PI

THE FIRST AND ONLY LICENSED SYSTEMIC THERAPY

FOR ADULTS WITH CERTAIN VHL-ASSOCIATED TUMOURS[1-4]

WELIREG is indicated 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.[5]

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Merck Sharp & Dohme (UK) Limited (Tel: 0208 154 8000).

Intended for UK Healthcare Professionals only.
For Prescribing Information, click the PI button located on each slide.
Refer to the Summary of Product Characteristics and Risk Minimisation Materials before prescribing to help minimise the risks associated with treatment.

MSD

GB-BEL-00077 I January 2025

WELIREG® (belzutifan)

VHL is a rare, genetic disease associated with an increased risk of developing certain tumours[6,7]

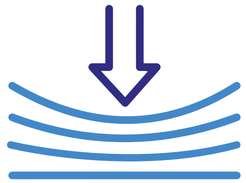
Caused by a mutation in the VHL gene[8]

Cells grow unchecked, and mutate more easily vs. no mutation[8]

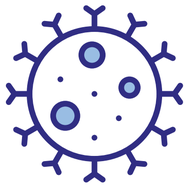
People with VHL are prone to developing certain tumours[8]

Tumours may cause pain and significant morbidity depending on mass and location, while surgical intervention may be associated with operative/post-operative complications[9,10]

Tumours can grow in **several different sites** at the same time[11]



Most tumours are **benign**. They can cause **pressure on surrounding tissues** as they grow[9]



Some tumours can become **cancerous**. Especially those that grow in the kidneys and pancreas[9]

VHL: von Hippel-Lindau disease.

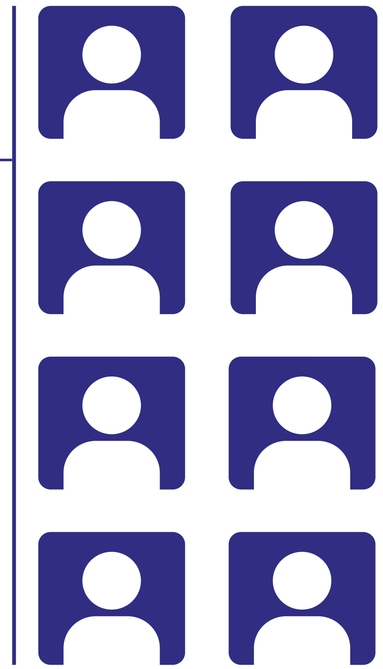
A known family history of VHL can affect the path to diagnosis[12]

Inheritance is autosomal dominant:
Children of affected parents have a 50/50 chance of also being affected[13]

80%

of people with VHL have a **known family history**[14]

- **Children** of affected parents receive **genetic service input and surveillance from an early age**[15]
- For most people, **surveillance** begins **prior to manifestation onset**[15]
- **Attitudes and acceptance** of surveillance **and treatment** can be affected by observing family member experiences[16]



20%

of people with VHL are **de novo** cases with NO known family history[14]

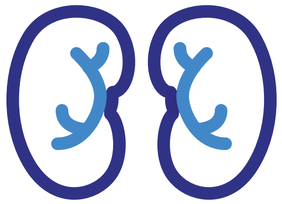
- May experience a **diagnostic delay** following the onset of VHL manifestations[12,17]
- **Diagnostic lag** can be affected by the **type and location of tumours** and **clinician awareness** of VHL[12,17]
- May require **intensive surgery** to remove dozens of tumours in a single operation[18]

VHL: von Hippel-Lindau disease.

VHL is a rare disease, affecting ~1 in 69,000 people in the UK[5,6] and tumours often develop in the third decade of an affected person's life[7,19,20]

Males, females, and all ethnic groups are EQUALLY affected[6]

Multiple generations of families are likely to be affected[13]

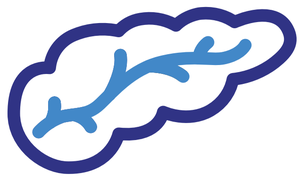


Up to 70% Are affected by **renal cell carcinoma** by 60 years of age[7]

Median age of onset: **31 years**[19]

Up to 80% Are affected by **CNS haemangioblastomas**[7]

Mean age of onset: **33 years**[7]

