Medicines Management Programme

Managed Access Protocol – Medicines for the treatment of solid tumours displaying a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion

Medicine	Date of addition to Managed Access Protocol
Larotrectinib (Vitrakvi®)	19/04/2023
Entrectinib (Rozlytrek®)	01/10/2024

Approved by	**Professor Michael Barry, Clinical Lead, MMP**	
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ALK	Anaplastic lymphoma kinase
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. Medicines for the treatment of solid tumours that display a neurotrophic tyrosine receptor kinase (NTRK) gene fusion

There are two medicines available under the High Tech Arrangement for the treatment of solid tumours that display an NTRK gene fusion (NTRK gene fusion therapies); entrectinib (Rozlytrek®) and larotrectinib (Vitrakvi®).

Rozlytrek® contains entrectinib. Entrectinib is an inhibitor of the tropomyosin receptor kinases (TRKs) TRKA, TRKB and TRKC (encoded by the NTRK genes NTRK1, NTRK2 and NTRK3 respectively), proto-oncogene tyrosine-protein kinase ROS (ROS1) and anaplastic lymphoma kinase (ALK). Fusion proteins that include TRK, ROS1 or ALK kinase domains drive tumorigenic potential through hyperactivation of downstream signaling pathways leading to unconstrained cell proliferation.

From 1 June 2022, two presentations of entrectinib are available on the High Tech Arrangement:

- Rozlytrek® 100 mg hard capsules (30)
- Rozlytrek® 200mg hard capsules (90)

Vitrakvi® contains larotrectinib. Larotrectinib is an adenosine triphosphate (ATP)-competitive and selective TRK inhibitor. The target for larotrectinib is the TRK family of proteins inclusive of TRKA, TRKB, and TRKC that are encoded by the 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)
- 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 entrectinib and larotrectinib; these are available on the website of the NCCP:

https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/

1.1 Licensed indications

Entrectinib (Rozlytrek®) and larotrectinib (Vitrakvi®) are indicated as monotherapy for patients with solid tumours that display an 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.

Entrectinib is authorised for use in adult and paediatric patients older than 1 month, who have not received a prior NTRK gene fusion therapy. Larotrectinib is authorised for use in adults and paediatric patients.

Both drugs are available subject to a conditional marketing authorisation, granted when the medicine addresses an unmet medical need, and the benefit of immediate availability is deemed to outweigh the risk from less comprehensive data than normally required.

Entrectinib (Rozlytrek®) is also indicated as monotherapy for the treatment of adult patients with ROS1-positive advanced non-small cell lung cancer not previously treated with ROS1 inhibitors, which is outside the scope of this MAP.

1.2 Reimbursement

Reimbursement of entrectinib (Rozlytrek®) and larotrectinib (Vitrakvi®) on the High Tech Arrangement is supported for the treatment of patients with solid tumours that display an NTRK gene fusion, as outlined in section 1.1, who meet the criteria outlined in this MAP.

An application for reimbursement approval is required to be submitted on an individual patient basis. The *NTRK Gene Fusion Therapies Application Form* should be completed and sent by secure email to the Health Service Executive (HSE)-Medicines Management Programme (MMP) at mmp@hse.ie.

Table 1 outlines the licensed therapeutic dosage of entrectinib (Rozlytrek®) and larotrectinib (Vitrakvi®) for the treatment of patients with solid tumours that display an NTRK gene fusion. Please refer to the Summary of Product Characteristics (SmPC) for Rozlytrek® and Vitrakvi®, and the NCCP national regimens for further prescribing information.

Table 1 Licensed therapeutic dosage of NTRK gene fusion therapies

Medicine	Patient population	Route	Licensed therapeutic dosage
Entrectinib	Adults	Oral	600 mg once daily*
	Adolescent patients aged 12 years and older	Oral	Target dose 300 mg/m^2 once daily* ^For patients with a BSA of 1.11 m^2 to 1.50 m^2, recommended dose is 400 mg once daily ^For patients with a BSA ≥ 1.51 m^2, recommended dose is 600 mg once daily
Larotrectinib	Adults	Oral	100 mg twice daily*
	Paediatric	Oral	100 mg/m^2 twice daily (maximum of 100 mg per dose)*

BSA: body surface area
*until disease progression or unacceptable toxicity occurs
^as reimbursement is supported for individuals aged 12 years and older, only dosages likely to be relevant for this cohort are provided. Further prescribing information is available in the SmPC for entrectinib (Rozlytrek®).

If a patient is recommended for reimbursement of entrectinib or larotrectinib, reimbursement is supported up to the maximum licensed dosage specified in **Error! Reference source not found.**. R eimbursement of dosages in excess of the licensed therapeutic dosages (as outlined in Table 1) is not supported.

See Section 3 for further details on Reimbursement criteria – Requirement for outcome data.

Reimbursement of entrectinib (Rozlytrek®) on the High Tech Arrangement is also supported as monotherapy for the treatment of adult patients with ROS1-positive advanced non-small cell lung cancer not previously treated with ROS1 inhibitors, subject to a separate MAP.

