

Medicines Management Programme

Managed Access Protocol – Larotrectinib (Vitrakvi[®]) for the treatment of solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion

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List of abbreviations

ATP	Adenosine triphosphate
HSE	Health Service Executive
HTH	High Tech Hub
MAP	Managed Access Protocol
MMP	Medicines Management Programme
NCCP	National Cancer Control Programme
NGS	Next generation sequencing
NTRK	Neurotrophic tyrosine receptor kinase
PCRS	Primary Care Reimbursement Service
RNA	Ribonucleic acid
SACT	Systemic anti-cancer therapy
SmPC	Summary of Product Characteristics
TRK	Tropomyosin receptor kinase

1. Larotrectinib

Larotrectinib (Vitrakvi®) is an adenosine triphosphate (ATP)-competitive and selective tropomyosin receptor kinase (TRK) inhibitor. The target for larotrectinib is the TRK family of proteins inclusive of TRKA, TRKB, and TRKC that are encoded by the neurotrophic tyrosine receptor kinase (NTRK) genes NTRK1, NTRK2 and NTRK3, respectively. Larotrectinib inhibits the activation of these oncogenic TRK fusion proteins that form as a result of NTRK gene fusions, resulting in anti-tumour activity.

From 1 June 2023, three presentations of larotrectinib are available on the High Tech Arrangement:

- Vitrakvi® 25 mg hard capsules (56) ▼ⁱ
- Vitrakvi® 100 mg hard capsules (56) ▼
- Vitrakvi® 20 mg/ml oral solution (100 ml) ▼

The National Cancer Control Programme (NCCP) has developed national regimens for larotrectinib for adults and paediatric patients; these are available on the website of the NCCP:

<https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/tumour%20agnostic%20therapy/>.

1.1 Licensed indication

Larotrectinib (Vitrakvi®) received a conditional marketing authorisation valid throughout the European Union on 19 September 2019. It is licensed as monotherapy for the treatment of adult and paediatric patients with solid tumours that display a NTRK gene fusion

- who have disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
- who have no satisfactory treatment options.ⁱⁱ

1.2 Reimbursement

Reimbursement of larotrectinib on the High Tech Arrangement is supported only for the licensed indication as outlined in section 1.1; reimbursement is not supported for any other indication. Larotrectinib should be prescribed and administered as monotherapy in line with its licensed indication.

ⁱ ▼ This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

ⁱⁱ Please refer to the Summary of Product Characteristics for Vitrakvi® for full prescribing information.

Prescribers are required to apply for reimbursement approval on an individual patient basis. The *Larotrectinib (Vitrakvi®) Application Form* should be completed and sent by secure email to the Health Service Executive (HSE)-Medicines Management Programme (MMP) at mmp@hse.ie.

If a patient is recommended for reimbursement by the MMP, the high tech prescription for larotrectinib should be generated on the High Tech Hub (HTH). High tech prescriptions that are not hub generated for larotrectinib will not be eligible for reimbursement by the HSE-Primary Care Reimbursement Service (PCRS).

Table 1 outlines the licensed therapeutic dosage of larotrectinib (Vitrakvi®) for the treatment of adult and paediatric patients with solid tumours that display a NTRK gene fusion.

Table 1: Licensed therapeutic dosage of larotrectinib (Vitrakvi®) for the treatment of adult and paediatric patients with solid tumours that display a NTRK gene fusion

Patient population	Route	Licensed therapeutic dosage
Adults	Oral	100 mg twice daily*
Paediatric	Oral	100 mg/m ² twice daily (maximum of 100 mg per dose)*

*until disease progression or unacceptable toxicity occurs

Please refer to the Summary of Product Characteristics (SmPC) for Vitrakvi® and the NCCP national regimens for larotrectinib for further information on management of missed doses, and dose modifications for patients who experience adverse reactions.

Reimbursement is supported up to the maximum licensed dosage of 100 mg twice daily. See Section 3 for further details on Reimbursement Criteria - Continuation.

1.3 Reimbursement price

The reimbursement prices of the presentations of larotrectinib available on the High Tech Arrangement as of 1 June 2023 are outlined in table 2.

Table 2: Reimbursement codes and prices for the presentations of larotrectinib (Vitrakvi®) available on the High Tech Arrangement

Medicinal product (pack size)	Reimbursement	
	Code	Price
Vitrakvi® 25 mg hard capsules (56)	89281	€2,492.10
Vitrakvi® 100 mg hard capsules (56)	89282	€9,968.40
Vitrakvi® 20 mg/ml oral solution (100 ml)	89283	€3,560.14

A commercial-in-confidence arrangement is in place with the marketing authorisation holder to reduce the net acquisition cost of Vitrakvi® to the HSE.

2. Reimbursement criteria - Initiation

This section outlines the criteria that must be satisfied in order for an adult or paediatric patient to be recommended for reimbursement of larotrectinib under the High Tech Arrangement for the treatment of solid tumours that display a NTRK gene fusion.

2.1 Prescribers

The prescribing of larotrectinib under the High Tech Arrangement will be confined to consultant medical oncologists registered with the Irish Medical Council, who have agreed to the terms of this Managed Access Protocol (MAP) and who have been approved by the HSE.

Applications for reimbursement approval will only be considered from these prescribers.

2.2 Patient diagnosis: locally-advanced, metastatic or unresectable solid tumour

Clinicians are required to provide information to demonstrate that the patient has a histological diagnosis of a malignant solid tumour (i.e. a carcinoma, sarcoma, melanoma, brain or spinal cord tumour) and does not have a leukaemia, lymphoma or myeloma. The patient's tumour should be locally-advanced or metastatic, or require surgical resection that would likely result in severe morbidity.