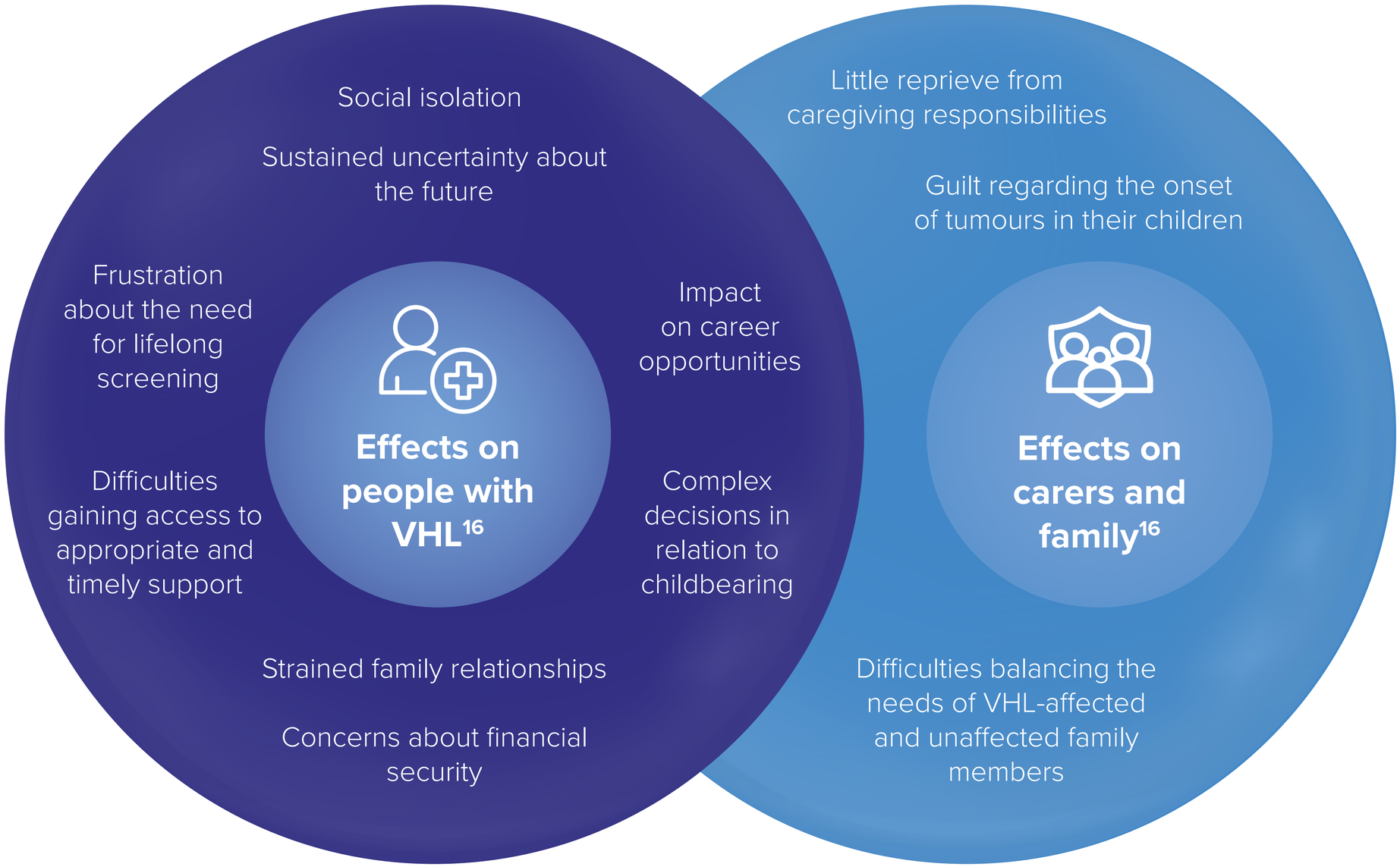


Up to 18% Are affected by **pNET**[20]

Mean age of onset: **35 years**[20]

CNS: central nervous system, pNET: pancreatic neuroendocrine tumour.

People with VHL, and their families, experience a range of emotional, social, and practical challenges[16]



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

VHL: von Hippel-Lindau disease.

Management of VHL disease involves lifelong surveillance and repeat surgical interventions where required[18]

Example of a typical surveillance schedule[21,22]

Retinal angioma screening

Annual ophthalmic examinations, beginning in **infancy or early childhood**

CNS haemangio-blastoma screening

Head MRI scans every **12–36 months,** beginning in **adolescence**

RCC & pancreatic tumour screening

Annual abdominal MRI (or ultrasound), beginning from the age of **16 years**

Phaeochro-mocytoma screening

Annual blood pressure monitoring and 24-hour urine studies for catecholamine metabolites

More intense surveillance in families considered at high risk

Active surveillance requires significant healthcare resource, co-ordination, and incurs a quality-of-life burden on people with VHL and their families[15,16,23]

