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

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
T +31 (0)6-11048980

2023020959

Our reference
2023020959

Date 06 July 2023
Re: Package advice lenvatinib (Lenvima®) in combination with pembrolizumab

Dear Mr Kuipers,

The National Health Care Institute advises you about the assessment of lenvatinib (Lenvima®) in combination with pembrolizumab for the treatment of adult patients with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with platinum-containing therapy in any setting and are not candidates for curative surgery or radiation. The reason for this advice was that lenvatinib was being placed in what is known as the 'lock procedure' for expensive medicinal products.

Lenvatinib meets the established medical science and medical practice for the above indication and has a therapeutic added value compared to comparative treatment.

The National Health Care Institute therefore advises you to include lenvatinib (Lenvima®) in the basic healthcare package for this indication. A price reduction of at least 65% is recommended.

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

General

At your request, the National Health Care Institute assesses whether new care should be part of the standard health insurance package from the perspective of the basic healthcare package paid from joint premiums. In this decision, we weigh the matter, both in a scientific sense and from a social basis, and we weigh the aspects of efficiency and transparency. The National Health Care Institute assessed lenvatinib on the basis of the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity and feasibility. The National Health Care Institute is advised by the Scientific Advisory Board (WAR) for advice on established medical science and medical practice and on determining the budget impact and cost-effectiveness; and by the Insured Package Advisory Committee for the social

[1] Real-world package management 4 (2023). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl
[2] Assessment of the established medical science and medical practice 2023. National Health Care Institute, Diemen. Via: www.zorginstituutnederland.nl
[3] Cost-effectiveness report (2015). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl

assessment. We also consulted stakeholders during the assessment process.

National Health Care Institute
Care
Medicinal Products

Date
06 July 2023

Our reference
2023020959

Integral weighting of package criteria

Established medical science and medical practice

Lenvatinib (Lenvima®) in combination with pembrolizumab (hereinafter: lenvatinib + pembrolizumab) has been studied for the treatment of adult patients with advanced or recurrent endometrial carcinoma in Study 309/KEYNOTE-775. In this study, the treatment with lenvatinib + pembrolizumab was directly compared with the physician's choice of chemotherapy (doxorubicin or paclitaxel). The included patients' age ranged between 32 and 86 years, with a median age of 64 years. Lenvatinib + pembrolizumab had a clinically relevant increase in median overall survival (OS) of 6.9 months (HR: 0.62 (95% CI: 0.51; 0.75)) compared to chemotherapy selected by the attending physician. The treatment also had a clinically relevant effect on progression-free survival (PFS). The absolute difference in median PFS was 3.4 months (HR: 0.56 (95% CI: 0.47; 0.66)). Lenvatinib + pembrolizumab is unlikely to have a clinically relevant effect on quality of life. However, treatment is likely to result in a clinically relevant increase in both the incidence of intervention-related severe adverse events and the discontinuation rate due to adverse events. However, in relation to the severity of the disease (life-threatening) and the effect achieved with treatment, the National Health Care Institute considers the undesirable effects of lenvatinib + pembrolizumab to be acceptable. The added value of treatment with lenvatinib + pembrolizumab for the above indication has only been adequately demonstrated for patients with ECOG status 0-1. There is uncertainty about the contribution of the individual components of the combination therapy because there is no direct comparison available between the combination therapy and the lenvatinib and pembrolizumab monotherapies. It is therefore unclear to what extent the beneficial effect compared to chemotherapy is due to the synergistic effect of the combination therapy or the contribution of one of the two components.

In conclusion, lenvatinib + pembrolizumab in the above indication meets the established medical science and medical practice for patients with ECOG status 0 or 1 and has added value compared to current standard chemotherapy treatment.

Budget impact analysis

More than 2,000 new cases of endometrial carcinoma (EC) are diagnosed each year. The National Health Care Institute estimates that 105 patients per year will be treated with lenvatinib + pembrolizumab for this indication in year 3 after inclusion in the package. The cost of treatment is approximately €114,000 per patient, for an average treatment duration of approximately 10 months. The use of lenvatinib + pembrolizumab for the above indication will incur additional costs estimated at €11 million in the third year following market authorisation. There is uncertainty about the number of patients that will actually be treated with lenvatinib + pembrolizumab. It is unclear how many patients relapse or have a high risk of metastases upon disease progression following platinum-containing treatments.

Pharmaco-economic analysis

After the assessment of the cost-effectiveness analysis, the National Health Care Institute concludes that the pharmaco-economic analysis is of sufficient methodological quality and suitable for decision-making. Scenario analyses show that the marketing authorisation holder's assumption about a lifelong treatment

National Health Care Institute
Care
Medicinal Products

Date
06 July 2023

Our reference
2023020959

effect has a major impact on the results. The National Health Care Institute expects that the effect will decrease over time after discontinuation of treatment (*treatment waning*). There is great uncertainty as to how long the treatment effect observed in the study lasts.

Because of the uncertainties surrounding the application of *treatment waning*, the National Health Care Institute chooses to present two scenarios in the final conclusion of the appraisal:

Scenario a) in which lenvatinib + pembrolizumab has not been included as a follow-up treatment option in the chemotherapy arm. This scenario would be most realistic if there is sufficient evidence for a life-long treatment effect. This scenario results in an ICER of €124,700 per QALY, where the price discount must be at least 40% to fall below the maximum reference value of €80,000 per QALY.

Scenario b) in which scenario a) is combined with *treatment waning* from year 5 after the start of treatment. This scenario results in an ICER of €197,645 per QALY, where the price discount must be at least 65% to fall below the maximum reference value of €80,000 per QALY.

At the time of writing this advisory report, there are OS and PFS data available for up to 2.5 years after starting lenvatinib + pembrolizumab treatment. There is currently no evidence for the life-long continuation of the treatment effect of lenvatinib + pembrolizumab after discontinuation of treatment in this clinical picture. Therefore, scenario B is currently considered the main scenario. Scenario A is an alternative when there is evidence of lifelong maintenance of the treatment effect.

Package advice
The National Health Care Institute advises you to include lenvatinib (Lenvima®) in combination with pembrolizumab in the basic health care package for the above indication. Based on the ICER taking into account the fact that there is currently no evidence of a lifelong treatment effect, the National Health Care Institute considers a discount of at least 65% appropriate. No direct comparative study of the effects of monotherapy of the individual components compared to the combination treatment has been conducted. As a result, it is unclear what the contribution in effectiveness of the individual components to the combination treatment is.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board