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*2021025716*

Date 16 August 2021
Subject Follow-up advice on conditional inclusion of entrectinib (Rozlytrek®) for solid tumours with NTRK gene fusion (procedure: orphan drugs, conditionals and exceptionals)

**Our reference**
2021030618

Dear Ms van Ark,

Based on our advice issued on 10 March 2021[1], you designated entrectinib (Rozlytrek®) for treating adult and paediatric patients with solid tumours (cancer) that express a neurotrophic tyrosine receptor kinase (NTRK) gene fusion; it was designated as a potential candidate for conditional inclusion (hereinafter also "VT") to the basic health care package under the Health Insurance Act. The parties subsequently made agreements in a covenant about additional data collection linked to conditional inclusion and about the settlement after the end of the conditional inclusion period.

It was not possible to determine whether the medicinal product entrectinib (Rozlytrek®) complies with established medical science and medical practice. The current assessment framework is not sufficient at this moment for this type of medicinal product (tumour-agnostic medicines). The VT period for the tumour-agnostic drugs is divided into two phases. The focus in the first phase is not on answering the 'package question'[2] but on collecting additional data (in the international studies required by the EMA and the Dutch data collection) and on developing an assessment framework and methodology for tumour-agnostic medicines. The 'normal' VT (conditional inclusion) criteria apply for Phase 2. This means that it must be possible to answer the package question within the conditional inclusion period using the research proposal submitted. Neither the process nor the responsibilities in Phase 2 are any different from the usual working method as described in the VT for orphan drugs, *conditionals* and *exceptionals*. To make that phased approach possible, you expanded the VT policy framework specifically for tumour-agnostic medicines [parliamentary letter GMT-218292[3]].

[1] https://www.zorginstituutnederland.nl/werkagenda/publicaties/adviezen/2021/03/10/advies-over-kandidaat-voorwaardelijke-toelating-entrectinib-Rozlytrek
[2] The question as to whether the medicinal product in question can be included in the basic health care package.
[3] https://www.rijksoverheid.nl/documenten/kamerstukken/2021/02/25/kamerbrief-over-voorwaardelijke-toelating-tumor-agnostische-geneesmiddelen

That letter concerns a positive recommendation by the National Health Care Institute for Phase 1 of the VT for entrectinib.

We have established that all the conditions mentioned in your parliamentary letter about VT[4] (taking account of the expansions of the policy framework specifically for tumour-agnostic medicines as stated in your parliamentary letter GMT-218292) have been included in the covenant and that all the relevant parties have signed the covenant. We estimate that the agreements made provide sufficient guarantees for the conditional inclusion process to proceed carefully and successfully. We assume that it will be possible to draw a conclusion at the end of Phase 1 of the amended policy framework for the VT process for tumour-agnostic medicines about the established medical science and medical practice for entrectinib based on the new assessment framework and the data from ongoing international studies. We therefore recommend including entrectinib conditionally in the basic health insurance package for a 3.5-year period for treating adult patients and paediatric patients with solid tumours (cancer) that express an NTRK gene fusion and amending the regulations correspondingly.

There is a great deal of uncertainty about the number of patients in the Netherlands who are eligible for treatment with an NTRK inhibitor. This is primarily because the diagnostics for NTRK gene fusions still have to be organised.
Only a small proportion of cancer patients are currently tested for NTRK gene fusion. The sources range from a minimum incidence of 50 patients to 203 patients if all patients in the Netherlands were to be tested for NTRK gene fusion. A figure of 10 to 20 patients per year has been given as a realistic estimate for the current Dutch situation, in which the diagnostics need to be organised further. The average treatment duration is estimated at 27.4 months.

It is possible that not only entrectinib but also larotrectinib (Vitrakvi®), another NTRK inhibitor for the same indication, will embark upon this modified tumour-agnostic VT pathway. The National Health Care Institute will make an effort to complete the conditional inclusion processes for these medicines simultaneously and to assess the medicines as soon as the new assessment framework for tumour-agnostic medicines is available.

If it cannot yet be determined at the end of Phase 1 of the VT period (if the new assessment framework for tumour-agnostic medicinal products is available, and based on the data available at that time) whether entrectinib meets established medical science and medical practice, a research proposal for Phase 2 of the VT must be submitted by the marketing authorisation holder at the end of Phase 1. Phase 2 can only start if it is possible to use this research proposal to answer the package inclusion question by the end of Phase 2 of the conditional inclusion period.