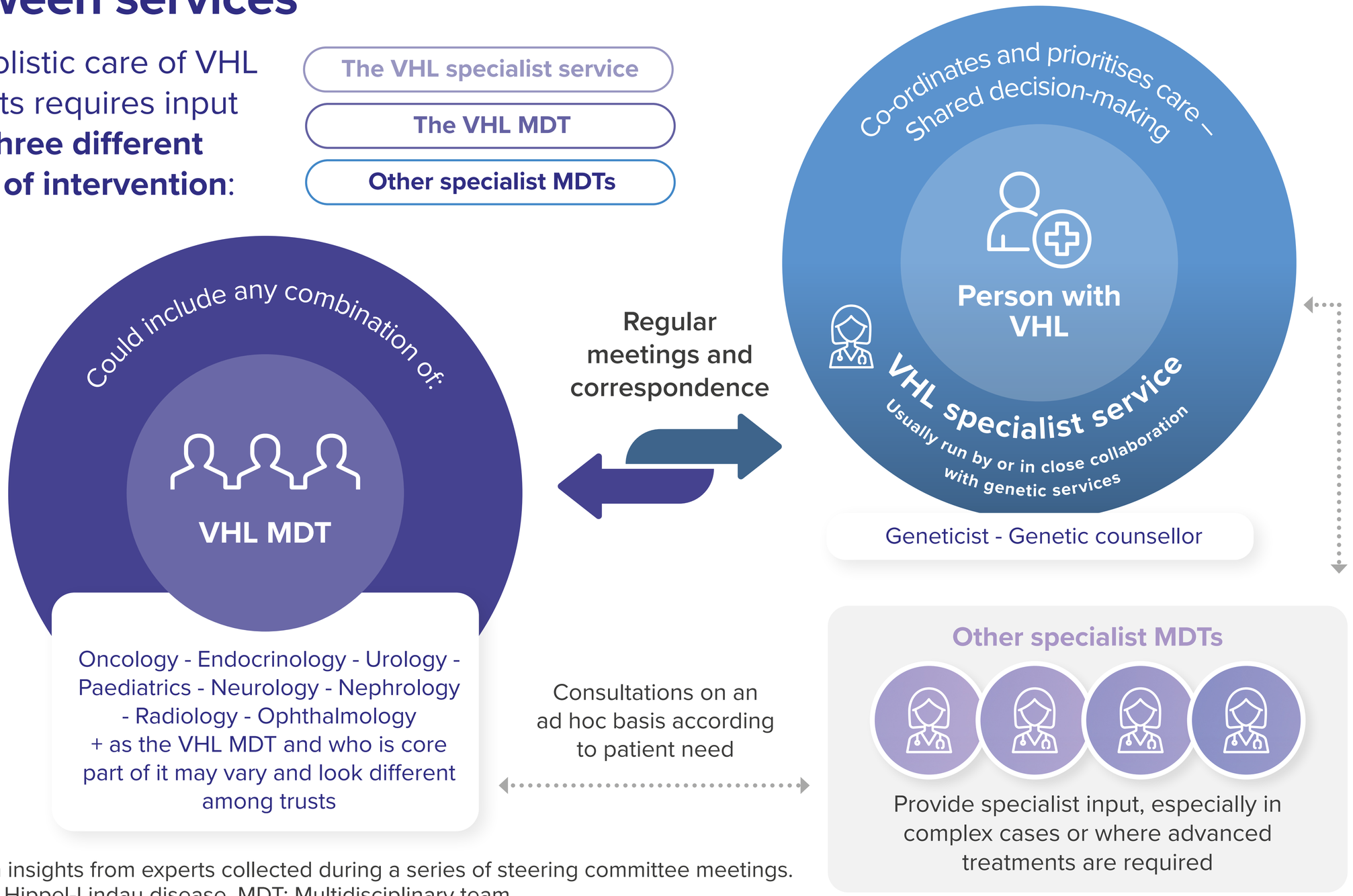
WELIREG is indicated for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for VHL associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumours (pNET), and for whom localised procedures are unsuitable or undesirable.[5] It should not be used for any other tumour types.

VHL: von Hippel-Lindau disease, MRI: magnetic resonance imaging, CNS: central nervous system, RCC: renal cell carcinoma.

VHL specialist services in the UK are mostly multidisciplinary and genetic service-led, but there is a large range of variation between services[15]

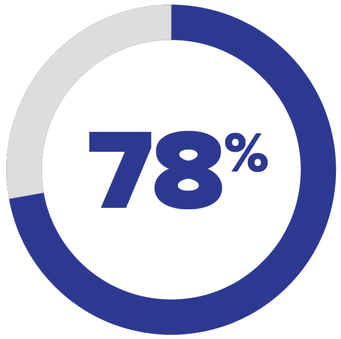
The holistic care of VHL patients requires input from **three different levels of intervention**:

- The VHL specialist service
- The VHL MDT
- Other specialist MDTs



Based on insights from experts collected during a series of steering committee meetings.
VHL: von Hippel-Lindau disease, MDT: Multidisciplinary team.

People with VHL often require repeated surgeries – and each one can take its toll[18,24]



of people with VHL with renal cell carcinoma, pancreatic neuroendocrine tumours, or CNS haemangioblastomas had **experienced multiple surgeries**[24]

The interval between surgeries in some people with VHL[18]

EROSION OF FUNCTION

Surgical resection may lead to **impairment or removal of the entire organ**[12,25]
Pancreatectomy for pNET can result in **absolute insulin deficiency requiring lifelong insulin therapy**[25]

Repeated surgeries can have a
QUALITY OF LIFE IMPACT
Including:[24]


Fatigue


Mental health


Ability to live daily life

VHL: von Hippel-Lindau disease, CNS: central nervous system, pNET: pancreatic neuroendocrine tumour.

~50% selected 'reduce the number of surgeries' as the top treatment goal in a survey of 220 people with VHL[24]

73% would prefer to take a pill which would possibly delay the time until surgery, rather than watch and wait to see if the tumor would grow[24*]

Some people have **inoperable tumours,** or surgery would result in catastrophic injury[25]

There is a need for an **licensed systemic therapy for people with certain VHL-associated tumours where surgery is unsuitable or undesirable**

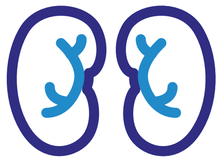
WELIREG is indicated for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for VHL associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumours (pNET), and for whom localised procedures are unsuitable or undesirable.[5]

*Based on survey of people with VHL (n=220; RCC 66.4%, pNET 55.5%, and/or CNS haemangioblastomas 86.4%), presented two scenarios "watch and wait" and potentially need surgery, or "take a once-daily pill" to delay a potential surgery.[24]

WELIREG® (belzutifan) is the FIRST and ONLY licensed systemic therapy for adults with certain VHL-associated tumours[1]

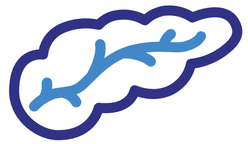
Indication:

