Zorginstituut Nederland

> Return address PO Box 320, 1110 AH Diemen

To the Minister of Health, Welfare and Sport
PO Box 20350
2500 EJ THE HAGUE

2023028963

National Health Care Institute
Care
Medicinal Products

Willem Dudokhof 1
1112 ZA Diemen
PO Box 320
1110 AH Diemen
www.zorginstituutnederland.nl
info@zinl.nl

T +31 (0)20 797 85 55

Contact
Ms J.E. de Boer
warcg@zinl.nl

Our reference
2023028963

Date 27 July 2023
Re: Package advice NTRK inhibitors

Dear Mr Kuipers,

The National Health Care Institute advises you on the assessment of entrectinib and larotrectinib (Rozlytrek® and Vitrakvi®) as monotherapy for the treatment of adults and paediatric patients (*entrectinib: 12 years and older*) with locally advanced or metastatic solid tumours that display a neurotrophic tyrosine receptor kinase (NTRK) gene fusion and who have no satisfactory reaction to standard treatment(s) or where no standard treatment exists or is indicated. This assessment is prompted by the placement of these products in the conditional inclusion (CI) for orphan drugs, conditionals and exceptionals.

The National Health Care Institute advises you to include entrectinib and larotrectinib (Rozlytrek® and Vitrakvi®) in the basic health care package for the above indication. We would like to explain our findings and final conclusion below.

Reason
Entrectinib and larotrectinib are tumour-agnostic drugs: they are effective in solid tumours with a (NTRK) gene fusion regardless of the histology of these tumours and regardless of their location in the body. Larotrectinib was placed in the lock procedure for expensive medicinal products on 28 August 2019. The health care insurers have asked the National Health Care Institute for advice on the inclusion of entrectinib in the basic health care package.

The medicinal products were considered promising by the medical specialists but at the time, the evaluation framework of the National Health Care Institute was not yet sufficient for tumour-agnostic drugs, so it was not possible to determine whether these products met the established medical science and medical practice. To give patients access, the two medicinal products were conditionally included in the basic health care package from 1 October 2021 until 1 January 2025.

For this conditional inclusion, the policy framework for CI orphan drugs, conditionals and exceptionals was extended in 2021 specifically for tumour-agnostic drugs. This means that there is a phase (phase 1) prior to the regular procedure (phase 2) of the conditional inclusion, which focused on the development of an appropriate research methodology and associated evaluation

framework by the National Health Care Institute. In addition, data collection about Dutch patients treated with the relevant medicinal products via the DRUG access platform (DAP) was carried out in this phase.

In the meantime, the evaluation framework *Assessment of established medical science and medical practice 2023* has been updated. A module has also been developed that can be applied to the present assessment: *Module evaluation SWP for tumour-agnostic drugs and for other oncological drugs that have been studied in single-arm studies only*.

The National Health Care Institute has been advised by the Scientific Advisory Board (WAR) about the assessment of the scientific data. Stakeholders were also consulted during the assessment process.

Comprehensive weighting of package criteria

Therapeutic value

The effectiveness and safety of larotrectinib and entrectinib in patients with solid tumours with NTRK gene fusion has been studied in several single-arm studies. Since only single-arm studies have been conducted and there is no historical control cohort with which to compare the data, an absolute or relative difference in progression-free or overall survival compared to best supportive care cannot be determined. Pooled analyses show that the overall response rate (ORR) combined with the duration of response (DoR) for both NTRK inhibitors amply meets the clinical relevance limits (ORR >40% and DoR > 4 months) defined by the occupational group (BOM committee). Few patients discontinued NTRK inhibitor treatment prematurely, indicating that the treatment is well tolerated.

Based on the above, the National Health Care Institute concludes that larotrectinib and entrectinib comply with the established medical science and medical practice for the registered indications. Since larotrectinib and entrectinib have not been directly compared, no firm conclusions can be drawn about differences in beneficial and/or undesirable effects between the two medicinal products. It is up to the treating physician to determine which NTRK inhibitor is suitable for an individual patient.

Budget impact analysis

Based on a consensus document from an expert group in 2020, it is estimated that potentially 100-200 adult patients and 3-6 paediatric patients per year are eligible for NTRK inhibitor treatment (1).

It should be borne in mind that the testing landscape is still evolving and the number of patients who are eligible for treatment with NTRK inhibitors in practice is directly related to the extent to which NTRK gene fusion testing will be performed. In addition, some patients will not be able or willing to receive treatment with an NTRK inhibitor, given the stage of the disease when this treatment is initiated. The 2022 CI progress report shows that only 8 patients with different types of solid tumours in the Netherlands have been treated with an NTRK inhibitor within the CI during the period from October 2021 to December 2022.

The costs per patient per treatment with entrectinib or larotrectinib are high:

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€89,441 and €100,891, respectively. The high treatment costs per patient of (and the difference between) the two medicinal products are caused by (the difference in) the long treatment duration (on average 16.49 and 18.6 months, respectively).

The total additional costs for the inclusion of entrectinib or larotrectinib in the basic health care package are estimated at €5.9 to €19.6 million in the third year after inclusion in the basic health care package.

Pharmaco-economic analysis
In this specific assessment, the National Health Care Institute has not assessed a pharmaco-economic analysis, since a substantiated statement on this is not possible. This is mainly related to uncertainty about the testing landscape, the positioning of the NTRK inhibitor in the different treatment lines and lack of data on the natural course of patients with NTRK gene fusion.

Diagnostics and testing costs
The National Health Care Institute has chosen to perform a comprehensive budget impact analysis in which the testing costs are made transparent. The expert group estimates that 25,000 adult and 600 paediatric patients will be tested annually for an NTRK gene fusion in order to receive treatment with an NTRK inhibitor. If the test costs are also taken into account, the additional costs are €36 million to €60 million in the third year after inclusion of entrectinib and larotrectinib in the basic health care package. However, the test costs are not entirely attributable to the two medicinal products. For example, some of the patients are already widely tested, such as children and patients with lung carcinoma. In addition, the diagnostic RNA panel test also brings benefits to society by testing multiple tumour markers simultaneously, thus enabling the use of the most optimal targeted treatment.

Advice
The National Health Care Institute advises you to definitively admit entrectinib and larotrectinib (Rozlytrek® and Vitrakvi®) from the CI to the basic health care package as monotherapy for the treatment of adults and paediatric patients (*entrectinib: 12 years and older*) with locally advanced or metastatic solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion and who have no satisfactory reaction to standard treatment(s) or where no standard treatment exists or is indicated. There are no firm conclusions about a possible difference between the two medicinal products.

As you know, in light of the above-mentioned test costs associated with the use of the NTRK inhibitors, the National Health Care Institute has implemented the *Molecular Diagnostic Implementation Procedure.* Within this procedure, a framework is being developed in which the effectiveness and positioningof new tests are related to the accessibility and implementation in practice. This includes attention to the organisation and funding of this care. The implementation procedure runs until September 2023.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

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(1) Prof. dr. J.G.J.V. Aerts PdWNMD dMPJE, Prof. dr. K. Grünberg, Prof. dr. C.M.L. van Herpen, dr. H.W. Kapiteijn, Prof. dr. M.J.L. Ligtenberg, dr. J.H.M. Merks, Prof. dr. J. Morreau, dr. M.L. Wumkes., . Consensus diagnose en behandeling van NTRK-genfusie gerelateerde solide tumoren (translated title: Consensus on diagnosis and treatment of tumours associated with NTRK gene fusion.) 2020