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Date 10 March 2021
Subject Advice on a potential candidate for VT (conditional inclusion) of entrectinib (Rozlytrek®) for solid tumours with NTRK gene fusion (procedure: orphan drugs, *conditionals* and *exceptionals*)

Our reference
2021008063

Dear Ms van Ark,

On 25 February 2021, the parties submitted an application for VT (conditional inclusion) of entrectinib (Rozlytrek®) of orphan drugs, *conditionals* and *exceptionals*. Entrectinib is licensed for treating adult patients and children aged 12 and over with solid tumours (cancer) that express a neurotrophic tyrosine receptor kinase (NTRK) gene fusion. I am hereby informing you that the National Health Care Institute has concluded that entrectinib meets the extended criteria for VT (conditional inclusion) specifically for tumour-agnostic medicinal products.

Application for VT (conditional inclusion) of entrectinib
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). The parties in the field see entrectinib as a highly promising drug.

Entrectinib is an NTRK inhibitor with a tumour-agnostic indication. Because NTRK inhibitors are an innovation that may have a great deal of promise, the National Health Care Institute proposed to the marketing authorisation holder that this medicinal product should be put forward for VT (conditional inclusion).

Disorder and available effectiveness data
A tumour-agnostic medicine is a medicinal product that is used against tumours that exhibit a specific genetic mutation, irrespective of the location of the tumour. This is in contrast to the majority of medicinal products, which have been developed to treat tumours depending on the specific organ or tissue in which the tumour arose. The tumour-agnostic approach is innovative and raises new questions for us. There is insufficient knowledge worldwide about the research methodology that needs to be adopted in order to demonstrate that the drug can be proved effective. The National Health Care Institute too is therefore unable to assess now whether these drugs meet the statutory criteria for admission to the health care package: established medical science and medical practice. Also, the physicians association in the Netherlands (NVMO/cieBOM – the Oncological Drugs

Evaluation committee of the Netherlands Association for Medical Oncology) has not yet set criteria for assessing such medicines.

Given the uncertainty around the study data that is available at the present time, the EMA has authorised NTRK inhibitors on the condition that additional studies are carried out (*conditional approval*). More data is needed to allow an assessment of whether these medicinal products comply with established medical science and medical practice. Because it is not possible to formulate a package question[1], setting up a study to answer it is not possible either.

Developing an assessment framework
To allow a package question to be formulated and answered, the assessment framework needs to be developed or extended. A sufficiently clear picture of what is needed to answer the package question will only be available once the methodology and the assessment framework have been developed. The National Health Care Institute will ensure that the said assessment framework will be developed as quickly as possible and will be ready by no later than the end of 2024.

Tiered proposal for VT (conditional inclusion)
In principle, entrectinib meets the criteria for VT (conditional inclusion). However, it is not currently possible to formulate a research proposal that will answer the package question within 7 or 14 years. To fit the tumour-agnostic medicines into the VT (conditional inclusion) procedure, the National Health Care Institute has produced a tiered proposal, splitting the VT (conditional inclusion) into two phases. To that end, you temporarily expanded the VT (conditional inclusion) 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 [1826283-218292-GMT[2]].

Phase 1
The focus in the first phase is not on answering the package question but on collecting additional data (international studies required by the EMA and Dutch data collection) and on developing an assessment framework and methodology for tumour-agnostic medicines. When the assessment framework is ready, the marketing authorisation holder submits a reimbursement file. This may include data that has become available from the additional data collection. The National Health Care Institute will inform the marketing authorisation holder in good time about the criteria for the reimbursement file that then apply. Based on the newly developed assessment framework, the National Health Care Institute will assess whether entrectinib complies with established medical science and medical practice. If it can be determined that entrectinib complies with established medical science and medical practice, the VT (conditional inclusion) will be terminated and the National Health Care Institute will recommend that you include entrectinib in the health insurance package, after arranging any preconditions.

If it cannot yet be determined whether entrectinib complies with established medical science and medical practice, a research proposal must follow at the end

[1] The question as to whether the medicinal product in question can be included in the basic health care package.