WELIREG is indicated for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for VHL-associated:[5]



renal cell carcinoma

CNS haemangioblastomas



pancreatic neuroendocrine tumours

and for whom localised procedures are unsuitable or undesirable[5]

Mechanism of action:

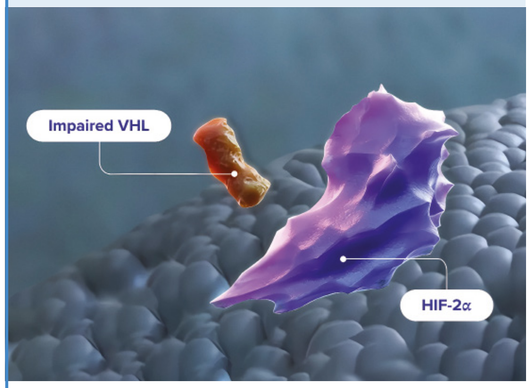
WELIREG is a selective HIF-2α inhibitor, which reduces the transcription of certain target genes associated with tumour growth[5]

CNS: central nervous system, HIF-2α: hypoxia-inducible factor 2α.

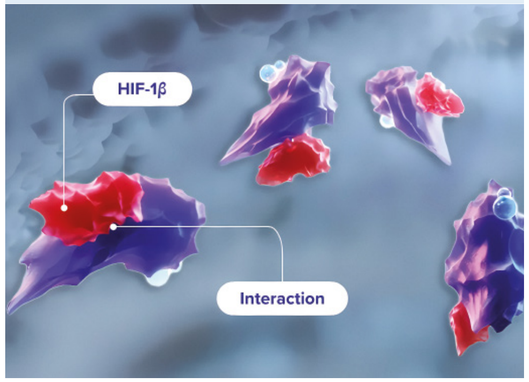
WELIREG is an inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α)[5]

Under normal oxygen levels, HIF-2α is targeted for ubiquitin-proteasomal degradation by VHL protein[5]

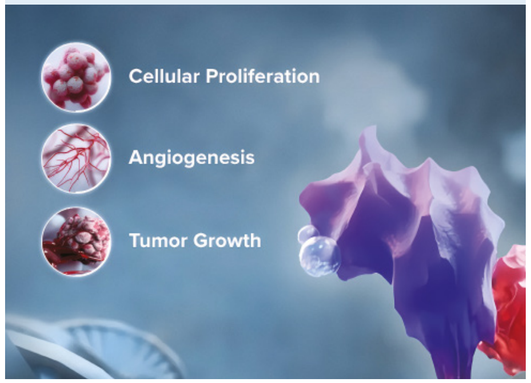
Lack of functional VHL protein results in accumulation of HIF-2α



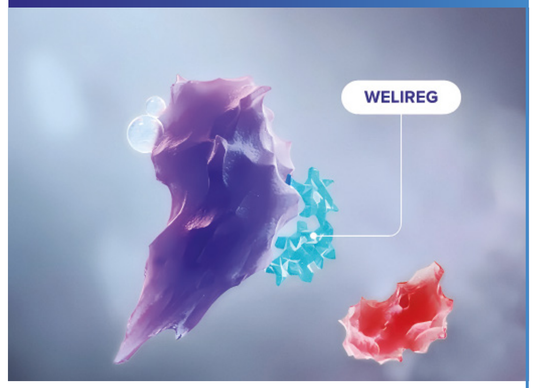
Upon stabilisation, HIF-2α translocates into the nucleus and interacts with hypoxia-inducible factor 1 beta (HIF-1β) to form a transcriptional complex



This regulates expression of downstream genes, including genes associated with cellular proliferation, angiogenesis, and tumour growth



WELIREG blocks HIF-2α–HIF-1β interaction, leading to reduced expression of target genes associated with cellular proliferation, angiogenesis, and tumour growth



WELIREG binds to HIF-2α and, in conditions of hypoxia or impairment of VHL protein function, blocks HIF-2α–HIF-1β interaction

LITESPARK-004 is an ongoing Phase 2, open-label, single-arm clinical trial which evaluated WELIREG in adult patients with VHL-disease associated RCC (N=61) who did not require immediate surgery[26]

61 patients with VHL-associated RCC*

50 also had CNS haemoangioblastomas
22 also had pNET

Treatment

40 mg | 40 mg | 40 mg

Belzutifan 120 mg once daily, continued until:

Patients were evaluated radiologically approximately 12 weeks after initiation of treatment and every 12 weeks for a minimum of 3 years, then every 24 weeks thereafter[26-28]

Unacceptable toxicity
OR
Disease progression

Primary endpoint:[26]

- Objective response rate (ORR) in VHL disease-associated RCC†

Secondary endpoints:[26]

- Duration of response (DOR)
- Time to response (TTR)
- Progression-free survival (PFS)

Other secondary endpoints:[26]

- ORR in CNS hemangioblastomas†
- ORR in pNETs†
- Safety of WELIREG

*≥1 measurable solid tumour localised to the kidney as defined by response evaluation criteria in RECIST v1.1. †Per RECIST v1.1 as assessed by IRC. ORR: Complete response defined as disappearance of all target and nontarget lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm. Partial response defined as ≥30% decrease in the sum of the longest diameters of target lesions compared with baseline. 95% CIs for ORR in RCC and non-RCC neoplasms were calculated using the 2-sided Clopper-Pearson method. The effect of intermittent use and long treatment interruptions of belzutifan have not been evaluated

IRC: Independent review committee, ORR: Objective response rate, RCC: renal cell carcinoma, VHL: von Hippel-Lindau disease, CNS: Central nervous system, pNET: pancreatic neuroendocrine tumour.

