Highly Specialised Technologies (HST) criteria checklist

ID3932 Belzutifan for treating tumours associated with von Hippel-Lindau disease

### Introduction

The NICE HST criteria checklist is to highlight where a technology meets/partially meets or does not meet the criteria for routing to the HST programme. Its purpose is to show the details of why a technology may not be appropriate for HST evaluation, but also where it has been identified as suitable. For more information, please see [section 7 of NICE health technology evaluation topic selection: the manual](https://www.nice.org.uk/process/pmg37/chapter/highly-specialised-technologies)

### Key – Please use the colour key to advise if the technology meets the criteria

|  |  |
| --- | --- |
| Met  | There is clear and strong evidence that the criterion is met |
| Not met | There is some, but not enough clear evidence that the criterion is met or There is no evidence or limited evidence that the criterion is met.  |

MA wording: Belzutifan for the treatment of adult patients with 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

Previous MA wording (for clarity only): Belzutifan for the treatment of von Hippel-Lindau disease-associated clear cell renal carcinoma. (as per company response sent to TS in February 2021, also indication noted on sps on 11 May 2022: <https://www.sps.nhs.uk/medicines/belzutifan/> and scoping report, where the mini workshop took part 30 July 2021)

| **Number** | **Criterion** | **Description of how the technology meets the criteria**  | **Does the technology meet the criteria?** |
| --- | --- | --- | --- |
|  | The disease is very rare defined by 1:50,000 in England  | The disease in the anticipated marketing authorisation is ‘von Hippel-Lindau disease’ (VHL) – a genetic condition characterised by blood vessel growth in various areas of the body. Its use is expected to be related to three tumour types, which are associated with VHL. For this criterion, the disease is VHL, as the genetic condition targeted by the therapy. VHL has a penetrance of 87% by age 60 in one study4 – meaning there are people with diagnosed VHL who do not have manifestations. This complicates interpretation of prevalence data.As per scoping report from August 2021, the prevalence of VHL in the EU is approximately 0.3 per 10,000, which is about 1,300 adults in England (1.5 per 50,000). This data has been taken from the European medicines agency (EMA)1. The company considers that a new study showed that the prevalence is lower, of between 1 in 77,340 to 1 in 68,493 in England, according to Maher *et al.*2 This would equate to approximately 620 people.The company have provided a non-systematic literature review that shows a wide range of prevalence estimates. The estimates span the range that includes 1:50,000 patients in England. Therefore, there is some evidence this criterion would be met, but uncertainty around the total number of people with VHL in England. | Not met |
|  | Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications  | The total number of people with VHL is estimated to be 1300 using the EMA estimate or 620 as per the estimate provided by the company using the Maher et al study.Using the refined MA wording, to be eligible for belzutifan, people must have VHL disease and as one of the tumours (renal cell carcinoma, central nervous system hemangioblastomas or pancreatic neuroendocrine tumours) and not suitable for localised procedures, such as surgery.* 46% of people with VHL have one of the three tumours, although this is likely to be an overestimate as some people with VHL will have more than one tumour at the same time. This percentage is based on the audit published by Maher *et al*.
* 20% of the patient population are ineligible for localised treatment, such as surgery (based on clinical feedback the company has requested).