[4] https://www.rijksoverheid.nl/documenten/kamerstukken/2019/10/22/kamerbrief-over-beleidskader-voorwaardelijke-toelating-geneesmiddelen

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If the National Health Care Institute concludes at the end of Phase 1 of the VT period that entrectinib does not meet the criterion of 'established medical science and medical practice', this means that the drug may no longer be reimbursed from the basic health insurance package after the end of the VT period. The stakeholders have agreed in the covenant that they will acquiesce to that ruling. In that situation, entrectinib will stop being funded from the basic health care package. The parties have set out additional agreements in Article 6 of the covenant. The marketing authorisation holder will continue to make the medicine available *free of charge* for patients who are still being treated at the moment when the National Health Care Institute issues a negative recommendation. Such patients can continue treatment with entrectinib for as long as they benefit from it, as per the assessment by the physician treating them. The same applies if the minister decides to terminate the conditional inclusion (or to do so prematurely) for any reason whatsoever on the advice of the National Health Care Institute.

Please find attached the explanatory notes on which we based the advice that entrectinib should be conditionally included in the basic health care package for treating adult patients and paediatric patients with solid tumours (cancer) that express an NTRK gene fusion.

Yours sincerely,

Sjaak Wijma
*Chair of the Executive Board*

cc: the applicants/co-applicants submitting the request

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Appendix 1. Explanatory notes on the advice for entrectinib

The intervention involves entrectinib for treating adult patients and paediatric patients with solid tumours (cancer) that express a neurotrophic tyrosine receptor kinase (NTRK) gene fusion. It was not possible to determine whether the medicinal product entrectinib (Rozlytrek®) complies with established medical science and medical practice. The current assessment framework is not sufficient at this time for this type of medicinal product (tumour-agnostic medicines).

In principle, entrectinib meets the criteria for conditional inclusion.
However, it is not currently possible to formulate a research proposal that will answer the package inclusion question within 7 or 14 years. To fit the tumour-agnostic medicines into the conditional inclusion (VT) procedure, the National Health Care Institute has produced a tiered proposal, splitting the VT into two phases. To that end, you temporarily expanded the VT policy framework on 25 February 2021 specifically for tumour-agnostic medicines. You informed the Lower House of the Dutch Parliament about that decision in a parliamentary letter of 25 February 2021 [GMT-218292[3]].

The covenant that has been drawn up covers the conditions listed in your parliamentary letter about VT[1] of 22 October 2019. We briefly discuss those elements of the covenant below that are crucial to the success of data collection in Phase 1 of the modified tumour-agnostic conditional inclusion pathway.

1. *Collecting additional data*
   Two international non-randomised open-label phase 2 studies for market authorisation, as required by EMA, are currently running (STARTRK-2 and STARTRK-NG). These studies are collecting more data about the effectiveness and safety of entrectinib. Not all Dutch patients can take part in this ongoing research. As no package inclusion question can currently be formulated for tumour-agnostic medicinal products, only additional data collection from the Dutch patients is required in Phase 1. The parties have agreed that additional data collection will be done through the DRUG Access platform. Information will be gathered about the effectiveness of treatment with entrectinib (including the overall response percentage, the duration of the response, the time until response, progression-free survival and the overall survival rate and safety). Additionally, information about the diagnostics and previous treatment guidelines will be recorded.

2. *Exit criteria and exit strategy*
   In the covenant, the stakeholders undertake to cooperate in the outflow from the conditional inclusion procedure after it has ended, even in the event of a negative decision about inclusion in the health insurance package. Clear agreements have been made about communication to patients through the communication plan.

3. *Criteria for starting and stopping*
   The criteria for starting and stopping treatment with this medicinal product are in line with the criteria on the label and have been laid down in the DRUG Access Protocol. The determination of the indication is independently verified twice as part of the protocol, thereby fulfilling the

requirement for an independent assessment committee for the indication.

4. *Patient education*
   Agreements were made in the covenant via the communication plan about informing patients about the conditions of the conditional inclusion of entrectinib. The centres participating in DRUG Access will ensure that an explanation is given to patients about the fact that treatment with the medicine involves temporary reimbursement in a research context. This is part of the informed consent procedure within the DRUG Access protocol.

5. *Monitoring the progress of additional data collection*
   During the conditional inclusion period, the National Health Care Institute will organise a meeting once a year to discuss progress and any relevant interim findings from the studies. The NVMO (Dutch Society for Medical Oncology) will submit a progress report to the parties and the National Health Care Institute in time for a meeting. Based on these annual monitoring points, the National Health Care Institute assesses the progress based on inter alia patient inclusion and feasibility of the research process. The National Health Care Institute informs the minister annually about progress and whether there are grounds for adjusting or terminating the conditional inclusion process.

In conclusion, the National Health Care Institute is confident that the conditional inclusion of entrectinib in the basic health care package can be a success. This will allow the cost-effectiveness of entrectinib for treating adult patients and paediatric patients with solid tumours (cancer) that express a neurotrophic tyrosine receptor kinase (NTRK) gene fusion to be assessed within 3.5 years using the new assessment framework for tumour-agnostic medicinal products.