LITESPARK-004 is an ongoing Phase 2, open-label, single-arm clinical trial which evaluated WELIREG in adult patients with VHL-disease associated RCC (N=61) who did not require immediate surgery[26]

Key eligibility criteria:[5,26]

- **VHL disease diagnosis** based on germline alteration
- ≥ **1** measurable **RCC tumour**
- **No** prior **systemic anticancer therapy**
- **No metastatic** disease
- ECOG PS 0 or 1
- **No major surgical procedure** within 4 weeks before study enrolment
- **No major cardiovascular event** within 6 months before WELIREG administration

Baseline trial characteristics:[26]

41 years
Median age (range 19-66)

52%
Male

82%
ECOG PS 0

75% had prior RCC surgery

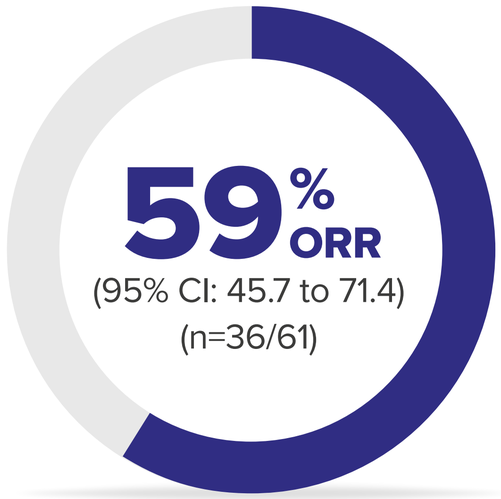
2.2 cm median size of RCC target lesions

ECOG PS: Eastern Co-operative Oncology Group Performance Status, RCC: Renal cell carcinoma.

WELIREG reduced tumour size in VHL disease–associated RCC at a median follow up time of 29.2 months (range 4.2 - 37.5)[5]

Primary efficacy endpoint:[5]

Best overall RCC tumour response (N=61)



Secondary efficacy endpoints (N=61):[5]

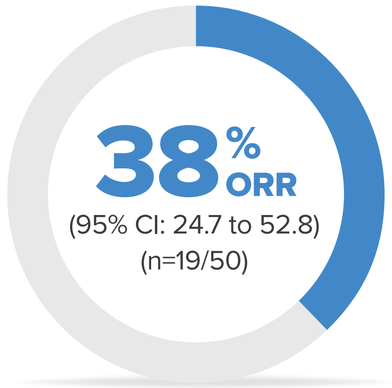
Median DOR was not reached
(range: 36.1 to 119.9 weeks)

Median TTR from 46.7 weeks
(range: 11.6 to 96.6 weeks)

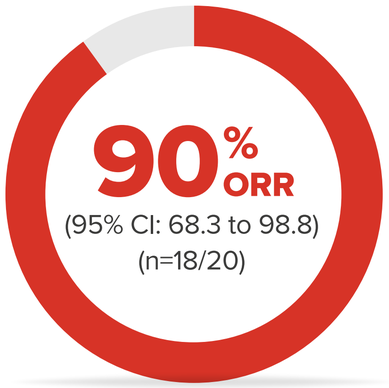
Median PFS not estimated*
(24-month PFS rate 94.6%)

Other efficacy endpoints:[5]

Best CNS haemangioblastoma response (N=50)



Best pNET response (N=20)



Best objective response. Median follow-up range was 4.2 to 37.5 months.

*Reliable median could not be estimated due to the number of progression events (n=7) and a progression event that occurred at the latest timepoint when only 1 patient was at risk.

RCC: renal cell carcinoma, CNS: central nervous system, pNET: pancreatic neuroendocrine tumour, CI: confidence interval, ORR: objective response rate, DOR: Duration of response, TTR: Time to response, PFS: Progression-free survival.

All patients reported at least one treatment-related adverse event[26]

At a median follow up of 29.2 months (median duration of exposure 28.9 months, range: 1.9 to 37.5):[5]

The most common adverse reactions with WELIREG were anaemia (90%), fatigue (71%), dizziness (44%) and nausea (36%)[5]

- **Most common Grade 3 or 4** adverse reactions were anaemia (10%), and fatigue (5%)[5]

- **Serious** adverse reactions occurred in 5% of patients who received WELIREG, including anaemia, dyspnoea and hypoxia (1 patient each)[5]

- **Dose interruption** of WELIREG due to adverse reactions occurred in 23% of patients
- Most common adverse reactions resulting in dose interruption; fatigue (13.1%), nausea (8.2%), anaemia (4.9%)[5]

- **Dose reduction** of WELIREG due to adverse reactions occurred in 11.5% of patients
- Adverse reactions resulting in dose reduction; fatigue (8.2%), anaemia (1.6%), hypoxia (1.6%)[5]

Grade 3 anaemia occurred in 9.8%. Three (4.9%) participants had anaemia events leading to study drug interruption and 1 participant (1.6%) had a dose reduction due to anaemia. 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.[5]

The case of hypoxia occurred within 2 months of treatment initiation in a patient with previously undiagnosed restrictive lung disease and was asymptomatic. The patient did not receive supplemental oxygen and was managed with dose reduction to 80 mg once daily with no recurrence of hypoxia.[5]

