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2021016266

Our reference
2021016266

Date 21 July 2021
Subject Package advice on entrectinib (Rozlytrek) in ROS1 fusion-positive advanced NSCLC

Dear Ms van Ark,

This letter from the National Health Care Institute of the Netherlands is advising you about entrectinib as monotherapy for the treatment of adult patients with ROS1 fusion-positive advanced non-small cell lung cancer (NSCLC) who have not previously been treated with ROS1 inhibitors. The reason for this advice was the placement of entrectinib for the said indication in the package lock for expensive medicinal products.

The National Health Care Institute has assessed entrectinib on the basis of the four package criteria[1]: efficacy[2], cost-effectiveness[3], necessity and feasibility. Through this letter, I would like to inform you about the result of the full weighting of these package criteria. I hereby recommend that you should not include entrectinib for the above-mentioned indication in the basic insured package. I will explain the advice in more detail below.

General
At your request, the National Health Care Institute assesses whether new care should be part of the insured package. The National Health Care Institute makes its decision based on the basic insured package paid from joint premiums. The National Health Care Institute is advised by two independent committees: the Scientific Advisory Board (WAR) for advice on established medical science and medical practice and on cost-effectiveness, and the Insured Package Advisory Committee (ACP) for the social appraisal. The National Health Care Institute has also consulted relevant stakeholders during the assessment procedures.

No established medical science and medical practice
In a set of three single-arm studies with small numbers of patients, a positive effect was seen on the tumour response in patients with the registered indication. However, it is at present insufficiently clear how the tumour response correlates with the crucial outcome measure of overall survival (OS). For this reason, the

[1] Real-world package management 3 (2013). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl

[2] Current established medical science and medical practice: updated version (2015). National Health Care Institute. Via www.zorginstituutnederland.nl

[3] Cost-effectiveness report (2015). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl

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National Health Care Institute has concluded that the effects of entrectinib on the crucial outcome measure of progression-free survival are insufficient to allow interpretation.

Based on the above-mentioned considerations, the National Health Care Institute concludes that entrectinib as monotherapy for the treatment of adult patients with ROS1 fusion-positive advanced non-small cell lung cancer (NSCLC) who have not previously been treated with ROS1 inhibitors does *not* yet conform to established medical science and medical practice due to insufficient evidence and is therefore not a service that can be insured.

The National Health Care Institute has furthermore reached the conclusion that the quality of evidence for the effect of the standard treatment with which entrectinib has been compared, namely the medicine crizotinib, is very low. Crizotinib was however not included in 2016 in the lock procedure upon indication extension for ROS1 fusion-positive NSCLC and it entered the basic insured package without assessment by the National Health Care Institute.

Considerations and conclusion of the National Health Care Institute
Based on our current assessment framework, entrectinib for ROS1 fusion-positive NSCLC is not in line with established medical science and medical practice and therefore does not qualify for inclusion in the basic insured package.
Because crizotinib is available for treating Dutch insured people with ROS1 fusion-positive NSCLC, entrectinib for this indication does not meet the criteria for eligibility for the VT scheme (conditional inclusion of orphan drugs, conditionals and exceptionals).

The National Health Care Institute notes that assessing single-arm studies, as in the case of entrectinib for the registered indication, is difficult to do within our assessment framework. CieBOM (the Oncological Medicines Assessment Committee) also currently lacks the tools for assessing the clinical relevance of drugs that have been investigated in single-arm studies. However, the CieBOM of the NVMO (Dutch Society for Medical Oncology) recently proposed new PASKWIL criteria (palliative, adjuvant, specific side effects, quality of life, impact of treatment and level of evidence) for non-randomised studies; this will therefore be possible in the future. These criteria will be presented for approval to the members' meeting in November 2021. We are discussing this with the CieBOM and will include these criteria during further development of our assessment framework. Once that framework is ready, we will reassess entrectinib for the indication currently under discussion on the basis of the criteria applicable at that time. We will keep the manufacturer informed about this.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board