[2] https://www.rijksoverheid.nl/documenten/kamerstukken/2021/02/25/kamerbrief-over-voorwaardelijke-toelating-tumor-agnostische-geneesmiddelen

of Phase 1 to answer the package question and continue the VT (conditional inclusion) in Phase 2. After the positive evaluation of the research proposal by the National Health Care Institute, in which the Scientific Advisory Board (WAR) is also involved, there will be a 'normal' VT (conditional inclusion) procedure in Phase 2 (according to the standards defined in the procedure[3]). The research proposal must be assessed and the covenant for Phase 2 drawn up before the end of Phase 1. Phase 1 will run until no later than 31 December 2024.

If another medicinal product for the same indication appears during the VT (conditional inclusion) of entrectinib that complies with established medical science and medical practice and is reimbursed through the standard health care package, there will no longer be an *unmet medical need*. The VT (conditional inclusion) of entrectinib will then be ended.

Phase 2
The 'normal' VT (conditional inclusion) criteria apply for Phase 2. This means that it must be possible to answer the research proposal submitted for the package question within the maximum VT (conditional inclusion) period. Neither the process nor the responsibilities in Phase 2 are any different from the usual working method as described in the VT (conditional inclusion) for orphan drugs, *conditionals* and *exceptionals*.

Additional data collection in the Netherlands
The intended aim of treatment with entrectinib is to inhibit tumour growth in patients with cancer that is related to NTRK gene fusion. Two international non-randomised open-label phase 2 studies for market authorisation, as required by EMA, are currently ongoing (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.

The procedure for VT (conditional inclusion) states that an obligation to do research is linked to the entitlement to conditionally included care. This means that patients are only entitled to reimbursement for care if they participate in the study into its effectiveness (or cost-effectiveness). As no package 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 made a proposal for additional data collection in which information will be gathered about the effectiveness of treatment with entrectinib (including the overall response percentage, the duration of the response, the time to response, progression-free survival, overall survival rate and safety). Additionally, information about the diagnostics and previous treatment guidelines will be recorded.

The conclusions of National Health Care Institute
The broadening of the policy framework for VT (conditional inclusion) of tumour-agnostic medicinal products means that entrectinib meets the criteria imposed, namely:

- Entrectinib has been granted marketing authorisation by the EMA and has orphan drug and conditional status;

[3] https://www.zorginstituutnederland.nl/werkagenda/publicaties/publicatie/2019/08/27/procedure-voorwaardelijke-toelating-weesgeneesmiddelen-conditionals-exceptionals

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Date
9 March 2021

Our reference
2021008063

- It is a case of an *unmet medical need*;
- The marketing authorisation holder is the main applicant and this request is backed by an independent research institution, the physicians association and the patients' association;
- Additional data will be collected during Phase 1 in the international studies that have been made mandatory by the EMA. Furthermore, the Dutch patients will be included in a register to ensure that the VT (conditional inclusion) research requirement is complied with.
- After an assessment framework for tumour-agnostic medicinal products has been produced, the National Health Care Institute will carry out a health care package assessment using the data gathered up to that point (including international data).
- If it is not possible to answer the package question after Phase 1, Phase 2 of the VT (conditional inclusion) process will have to commence.

Recommendations from the National Health Care Institute
Based on these conclusions, we recommend that entrectinib should be designated as a potential candidate for VT (conditional inclusion).

If you follow this recommendation, the National Health Care Institute asks the parties to formulate their plans in greater detail and to draw up a covenant setting out the agreements needed to ensure that the VT (conditional inclusion) process is conducted carefully and successfully. The Ministry of Health, Welfare and Sport will have to conclude a financial arrangement with the marketing authorisation holder. Once the covenant has been drawn up and a financial arrangement concluded, we will send you follow-up advice on which you can base your final decision regarding the inclusion of entrectinib in the VT (conditional inclusion).

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board
cc. the applicants/co-applicants submitting the request

Annex 1. Expected patient numbers, price and dosage for entrectinib (Rozlytrek®)

Estimated number of patients
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.