Adverse reactions reported in clinical studies of WELIREG

The safety of WELIREG was evaluated in a Phase 1 clinical study, in 58 patients with non-VHL disease-associated advanced solid tumours (median duration of exposure 25.4 weeks, range: 1.1 to 145.9 weeks), and an open-label Phase 2 clinical study, in 61 patients with VHL disease-associated RCC and who did not require immediate nephrectomy or partial nephrectomy duration of exposure 28.9 months, range: 1.9 to 37.5). Patients were treated with WELIREG 120 mg once daily.[5]

Adverse Drug Reaction	All Grades	Grades 3-4
Blood and lymphatic disorders		
Anaemia	Very common	Common
Nervous system disorders		
Dizziness	Very common	Very rare
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	Very common	Common
Hypoxia	Common	Common
Gastrointestinal disorders		
Nausea	Very common	Very rare
General disorders and administration site disorders		
Fatigue	Very common	Common
Investigations		
Weight Increased	Very common	Common

Frequencies defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), and very rare (< 1/10,000).

Special warnings and precautions for use

Always refer to the WELIREG Summary of Product Characteristics before prescribing

Anaemia due to decreased erythropoietin[5]

- Anaemia occurred very commonly in patients receiving WELIREG
- Patients should be monitored for anaemia before initiation of and periodically throughout treatment with more frequent monitoring within the first 6 months of treatment
- For patients who develop Grade 3 anaemia (Hb <8 g/dL), WELIREG should be withheld and patients should be treated according to standard medical practice, including ESA administration until resolved to ≤ Grade 2 (Hb ≥8 g/dL). For recurrent Grade 3 anaemia, WELIREG should be discontinued. For patients who develop Grade 4 anaemia, the dose of WELIREG should be reduced or permanently discontinued

Hypoxia[5]

- WELIREG 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 WELIREG with more frequent monitoring within the first 6 months of treatment. In light of the risk of hypoxia, smoking cessation is recommended
- For Grade 2 hypoxia, providing supplemental oxygen and continuing or withholding treatment should be considered. If withheld, WELIREG should be resumed at a reduced dose. For patients who have Grade 3 hypoxia, WELIREG 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 WELIREG must be given the patient alert card

Special warnings and precautions for use

Always refer to the WELIREG Summary of Product Characteristics before prescribing

Embryo-foetal toxicity[5]

- Based on findings in animals, WELIREG may cause foetal harm, including foetal loss, in humans
- In a rat study, WELIREG 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 WELIREG and for 1 week after the last dose, since WELIREG can render some hormonal contraceptives ineffective
- Advise male patients and their female partners of reproductive potential to use highly effective contraception during treatment with WELIREG 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 WELIREG and 1 week after the last dose

Special populations

Always refer to the WELIREG Summary of Product Characteristics before prescribing

Elderly (≥ 65 years old)[5]	• No dose adjustment is recommended for elderly patients. There are limited data available on the use of WELIREG in patients aged 65 years and over
Renal impairment[5]	• No dose adjustment of WELIREG is recommended in patients with mild or moderate renal impairment (eGFR ≥ 30 mL/minute/1.73 m^2). WELIREG has not been studied in patients with severe renal impairment
Hepatic impairment[5]	• No dose adjustment of WELIREG is recommended in patients with mild hepatic impairment. WELIREG has not been studied in patients with moderate or severe hepatic impairment
Paediatric population[5]	• The safety and efficacy of WELIREG in children less than 18 years of age has not yet been established. No data are available

Contraindications and family planning

Always refer to the WELIREG Summary of Product Characteristics before prescribing

Contraindications[5]	• Hypersensitivity to the active substance or to any of the excipients
Fertility, pregnancy and lactation[5]	• There are no data from the use of WELIREG in pregnant women. Studies in animals have shown reproductive toxicity. WELIREG is not recommended during pregnancy and in women of childbearing potential not using contraception • It is unknown whether WELIREG or its metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with WELIREG and for 1 week after the last dose • The pregnancy status of females of reproductive potential should be verified prior to initiating treatment with WELIREG • WELIREG may cause embryo-fetal harm, including fetal loss, when administered to a pregnant woman • Females of reproductive potential should be advised to use highly effective contraception during treatment with WELIREG and for at least 1 week after the last dose. Use of WELIREG 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 WELIREG • Male patients and their female partner of reproductive potential should be advised to use highly effective contraception during male patient treatment with WELIREG and for at least 1 week after the last dose. Advise male patients with female partners who are pregnant to use barrier method of contraception during treatment with WELIREG and 1 week after the last dose • Based on findings in animals, WELIREG 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

Drug interactions

Always refer to the WELIREG Summary of Product Characteristics before prescribing

CYP3A4 substrates[5]	• Coadministration of WELIREG 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 WELIREG 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 WELIREG with hormonal contraceptives may lead to contraceptive failure or an increase in breakthrough bleeding
Inhibitors of UGT2B17 or CYP2C19[5]	• Co-administration of WELIREG with inhibitors of UGT2B17 or CYP2C19 increases plasma exposures of WELIREG, which may increase the incidence and severity of adverse reactions of WELIREG. Monitor for anaemia and hypoxia and reduce the dosage of WELIREG as recommended

WELIREG is taken as a once daily oral dose[5]

The recommended dose of WELIREG is 120 mg (three 40-mg tablets) once daily until disease progression or unacceptable toxicity[5]

Not actual size.

