. The Committee noted that the requested listing was consistent with the HSA-approved indication. It also noted that overseas HTA agencies such as Australia's Pharmaceutical Benefits Advisory Committee and Canada's Drug Agency have accepted broader criteria for belzutifan that included non-RCC tumours including CNS Hb or pNET without restrictions on timing of initiation or requiring genetically confirmed VHL disease. On balance, the Committee considered that broader listing of belzutifan, in line with overseas HTA criteria and its HSA-approved label, could be considered reasonable.

3.3. At a median follow up of 49.7 months (April 2023 data cut-off), results from the before-and-after analysis of belzutifan in LS-004 showed a reduction in surgeries across all tumour types, from 76 surgeries in 46 patients in the four years before treatment to 17 surgeries in 15 patients in the four years after treatment. Linear growth rate[a] (LGR) of RCC tumours was also reduced from a median of +3.38 mm/year to –2.20 mm/year.

[a] The linear growth rate was estimated for each treatment phase (before and after initiation of treatment) in patients with ≥3 scans including the screening scan.

3.4. In the absence of direct comparative evidence, the submission presented a matching-adjusted indirect comparison (MAIC) of the study populations from LS-004 and the VHL-Natural History Study (VHL-NHS), a retrospective observational study of medical records from a single U.S. centre. Results of the MAIC estimated an 85% reduction in RCC surgery rate (AS vs. belzutifan; 0.00487 vs. 0.00071 surgeries/person-week) and an 88% reduction in non-RCC surgery rate (AS vs. belzutifan; 0.00344 vs. 0.000407 surgeries/person-week) with belzutifan compared with AS alone. The Committee noted that these results are subject to substantial uncertainty due to limited methodological transparency, lack of validation and sensitivity analyses, unmatched key prognostic variables, and reduced effective sample sizes.

3.5. In terms of safety, belzutifan was associated with higher rates of Grade 3 and above adverse events (AEs) compared with AS alone, with the most common AEs being anaemia and fatigue.

3.6. The submission described belzutifan as superior in terms of effectiveness compared with AS alone, with a manageable safety profile for patients with VHL-associated non-metastatic RCC, CNS Hb and pNET. Based on the evidence submitted, the Committee concluded that the extent of clinical benefit with belzutifan is highly uncertain due to limitations of the MAIC, the unclear relationship between interim outcomes (reduction in number of surgeries or LGR) and meaningful long-term outcomes (quality of life, overall survival), and uncertain generalisability to the Singapore population. Additionally, belzutifan is likely to have an inferior safety profile compared with AS alone.

## Cost effectiveness

4.1. The Committee considered the results of the submission's cost-utility analysis that compared belzutifan with AS alone, for treating patients with VHL-associated non-metastatic RCC, VHL-associated CNS Hb and VHL-associated pNET (referred to as the RCC model, CNS model and pNET model respectively). Key components of the base-case economic evaluation provided in the submission are summarised in Table 1.

**Table 1: Key components of the company-submitted base-case economic evaluation**

| Component | Description |
|---|---|
| Type of analysis | Cost-utility analysis |
| Population | Patients with VHL-associated RCC, VHL-associated CNS Hb and VHL-associated pNET, not requiring immediate surgery |
| Outcomes | Total and incremental costs; total and incremental LYs gained; total and incremental QALYs; ICER |
| Perspective | Singapore healthcare system |
| Type of model | Markov cohort model, one each for RCC, CNS Hb and pNET populations |
| Time horizon | 25 years in the base case versus a mean follow-up duration of 49.2 months in LS-004 trial<br>5, 10, 30, 40, 50 years modelled in scenario analysis. |
| Health states | • Pre-surgery (PS)<br>• Surgery (S; with tunnel states for 1st, 2nd or 3rd and subsequent surgery)<br>• Event-free after surgery (EF; with tunnel states of post 1st, 2nd or 3rd and subsequent surgery)<br>• Metastatic disease (MD)<br>• Death<br><br>Pre-surgery, surgery and event-free after surgery states in belzutifan arm are further divided by whether patients are on or off belzutifan treatment |
| Cycle length | 1 week |
| Transition probabilities | Transition probabilities for the AS arm were sourced from the LS-004 pre-treatment period, and VHL-Natural History Study reweighted from MAIC. Transition probabilities for the belzutifan arm were derived from the LS-004 post-treatment period. Death from surgery in both arms were informed by published literature. |
| Health-related quality of life | No utility data were collected in LS-004 trial. Health state utilities by response were instead informed by the QoL Disease Burden Study (informing metastatic utilities and PR, SD, PD of non-metastatic disease) and KEYNOTE-564 (informing CR in non-metastatic disease), assuming UK value sets. |
| Types of healthcare resources included | • Drug acquisition and drug administration costs<br>• Disease management costs<br>• Subsequent treatment costs<br>• AE management costs<br>• Terminal care costs |

Abbreviations: AE, adverse event; AS, active surveillance; CNS Hb, central nervous system hemangioblastoma; CR, complete response; LY, life year; MAIC, matching-adjusted indirect comparison; PD, progressive disease; PF, progression-free; pNET, pancreatic neuroendocrine tumour; PR, partial response; QALY, quality-adjusted life year; RCC, renal cell carcinoma; SD, stable disease.