This leads to an estimate of between 120 to 55 people eligible for treatment.Despite uncertainties with eligibility for localised treatment and total population, it is likely that less than 300 people will be eligible for treatment with belzutifan in this indication and therefore the criterion is met. | Met |
|  | The very rare disease for which the technology is indicated significantly shortens life or severely impairs quality of life  | Onset of symptomatic VHL disease typically starts by age 40, with childhood onset being rare. Most often, onset starts in late teens or twenties. However, some people with VHL only develop complications in their fifties or sixties.3 VHL disease presentation and severity is heterogeneous amongst patients and the organs affected. The natural course of VHL disease can range from asymptomatic or effective surgery, to multisystemic tumour growth, loss of organs and potential metastatic disease. Active clinical monitoring of people with VHL disease is effective, which means that in most cases VHL disease is managed effectively. The technology is indicated only if localised procedures are unsuitable or undesirable.For the indicated population, those whom localised procedures are unsuitable or undesirable, quality of life may be considered similar to patients with end stage renal disease, patients with full or partial pancreatectomy (including diabetes) or symptomatic CNS tumours for the indicated tumours, although tumours may be present in multiple organs simultaneously.For the indicated population, there may be highly heterogeneous life expectancy and quality of life dependent on tumour site, other available treatments and age when localised procedures are unsuitable.Because of this wide range of potential symptom burden and organ sites affected, it is uncertain how much VHL disease in the indicated population would shorten life expectancy and quality of life. | Not met |
|  | There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options. | Treatment options for those for whom localised procedures are unsuitable or undesirable are listed by each tumour type:* RCC – patients with RCC would have a full nephrectomy – this is similar to end stage renal disease and would require dialysis if both kidneys are affected.
* pNET – patients with pNET would have partial or full pancreatectomy – the Whipple procedure would be used for distal parts of the pancreas. Otherwise, loss of the pancreas would result in diabetes and other morbidities.
* CNS tumours – most patients with CNS tumours are asymptomatic. When surgery is inappropriate, stereotactic radiosurgery is used. This may be considered a localised procedure.

For RCC and pNET, there are treatment options that do not preserve organ function but still have potential for quality of life comparable to other diseases. There are limited treatment options for CNS if surgery and radiosurgery are unsuitable. There are also further treatment options available if the disease progresses to metastatic disease, none of which were appraised under HST criteria.  | Not met |

**References**

1 European Medicines Agency. EU/3/20/2324: Orphan designation for the treatment of von Hippel-Lindau disease. Sci. Med. Heal. 2022. https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3202324#about-section (accessed May 23, 2022).

2 Maher ER, Adlard J, Barwell J, *et al.* Evaluation of tumour surveillance protocols and outcomes in von Hippel-Lindau disease in a national health service. *Br J Cancer* 2022; **126**: 1339–45.

3 Oxford University Hospitals NHS Trust. Von Hippel-Lindau disease - An information leaflet for patients and families. Oxford Reg. Genet. Dep. 2014; : 1–8.

4 Binderup MLM, Jensen AM, Budtz-Jørgensen E, Bisgaard ML. Survival and causes of death in patients with von Hippel-Lindau disease. *J Med Genet* 2017; **54**: 11–8.

5 Wilding A, Ingham SL, Lalloo F, *et al.* Life expectancy in hereditary cancer predisposing diseases: an observational study. *J Med Genet* 2012; **49**: 264–9.

6 Office for National Statistics. Regional outlook of life expectancy in England. Life Expect. local areas UK between 2001 to 2003 2017 to 2019. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/lifeexpectancyforlocalareasoftheuk/between2001to2003and2017to2019#regional-outlook-of-life-expectancy-in-england (accessed May 23, 2022).

7 Feletti A, Anglani M, Scarpa B, *et al.* Von Hippel-Lindau disease: an evaluation of natural history and functional disability. *Neuro Oncol* 2016; **18**: 1011–20.

8 Lammens CRM, Bleiker EMA, Verhoef S, *et al.* Psychosocial impact of Von Hippel-Lindau disease: levels and sources of distress. *Clin Genet* 2010; **77**: 483–91.

9 National Institute for Health Research (NIHR). Belzutifan for von Hippel-Lindau diseaseassociated clear cell renal cell carcinoma – first line. 2021; 1–7.

10 Woltering N, Albers A,Müther M, Stummer W, Paulus W, Hasselblatt M,et al. DNA methylation profiling of centralnervous system hemangioblastomas identifies twodistinct subgroups. *Brain Pathology*. 2022; e13083. https://onlinelibrary.wiley.com/doi/10.1111/bpa.13083

11 Naber MR, Ahmad S, Verrijn Stuart AA, Giles RH, Valk GD, van Leeuwaarde RS. Is There a Role for Biomarkers in Surveillance of Pancreatic Neuroendocrine Neoplasms in Von Hippel-Lindau Disease? *J Endocr Soc.* 2021; Dec **22**;6(2)