WELIREG should be taken at the same time each day and may be taken with or without food.[5]

Swallowed whole, not chewed.[5]

WELIREG should not be chewed, crushed or split prior to swallowing.

Missed doses can be taken as soon as possible on the same day.[5]

Regular daily dosing should be resumed the next day.

Extra tablets should not be taken to make up for a missed dose.

If vomiting occurs any time after taking WELIREG, the dose should not be retaken.[5]

The next dose should be taken on the next day.

*Dose should be reduced if certain adverse effects occur. Always refer to the SmPC before prescribing WELIREG.

Adverse reactions associated with WELIREG can be managed with recommended dose modifications[5]

Adverse reaction	Severity*	Dose modification
Anaemia	**Grade 3: Haemoglobin (Hgb < 8g /dL) transfusion indicated**	• Withhold until resolved to ≤ Grade 2 (Hb ≥ 8 g/dL) • Resume at a reduced dose (reduce by 40 mg) or discontinue depending on the severity and persistence of anaemia
	Grade 4: Life-threatening or urgent intervention indicated	• Withhold until resolved to ≤ Grade 2 (Hb ≥ 8 g/dL) • Resume at a reduced dose (reduce by 40 mg) or permanently discontinue
Hypoxia	**Grade 2: Decreased oxygen saturation with exercise (e.g. pulse oximeter < 88%) intermittent supplemental oxygen**	• Consider withholding until resolved • Resume at the same dose or at a reduced dose depending on the severity of hypoxia
	Grade 3: Decreased oxygen saturation at rest (e.g. pulse oximeter <88% or PaO^2 ≤55 mm Hg)	• Withhold until resolved to ≤ Grade 2 • Resume at reduced dose (reduce by 40 mg) or discontinue depending on the severity and persistence of hypoxia
	Grade 4: Life-threatening	• Permanently discontinue
Other Adverse Reactions	**Grade 3**	• Withhold dosing until resolved to ≤ Grade 2 • Consider resuming at a reduced dose (reduce by 40 mg) • Permanently discontinue upon recurrence of Grade 3
	Grade 4	• Permanently discontinue

*Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

WELIREG is accepted for use in the NHS in England and Wales[25,29]

NICE

WELIREG is recommended with managed access as an option for treating von Hippel-Lindau (VHL) disease in adults:[25]

- 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.

AWMSG

The NICE recommendation will apply in Wales.[29]

WELIREG is accepted for use in the NHS in Scotland[4]

SMC

"**Belzutifan (Welireg®)** is accepted for use within NHS Scotland.

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."[4]

The SMC used data cut-off at 1st April 2022, with a median follow-up of 37.7 months.

VHL is a **rare, genetic disease associated with an increased risk of developing certain tumours**[6,7]

People with VHL need **lifelong surveillance** and often require **repeated surgeries** – and each one can take its toll[18,24]

Until now, there have been **no licensed systemic therapies** for people with certain VHL-associated tumours[18]

WELIREG reduced tumour size in people with VHL disease-associated RCC, CNS haemangioblastoma, or pNET[5]

At a median follow-up time of 29.2 months (range 4.2 - 37.5)

59%
RCC objective response rate[5]
(95% CI: 45.7 to 71.4, n=36/61)

38%
CNS haemangioblastoma objective response rate[5]
(95% CI: 24.7 to 52.8, n=19/50)

90%
pNET objective response rate[5]
(95% CI: 68.3 to 98.8, n=18/20)

A **once daily oral treatment**[5]

Three tablets per dose, once daily[5]

Not actual size.

Dose modifications are applicable to manage certain adverse reactions including adjustments and interruptions*[5]

WELIREG is indicated for:

Adult patients with von Hippel-Lindau disease who require therapy for:[5]
- von-Hippel-Lindau associated renal cell carcinoma, OR
- von-Hippel-Lindau associated central nervous system haemangioblastomas, OR
- von-Hippel-Lindau associated pancreatic neuroendocrine tumours

AND for whom localised procedures are unsuitable or undesirable

The most common adverse reactions with WELIREG at median follow-up of 29.2 months (median duration of exposure 28.9 months, range 1.9 to 37.5) were anaemia (90%), fatigue (71%), dizziness (44%) and nausea (36%).[5] There are special warnings and precautions of use in anaemia, hypoxia and embryofoetal toxicity.[5]* Always refer to the SmPC before prescribing WELIREG.

*Dose should be reduced if certain adverse effects occur. See the Summary of Product Characteristics for full details.
VHL: von Hippel-Lindau disease, RCC: renal cell carcinoma, CNS: central nervous system, pNET: pancreatic neuroendocrine tumours, CI: confidence intervals.

Would you like to stay up to date with the **latest information on WELIREG?**

Joining our WELIREG network can help you to:

- Stay informed about the latest news and data on WELIREG
- Support your clinical practice with tailored educational materials
- Receive exclusive invitations to practical, peer-driven events and meetings

Sign up to our mailing list now by scanning the QR code
or **clicking here**

This link will take you to an MSD website to give your consent to receive marketing or promotional emails from MSD about our products, services and events.