4.2. The base-case incremental cost-effectiveness ratio (ICER) of the RCC, CNS-Hb and pNET models in the submission were more than SG$365,000 per quality-adjusted life year (QALY) gained. The Committee considered the ICER to be uncertain and likely underestimated given:

- The submission was fundamentally constrained by limited data. The pivotal LS-004 trial was a single-arm study; external data sources were required to inform model parameters for the AS arm, raising concerns about population mismatch and generalisability to the local population.

- The treatment effectiveness of belzutifan was likely overestimated. The submission assumed that treatment with belzutifan would prolong time to surgery, time to metastatic disease, and time to death. However, there was limited clinical evidence to support these assumptions.

- QALYs gained in the early cycles were overestimated. The submission applied response-weighted utilities to the belzutifan arm from model simulation start time. This implied immediate improvements in quality of life upon treatment initiation, before any response could be reasonably expected (mean time to response for belzutifan was 13.5, 12.2, and 8.4 months for RCC, CNS-Hb, and pNET cohorts in LS-004, respectively).

- QALYs loss due to surgical complications was likely overestimated in the model, as disutilities were applied additively instead of multiplicatively.

- Cost of treatment with belzutifan was likely underestimated. The time-to-treatment discontinuation curve was immature, with less than 50% of patients having discontinued treatment. Additionally, in line with the HSA-approved label, patients may remain on treatment as long as any benefit was observed until metastatic disease, hence time on belzutifan could be equal to time in non-metastatic disease. This suggests that the actual cost of belzutifan treatment is likely higher than that estimated in the model, due to the extended duration.

4.3. The Committee considered the revised base case, which accounted for several uncertainties in the company's model. Key changes to the economic model included correcting the selling price of belzutifan, removing the benefit of belzutifan on time to metastatic health state, and applying response-based utility weights only when mean time to response was reached. Following these changes, the ICER for belzutifan increased substantially beyond the submission's base-case across all three models.

4.4. The Committee noted that based on a one-way sensitivity analysis of the revised base case, the ICER was sensitive to the time horizon, duration on treatment, and treatment-effect waning assumptions.

4.5. Overall, the Committee considered that belzutifan did not represent a cost-effective use of healthcare resources for the treatment of patients with VHL-associated RCC, CNS Hb or pNET, at the price proposed by the company.

## Estimated annual technology cost

5.1. Using an epidemiological approach, the submission estimated that the annual cost impact to the public healthcare system would increase from between SG$1 million and SG$3 million in the first year, to more than SG$10 million in the fifth year of listing belzutifan on the MOH List of Subsidised Drugs for treating VHL disease with associated non-metastatic RCC, CNS Hb, or pNET, in patients not requiring immediate surgery.

5.2. The Committee considered that the submission estimates were overestimated, as a mathematically flawed approach was used to calculate the eligible patient population, and assumed an overly optimistic uptake rate with 100% relative dose intensity.

5.3. In a revised budget impact model that addressed these issues, the annual cost impact to the public healthcare system was estimated to be less than SG$1 million in the first year, to between SG$3 million and SG$5 million in the fifth year of listing. The Committee also considered that the submission's price-volume agreement (PVA) caps were unacceptably high and inadequate to provide budget certainty.

## Recommendations

6.1 Based on available evidence, the Committee recommended not listing belzutifan on the MOH List of Subsidised Drugs for VHL disease with associated non-metastatic RCC, CNS Hb, or pNET, in patients not requiring immediate surgery. The decision was based on the uncertain extent of clinical benefit, unfavourable cost-effectiveness compared with AS alone, and the unacceptable PVA proposed by the company.

## ANNEX

### Recommendations by the MOH Drug Advisory Committee

| Drug preparation | Company-proposed clinical indication | Subsidy class (implementation date) | Eligible for MediShield Life claims (implementation date) |
|---|---|---|---|
| Belzutifan 40 mg tablet | Belzutifan for treating adult patients with von Hippel-Lindau disease who require therapy for associated non-metastatic renal cell carcinoma, central nervous system hemangioblastomas, or pancreatic neuroendocrine tumours, not requiring immediate surgery | Not recommended for subsidy | No |