Medicines Management Programme

Managed Access Protocol – Entrectinib as monotherapy for the treatment of adult patients with ROS1-positive advanced non-small cell lung cancer not previously treated with ROS1 inhibitors

Medicine	Date of addition to Managed Access Protocol
Entrectinib (Rozlytrek®)	01/10/2024

Approved by	**Professor Michael Barry, Clinical Lead, MMP**	
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List of abbreviations

ALK	Anaplastic lymphoma kinase
EPAR	European Public Assessment Report
HSE	Health Service Executive
MAP	Managed Access Protocol
MMP	Medicines Management Programme
NCCP	National Cancer Control Programme
NCSLC	Non-small cell lung cancer
NGS	Next-generation sequencing
NTRK	Neurotrophic tyrosine receptor kinase
RNA	Ribonucleic acid
SmPC	Summary of product characteristics
TRK	Tropomyosin receptor kinase

1. Entrectinib for ROS1-positive non-small cell lung cancer

Rozlytrek® contains entrectinib. It is an inhibitor of the tropomyosin receptor kinases TRKA, TRKB and TRKC (encoded by the neurotrophic tyrosine kinase [NTRK] genes NTRK1, NTRK2 and NTRK3 respectively), proto-oncogene tyrosine 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 June 2022, two presentation(s) of entrectinib are available on the High Tech Arrangement.

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

The National Cancer Control Programme (NCCP) has developed national regimens for entrectinib; these are available on the website of the NCCP:
https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/

1.1 Licensed indication(s)

Entrectinib (Rozlytrek®) has a conditional marketing authorisation granted by the European Medicines Agency, for two indications.

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

Entrectinib is indicated as monotherapy for adults and paediatric patients older than 1 month 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 not received a prior NTRK inhibitor,
- who have no satisfactory treatment options.

This managed access protocol (MAP) pertains only to the use of entrectinib in ROS1-positive advanced NSCLC. Entrectinib is subject to a separate MAP for NTRK gene fusion therapies.

1.2 Reimbursement

Reimbursement of entrectinib on the High Tech Arrangement for the treatment of ROS1-positive NSCLC is supported only for adult patients with ROS1-positive advanced NSCLC, who meet the criteria outlined in this MAP. All criteria must be satisfied in order for reimbursement to be supported.

An application for reimbursement approval is required to be submitted on an individual patient basis. The *Entrectinib for ROS1 Non-Small Cell Lung Cancer 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 for ROS1-positive advanced NSCLC. Please refer to the Summary of Product Characteristics (SmPC) for further prescribing information.

Table 1 Licensed therapeutic dosage of entrectinib

Medicine	Route of administration	Dosage
Entrectinib (Rozlytrek®)	Oral	600 mg once daily

mg: milligrams

If a patient is recommended for reimbursement of entrectinib, reimbursement is supported in line with the licensed therapeutic dosage specified in Table 1. Reimbursement of dosages in excess of the licensed therapeutic dosages (as outlined in Table 1) is not supported. Reimbursement is supported for entrectinib only as monotherapy for the treatment of ROS1-positive advanced NSCLC. Please refer to the SmPC for Rozlytrek® and the National Cancer Control Programme (NCCP) national regimen for further information on management of missed doses, and dose modifications for patients who experience adverse reactions.

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

1.3 Reimbursement price

The reimbursement prices of the presentations of entrectinib 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 to the HSE.

Table 2 Reimbursement codes and prices for the presentations of entrectinib available on the High Tech Arrangement

Strength (pack size)	Code	Reimbursement price*
Rozlytrek® 100 mg (30)	89193	€989.23
Rozlytrek® 200 mg (90)	89194	€5,934.23

mg: milligrams *Correct as at 01/06/2024

2.Reimbursement criteria – Initiation

This section outlines the criteria that must be satisfied in order for patients to be recommended for reimbursement of entrectinib for ROS1-positive advanced NSCLC under the High Tech Arrangement.

2.1 Prescribers

Applications for reimbursement approval for entrectinib for the treatment of ROS1-positive advanced NSCLC 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 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 Rozlytrek® for approved patients for the treatment of ROS1-positive advanced NSCLC 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 will only be considered for individuals aged over 18 years at time of application.

2.3 Patient diagnosis

Approved consultants are required to provide information to demonstrate that the patient has a confirmed diagnosis of ROS1-positive advanced NSCLC.

2.3.1 Advanced NSCLC

Approved consultants are required to provide information to demonstrate that the patient has a confirmed histological diagnosis of NSCLC which is advanced or metastatic (American Joint Committee on Cancer stage IIIB/C or IV).

2.3.2 ROS1 status

For reimbursement approval, approved consultants are required to confirm that the patient has a documented ROS1 rearrangement in the solid tumour, as demonstrated by an accurate and validated test method.

Reimbursement will not be supported for patients with a known acquired resistance mutation.

2.4 Patient clinical history/status

In line with the exclusion criteria from the clinical trials and SmPC for Rozlytrek®, applications for reimbursement approval will not be considered for individuals who:

- meet any of the contraindications for treatment as outlined in the Rozlytrek® 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 regimen for entrectinib for ROS1-positive advanced NSCLC. In addition, patients should have adequate haematological, hepatic and renal function.

2.4.1 Previous treatment with ROS1 inhibitors

For reimbursement approval, approved consultants must confirm that the patient has not received any prior treatment with a ROS1 inhibitor, in line with the product license. This includes medicines provided through clinical trials and compassionate use programmes.

3.Reimbursement criteria – Continuation

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 should be discontinued upon occurrence of any of the following:

- radiographic disease progression
- unacceptable toxicity.

3.1 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.

4.Prescribing of entrectinib for approved patients

Please refer to the SmPC for Rozlytrek® and the NCCP national regimen for entrectinib in ROS1-positive advanced NSCLC for full prescribing information including monitoring and patient counselling requirements.

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