References

1. Narayan V, *et al.* Systemic therapy development in Von Hippel-Lindau disease: an outsized contribution from an orphan disease. *Cancers (Basel).* 2022;**14**(21)
2. Center for Drug Evaluation and Research. Advancing health through innovation: New Drug Therapy Approvals 2021. 2022. Available from: https://www.fda.gov/media/155227/download. [Accessed November 2024]
3. MHRA. First Innovation Passport awarded to help support development and access to cutting-edge medicines. 2021. Available from: https://www.gov.uk/government/news/first-innovation-passport-awarded-to-help-support-development-and-access-to-cutting-edge-medicines. [Accessed November 2024]
4. SMC. Belzutifan (Welireg). 2023. Available from: https://www.scottishmedicines.org.uk/medicines-advice/belzutifan-welireg-full-smc2587/. [Accessed November 2024]
5. MSD (UK) Ltd. WELIREG SmPC
6. NORD. Von Hippel-Lindau Disease. 2021. Available from: https://rarediseases.org/rare-diseases/von-hippel-lindau-disease/. [Accessed November 2024]
7. Varshney N, *et al.* A review of Von Hippel-Lindau syndrome. *J Kidney Cancer VHL.* 2017;**4**(3):20-29
8. Johns Hopkins Medicine. Von Hippel-Lindau (VHL). 2024. Available from: https://www.hopkinsmedicine.org/health/conditions-and-diseases/von-hippellindau-vhl. [Accessed November 2024]
9. VHL Alliance. What is VHL? 2023. Available from: https://www.vhl.org/care-treatment/what-is-vhl/. [Accessed November 2024]
10. Rednam SP, *et al.* Von Hippel–Lindau and Hereditary Pheochromocytoma/Paraganglioma syndromes: Clinical features, genetics, and surveillance recommendations in childhood. *Clin Cancer Res.* 2017;**23**(12):e68-e75
11. Gläsker S, *et al*. Von Hippel-Lindau Disease: Current Challenges and Future Prospects. *Onco Targets Ther.* 2020;**13**:5669-5690
12. Binderup ML, *et al.* von Hippel-Lindau disease: Updated guideline for diagnosis and surveillance. *Eur J Hum Genet.* 2022;**65**(8):104538
13. van Leeuwaarde RS, *et al.* Von Hippel-Lindau Syndrome. In: Adam M, *et al.* (eds.). GeneReviews®. Seattle (WA): 2023; chapter Available from: https://www.ncbi.nlm.nih.gov/books/NBK1463/ [Accessed November 2024]
14. Nielsen SM, *et al.* Von Hippel-Lindau Disease: Genetics and role of genetic counseling in a multiple neoplasia syndrome. *J Clin Oncol.* 2016;**34**(18):2172-2181
15. Maher ER, *et al*. Evaluation of tumour surveillance protocols and outcomes in von Hippel-Lindau disease in a national health service. *Br J Cancer.* 2022;**126**(9):1339-1345
16. Kasparian NA, *et al.* Through the looking glass: an exploratory study of the lived experiences and unmet needs of families affected by Von Hippel–Lindau disease. *Eur J Hum Genet.* 2015;**23**(1):34-40
17. Binderup MLM, *et al.* Prevalence, birth incidence, and penetrance of von Hippel–Lindau disease (vHL) in Denmark. *Eur J Hum Genet.* 2017;**25**(3):301-307
18. Shepherd STC, *et al.* The road to systemic therapy in von Hippel-Lindau (VHL) disease: Are we there yet? *Eur J Cancer.* 2023;**182**:15-22
19. Feletti A, *et al.* Von Hippel-Lindau disease: an evaluation of natural history and functional disability. *Neuro Oncol.* 2016;**18**(7):1011-1020
20. Coco D, *et al.* Von Hippel-Lindau is Associated to Pancreatic Neuroendocrine Tumors: A Comprehensive Review. *J Kidney Cancer VHL*. 2023;**10**(2):13-20
21. Sandford D, *et al.* An audit of UK VHL surveillance clinic guidelines. 2018. Available from: https://vhl-uk-ireland.org/wp-content/uploads/2020/12/Dr-Sandford-Presentation.pdf. [Accessed November 2024]
22. Maher ER, *et al.* von Hippel-Lindau disease: a clinical and scientific review. *Eur J Hum Genet.* 2011;**19**(6):617-623
23. Jonasch E, *et al.* Epidemiology and economic burden of von Hippel-Lindau disease-associated renal cell carcinoma in the United States. *Clin Genitourin Cancer.* 2023;**21**(2):238-247
24. Sundaram M, *et al.* The impact of surgery on patients with VHL-associated tumors: An international patient survey. *J Clin Oncol.* 2023;**41**(16_suppl):4517-4517
25. NICE. Belzutifan for treating tumours associated with von Hippel-Lindau disease [TA1011]. 2024. Available from: https://www.nice.org.uk/guidance/ta1011. [Accessed November 2024]
26. Jonasch E, *et al.* Belzutifan for renal cell carcinoma in von Hippel–Lindau Disease. *NEJM.* 2021;**385**(22):2036-2046
27. Srinivasan R, *et al.* Belzutifan, a hypoxia-inducible factor-2α inhibitor, for von Hippel-Lindau Disease–associated neoplasms: long-term results of the phase 2 LITESPARK-004 study. American Association for Cancer Research Annual Meeting. 2024
28. Srinavasan R, *et al.* Belzutifan, a HIF-2a inhibitor, for von Hippel-Lindau disease-associated neoplasms: 36 months of follow-up of the Phase 2 LITESPARK-004 study. ESMO Congress 2022. Paris, France. 2022
29. AWMSG. Belzutifan (Welireg). 2023. Available from: https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/belzutifan-rybrevant/. [Accessed November 2024]