1.3 Reimbursement prices

The reimbursement prices of the presentations of entrectinib and larotrectinib available on the High Tech Arrangement are outlined in Table 2. Commercial-in-confidence arrangements are in place with the marketing authorisation holders to reduce the net acquisition cost of entrectinib and larotrectinib to the HSE.

Table 2 Reimbursement codes and prices for the presentations of NTRK gene fusion therapies available on the High Tech Arrangement

Drug name	Medicinal product (pack size)	Reimbursement	
		Code	Price*
Entrectinib	Rozlytrek® hard capsules 100 mg (30)	89193	€989.23
	Rozlytrek® hard capsules 200 mg (90)	89194	€5,934.23
Larotrectinib	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

**Reimbursement price correct as of 01 June 2024*

2. Reimbursement criteria - Initiation

This section outlines the criteria that must be satisfied in order for patients to be recommended for reimbursement of an NTRK gene fusion therapy under the High Tech Arrangement, for the treatment of solid tumours that display a NTRK gene fusion.

2.1 Prescribers

Applications for reimbursement approval for NTRK gene fusion therapies (i.e. entrectinib or larotrectinib) under the High Tech Arrangement will only be considered from consultant medical oncologists registered with the Irish Medical Council, who have agreed to the terms of this MAP and who have been approved by the HSE ('approved consultants').

Approved consultants are responsible for ensuring that the patient or their representative/guardian is aware that the application for reimbursement approval is being made on their behalf.

The prescribing of NTRK gene fusion therapies for approved patients under the High Tech Arrangement will be confined to the approved consultants and their teams. The governance of the team on the High Tech Hub, including access, rests with the approved consultant.

2.2 Patient age

Applications for reimbursement approval for entrectinib will only be considered for individuals aged 12 years and older at time of application.

Applications for reimbursement approval for larotrectinib will be considered for individuals of any age.

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

Approved consultants 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.

2.4 NTRK gene fusion status

For reimbursement approval, approved consultants 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. Reimbursement will not be supported for patients with a known acquired resistance mutation.

Approved consultants 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.

2.5 Patient clinical history/status

In line with the exclusion criteria from clinical trials, and the SmPCs of Rozlytrek® and Vitrakvi®, applications for reimbursement approval of NTRK gene fusion therapies will not be considered in individuals who:

- meet any of the contraindications for treatment as outlined in the relevant SmPC
- meet any of the exclusion criteria listed in the relevant NCCP national regimen.

Applications for reimbursement approval will be considered only for patients with good performance status, as outlined in the NCCP national regimens for entrectinib and larotrectinib.

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

2.6 Place in therapy

The benefit of NTRK gene fusion therapies has been established in single-arm trials encompassing a relatively small sample of patients whose tumours exhibit NTRK gene fusions. Favourable effects of NTRK gene fusion therapies 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 an NTRK gene fusion therapy on the High Tech Arrangement is supported for patients who have no satisfactory treatment options, in line with the licensed indications. They 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.

Approved consultants are required to submit information to demonstrate that reimbursement of an NTRK gene fusion therapy 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 NTRK gene fusion therapies as a first-line treatment for solid tumours that display an NTRK gene fusion.

Entrectinib and larotrectinib should be prescribed and administered as monotherapy in line with the licensed indication.

Patients should have had no prior treatment with an NTRK gene fusion therapy.

3. Reimbursement criteria – Requirement for outcome data

Follow-up data may be requested by the MMP for audit purposes and provision of same is a condition of ongoing reimbursement. It is the responsibility of the approved consultant to ensure that the patient or their representative/guardian is aware that the provision of follow-up data is a condition of reimbursement, and that audits may occur during which their personal data will be reviewed.

3.1 Reimbursement criteria - Continuation

Ongoing reimbursement support for treatment with NTRK gene fusion therapies (i.e. entrectinib or 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, all patients should be monitored on an ongoing basis for disease progression of the malignant solid tumour and toxicities due to treatment.

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

- radiographic disease progression,
- unacceptable toxicity.

Reimbursement of NTRK gene fusion therapies under the High Tech Arrangement may no longer be supported in patients who meet the criteria for discontinuation of entrectinib or larotrectinib as outlined above, and in the NCCP national regimens.

Therefore, following approval of a patient for reimbursement of entrectinib or larotrectinib under the High Tech Arrangement, the approved consultant 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, as requested. The approved consultant should also indicate if they intend to continue or discontinue treatment with entrectinib or larotrectinib.

4. Prescribing of NTRK gene fusion therapies

Please refer to the SmPCs for Rozlytrek® and Vitrakvi®, and the NCCP national regimens for entrectinib and larotrectinib for full prescribing information including monitoring and patient counselling requirements.

If a patient is recommended for reimbursement by the MMP, the High Tech prescription should be generated on the High Tech Hub (HTH). High Tech prescriptions which are not hub generated for entrectinib or larotrectinib will not be eligible for reimbursement by the HSE Primary Care Reimbursement Service (PCRS). Only approved consultants and their teams will have access to generate prescriptions.