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

2022043753

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 M.J.S. de Vries

Our reference
2022043753

Date 10 November 2022
Subject Package advice pralsetinib (Gavreto®)

Dear Mr Kuipers,

The National Health Care Institute advises you on the assessment of pralsetinib (Gavreto®) for the treatment of adult patients with rearranged during transfection (RET)-fusion-positive advanced non-small cell lung carcinoma (NSCLC), who have not previously been treated with a RET inhibitor.
The reason for this advisory report was the placement of pralsetinib in the lock procedure for expensive medicinal products.

The conclusion is that pralsetinib for the above indication does not meet the established medical science and medical practice. The National Health Care Institute therefore advises you not to include pralsetinib (Gavreto®) in the basic health care package for this indication.

We would like to explain our findings and final conclusions below.

General

At your request, the National Health Care Institute assesses whether new care should be part of the standard health insurance packageThe National Health Care Institute has assessed pralsetinib on the basis of the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity and feasibility. We consider these criteria from a scientific perspective and in terms of public support. We also review the aspects of efficiency and transparency. The National Health Care Institute is advised in this matter by the Scientific Advisory Board (WAR) for advice on established medical science and medical practice and on cost-effectiveness. We also consulted stakeholders during the assessment process.

Integral weighting of package criteria

Established medical science and medical practice
The effectiveness and safety of pralsetinib in adult patients with RET-fusion-positive advanced NSCLC, who have not previously been treated with a RET

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

[2] Established medical science and medical practice assessment: updated version (2015). National Health Care Institute,
Diemen. Via www.zorginstituutnederland.nl

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

National Health Care Institute
Care
Medicinal Products

Date
10 November 2022

Our reference
2022043753

inhibitor, has been studied in a single-arm, non-randomized phase 1/2 study (ARROW). At the request of the National Health Care Institute, the marketing authorisation holder supplied the most recent data of this study in a clinical study report. It reports that, after first-line patients had been followed for a median of 22 months, 25 out of 116 patients had died. The median overall survival has not yet been achieved at present. Of the second-line patients who had been followed for a median of 30 months, 65 out of 165 patients had died. The median survival rate is 44.3 months (95% confidence interval: 27.8 – not reached). Data on the quality of life of these patients have not been published.

To determine the effect of pralsetinib on overall survival compared to the current treatment, an indirect comparison between the ARROW study and external control cohorts was attempted. For the first-line treatment, a comparison was made with pembrolizumab in combination with pemetrexed and platinum-based chemotherapy (PPP) through a treatment arm of the KEYNOTE-189 study as well as data from the Flatiron health database. For the second-line treatment, a treatment arm from the OAK study was used to compare to docetaxel.

Despite the fact that the indirect comparisons of the data available to date on OS and PFS look promising, these comparisons are dealing with large uncertainties. It is currently unclear whether the presence of a RET fusion affects the prognosis of the disease. In addition, there are differences in baseline characteristics between the treatment arms. This results in a very serious risk of bias. The data from the ARROW trial is still very immature and the comparisons with the external control cohorts result in a very low quality of evidence. The relative effectiveness on overall survival compared to the KEYNOTE-189 study cannot be calculated by the National Health Care Institute. The published indirect comparison with the real-world data from the Flatiron health database for first-line patients reports a statistically significant hazard ratio, but the absolute effect is unknown. The indirect comparison of the median survival of pralsetinib compared to docetaxel in the second-line patients seems promising, but this comparison also results in a very low quality of evidence, where a relative effect cannot be calculated. Furthermore, the effects of pralsetinib on the quality of life have not been published and therefore cannot be compared to the current standard treatments.

Currently, a randomized phase 3 study (AcceleRET-Lung) is in progress, comparing pralsetinib directly with the standard of care (platinum-based chemotherapy with or without pembrolizumab) in patients with locally advanced or metastatic RET fusion-positive NSCLC. In addition to the relevant outcome parameters OS and PFS, quality of life data are also being collected. On the basis of the results of this study, the National Health Care Institute does expect to be able to make a statement about the relative effectiveness of the indication mentioned.

On the basis of the above considerations, the National Health Care Institute concludes that pralsetinib in adult patients with RET fusion-positive advanced NSCLC does not meet the established medical science and medical practice.

Package advice
The National Health Care Institute advises you to not include pralsetinib in the health insurance package for the specified indication. Despite the fact that the data is promising, pralsetinib does not meet the established medical science and

medical practice due to insufficient data.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

National Health Care Institute
Care
Medicinal Products

Date
10 November 2022

Our reference
2022043753