2.3 NTRK gene fusion status

For reimbursement approval, clinicians are required to confirm that the patient has a documented NTRK 1, 2 or 3 gene fusion without a known acquired resistance mutation in the solid tumour, determined by a ribonucleic acid (RNA)-based next generation sequencing (NGS) test.

Clinicians are required to submit the result of the RNA-based NGS test at time of application.

The NCCP has developed NTRK gene fusion testing guidance, which is available on their website:

<https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/tumour%20agnostic%20therapy/ntrk-gene-fusion-testing-guidance.pdf>.

2.4 Patient clinical history/status

In line with the exclusion criteria from the LOXO-TRK-14001, SCOUT and NAVIGATE trials, the SmPC of Vitrakvi® and the NCCP national regimens for larotrectinib, applications for reimbursement approval of larotrectinib will not be considered in individuals who:

- have symptomatic or unstable brain metastases
- have clinically significant active cardiovascular disease
- are currently in receipt of treatment with a strong or moderate cytochrome P450 3A4/P-glycoprotein inducer and are unable to discontinue treatment prior to initiation of larotrectinib
- have active uncontrolled systemic bacterial, fungal or viral infection
- are pregnant or lactating
- have received prior treatment with any NTRK inhibitor
- have hypersensitivity to larotrectinib or any of the excipients in Vitrakvi®.

Applications for reimbursement approval of larotrectinib will be considered only for patients with good performance status, as defined in the LOXO-TRK-14001, SCOUT and NAVIGATE trials and outlined in the NCCP national regimens for larotrectinib.

In addition, patients should have adequate haematological, hepatic and renal function.

2.5 Place in therapy

The benefit of larotrectinib has been established in single arm trials encompassing a relatively small sample of patients whose tumours exhibit NTRK gene fusions. Favourable effects of larotrectinib have been shown on the basis of overall response rate and response duration in a limited number of tumour types. The effect may be quantitatively different depending on the tumour type, as well on the concomitant genetic alterations.

Reimbursement of larotrectinib on the High Tech Arrangement is supported for patients who have no satisfactory treatment options, in line with its licensed indication. It should only be used if there are no treatment options for which clinical benefit has been established for the solid tumour in question, or where such treatment options have been exhausted.

All available systemic anti-cancer therapy (SACT) for the tumour site should have been previously trialled and exhausted, and surgery and/or radiation would lead to substantial morbidity.

Clinicians are required to submit information to demonstrate that reimbursement of larotrectinib is being sought at the appropriate place in therapy for the solid tumour in question. This will include copies of prescriptions and relevant sections of patient notes and/or clinic letters in order to validate prior treatments. In general, reimbursement will not be supported under the High Tech Arrangement for larotrectinib as a first-line treatment for solid tumours that display a NTRK gene fusion.

3. Reimbursement criteria - Continuation

Ongoing reimbursement support for treatment with larotrectinib on the High Tech Arrangement is provided for, following a positive reimbursement recommendation, until either of the following occurs:

- disease progression, or
- unacceptable toxicity.

After initiation of treatment with larotrectinib, all patients should be monitored on an ongoing basis for disease progression of the malignant solid tumour and toxicities due to larotrectinib.

Treatment with larotrectinib should be discontinued upon occurrence of any of the following:

- radiographic disease progression,
- unacceptable toxicity, or
- development of a grade 3 or 4 adverse reaction that does not resolve within four weeks of withholding larotrectinib.ⁱⁱⁱ

Reimbursement of larotrectinib under the High Tech Arrangement may no longer be supported in patients who meet the criteria for discontinuation of larotrectinib as outlined above.

ⁱⁱⁱ Please refer to the Summary of Product Characteristics for Vitrakvi® for full prescribing information.

Therefore, following approval of a patient for reimbursement of larotrectinib under the High Tech Arrangement, the prescribing clinician will be required to submit follow-up data by secure email to the MMP (mmp@hse.ie), including details of assessment of disease progression and management of adverse reactions experienced with larotrectinib, as requested. The prescribing clinician should also indicate if they intend to continue or discontinue treatment with larotrectinib.

Follow-up data may be requested by the MMP for audit purposes and provision of same is a condition of ongoing reimbursement.

4. Prescribing of larotrectinib (Vitrakvi® 25 mg/100 mg hard capsules, 20 mg/ml oral solution)

Please refer to the SmPC for Vitrakvi® and the NCCP national regimens for larotrectinib for full prescribing information including monitoring and patient counselling requirements. Prescriptions must be generated through the HTH (details outlined separately) and only approved prescriber(s) will have access to prescribe larotrectinib.

The following confirmations are required when prescribing larotrectinib (Vitrakvi®) on the HTH:

- confirmation that larotrectinib (Vitrakvi®) is being prescribed for a MMP approved patient in accordance with the MAP established in line with the terms of reimbursement approval given by the HSE
- confirmation that the prescriber will assist the HSE/MMP in their conduct of audits* through provision of information as requested, to provide assurance that the product is being prescribed in line with HSE reimbursement approval and the MAP
- confirmation that the patient is aware that the application for reimbursement approval is being made on their behalf and that audits may occur during which their personal data will be reviewed.

* Follow-up data may be requested by the HSE/MMP for audit purposes and provision of same is a condition of ongoing reimbursement.