There are three sources from which information can be obtained about estimated patient numbers:

- A systematic review has recently been published about the prevalence and incidence of NTRK-related cancer, putting the incidence at 0.52 per 100,000 people. [4] This would mean about 90 patients per year in the Netherlands. That estimate is a maximum, given that a correction is still needed for the testing capacity and the number of patients who will actually be treated with an NTRK inhibitor.
- The WIDE study, carried out among 1,200 cancer patients by the Netherlands Cancer Institute (NKI), identified 1 patient with NTRK-related cancer. The DRUG-ACCESS team believes that this would mean a maximum of 50 patients being found if we were to test everyone in the Netherlands. Realistically, they say that this will come to approximately 10 to 20 patients per year.
- The expert group has indicated that 3-6 paediatric patients and about 100-200 adult patients will be eligible for treatment with an NTRK inhibitor each year.[5] They made the assumption that all patients with locally advanced and metastatic cancers would be 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.

Price [6]

Entrectinib (adults)	
Dosage	600 mg once daily
Pharmacy purchasing price of entrectinib 100 mg capsules (30 capsules)	€891.67
Pharmacy purchasing price of entrectinib 200 mg capsules (90 capsules)	€5,350
100 mg capsule packages required per month	6.1
200 mg capsule packages required per month	1.0

[4] Forsythe et al. A systematic review and meta-analysis of neurotrophic tyrosine receptor kinase gene fusion frequencies in solid tumours. *Ther Adv Med Oncol* 2020, Vol. 12:1–10.

[5] Report (translated title) 'Consensus on diagnosis and treatment of tumours associated with NTRK gene fusion', 14 February 2020

[6] Prices are based on Taxe of January 2021

Entrectinib (children aged 12 and over)	
Dosage	300 mg/m^2 once daily Minimum: 400 mg (1.11-1.50 m^2) Maximum: 600 mg (≥1.51 m^2)
Pharmacy purchasing price of entrectinib 100 mg capsules (30 capsules)	€891.67
Pharmacy purchasing price of entrectinib 200 mg capsules (90 capsules)	€5,350
Average body surface area	Not reported
100 mg capsule packages required per month	4.1-6.1 (depending on the dosage)
200 mg capsule packages required per month	0.7-1.0 (depending on the dosage)

Duration of treatment
Entrectinib is prescribed until the patient's condition progresses or until unacceptable toxicity occurs. The studies with entrectinib showed that the median PFS was 11.2 months with a median follow-up duration of 14.2 months. It should be noted here that the inclusion of patients and the follow-up period are still ongoing. As the follow-up duration of the study gets longer, the median PFS for the patients may possibly increase as well. The calculations have used a median treatment duration of 27.4 months.

Total cost of treatment
The total cost of treatment per patient for entrectinib is estimated at € 148,731 for adults[7] and € 99,154 to €148,731 for children aged 12 and over (depending on the dosage)[8], based on a median duration of treatment of 27.4 months.

Assumptions
- The median treatment duration is 27.4 months.
- It is not yet certain whether substitution will be involved; no calculation for substitution has therefore been done.
- The costs of diagnosis have not been included in the cost estimate.

Disclaimer
The estimates in this annex have not been checked by the Scientific Advisory Board.

[7] Calculation for entrectinib for adults: 834 days * (6 * 100 mg) = 500,400 mg required. 500,400 ÷ 100 mg = 5,004 capsules of 100 mg. 5,004 capsules ÷ 30 capsules per package = 166.8 packs of capsules of 100 mg. The total cost of treatment when calculated using 200 mg capsules is the same.

[8] Calculation for entrectinib for children aged 12 and over: 834 days * (4 * 100 mg) = 333,600 mg required. 333,600 ÷ 100 mg = 3,336 capsules of 100 mg. 3,336 capsules ÷ 30 capsules per package = 111.2 packs of capsules of 100 mg. For calculation with entrectinib 600 mg, see footnote 5.