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To the Minister of Health, Welfare and Sport
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2023018914

National Health Care Institute
Care
Medicinal Products

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Our reference
2023018914

Date 4 August 2023
Re: Package advice lenvatinib (Kisplix®) in combination with pembrolizumab

This is a corrected version of the letter already sent (on 15 May 2023), in which prices have been corrected to pharmacy purchasing price (AIP). These corrections have been implemented in the budget impact analysis attached to this letter.

Dear Mr Kuipers,

The National Health Care Institute advises you on the assessment of lenvatinib (Kisplix®) in combination with pembrolizumab (Keytruda®) for the first-line treatment of adults with advanced renal cell carcinoma.

The reason for this advice is that lenvatinib in combination with pembrolizumab is being placed in the lock procedure for expensive medicinal products.

The National Health Care Institute has concluded that lenvatinib in combination with pembrolizumab as first-line treatment for adults with advanced renal cell carcinoma meets the legal criterion of 'established medical science and medical practice'. In this respect, the National Health Care Institute has determined that the therapeutic value of the combination of lenvatinib with pembrolizumab has an added value compared to sunitinib in patients regardless of IMDC risk score, a similar value to cabozantinib in combination with nivolumab and axitinib in combination with pembrolizumab in patients regardless of IMDC risk score, and a similar value to nivolumab in combination with ipilimumab in patients with an intermediate or unfavourable IMDC risk score. However, the added value of sunitinib remains very uncertain in the subgroup with a favourable prognosis. There may appear to be a clinically relevant effect on progression free survival in this patient group, but not on overall survival.

The National Health Care Institute advises you to include lenvatinib in combination with pembrolizumab in the basic health care package, provided that the net price after successful price negotiations with the marketing authorisation holder is not higher than the net price of one of the following combinations: cabozantinib in combination with nivolumab or axitinib in combination with pembrolizumab or nivolumab in combination with ipilimumab.
We would like to point out that the Insured Package Advisory Committee has recommended that the price for a treatment should be reduced when several drugs are available for the same indication.

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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 health insurance package, and makes a decision based on the health care 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 has assessed lenvatinib in combination with pembrolizumab on the basis of the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity and feasibility. We also consulted stakeholders during the assessment process.

Comprehensive weighting of package criteria

Established medical science and medical practice

Lenvatinib in combination with pembrolizumab has been investigated as first-line treatment of adults with advanced renal cell carcinoma in the randomised CLEAR study. In this study, the treatment with lenvatinib in combination with pembrolizumab was directly compared to sunitinib. Median progression free survival (PFS) increased significantly by 14.7 months when lenvatinib was used in combination with pembrolizumab (HR: 0.39 (95% - CI: 0.32, 0.49) compared to sunitinib. The median overall survival (OS) was not yet achieved, but the HR for OS was 0.66 (95% CI: 0.49, 0.88) statistically significant. The relative effect estimates for both OS and PFS meet the PASKWIL[4] criteria for a clinically relevant effect. A subgroup analysis shows that the effect on survival of lenvatinib in combination with pembrolizumab compared to sunitinib in patients with a favourable prognosis is not statistically significant.

In addition, lenvatinib in combination with pembrolizumab was indirectly compared, using a network meta-analysis, to the following 3 combinations: cabozantinib in combination with nivolumab, axitinib in combination with pembrolizumab, and nivolumab in combination with ipilimumab. No statistically significant difference in survival was found in this indirect comparison with the 3 combinations mentioned above. In terms of progression free survival, a statistically significant difference was found in favour of lenvatinib in combination with pembrolizumab compared to axitinib in combination with pembrolizumab and nivolumab in combination with ipilimumab. These relative effect estimates meet the PASKWIL criteria for a clinically relevant effect. The difference in PFS with cabozantinib in combination with nivolumab was not statistically significant.

In terms of undesirable effects, when lenvatinib is used in combination with pembrolizumab there is a statistically significant and probably clinically relevant higher incidence of intervention-related serious undesirable effects compared to sunitinib and compared to nivolumab in combination with ipilimumab. A numerically higher incidence was also reported compared to cabozantinib in

[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

[4] CieBOM (2016). PASKWIL criteria from https://www.nvmo.org/over-de-adviezen/.

combination with nivolumab and axitinib in combination with pembrolizumab, but this was not statistically significant.
The discontinuation rate due to intervention-related undesirable effects was similar to sunitinib and axitinib in combination with pembrolizumab when lenvatinib was used in combination with pembrolizumab. Compared to cabozantinib in combination with nivolumab, the discontinuation rate due to intervention-related undesirable effects was statistically significantly higher than for lenvatinib in combination with pembrolizumab. Compared to nivolumab in combination with ipilimumab, the discontinuation rate due to intervention-related undesirable effects was statistically significantly lower than for lenvatinib in combination with pembrolizumab.
In conclusion, lenvatinib in combination with pembrolizumab appears similar to other combination treatments based on survival, but treatment may improve the PFS. However, this is accompanied by more toxicity. These differences in effectiveness and safety between first-line treatments for advanced renal cell carcinoma will therefore be taken into account in the choice of treatment for an individual patient.

Lenvatinib in combination with pembrolizumab has added value compared to sunitinib (all International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk scores) and a similar value to cabozantinib in combination with nivolumab, axitinib in combination with pembrolizumab (all IMDC risk scores) and nivolumab in combination with ipilimumab (intermediate or unfavourable IMDC risk score).

Budget impact
591 patients are expected to be treated with lenvatinib in combination with pembrolizumab 3 years after inclusion in the package. First-line treatment with lenvatinib in combination with pembrolizumab for advanced renal cell carcinoma costs approximately € 126,522 per patient per year, based on a median treatment duration of 11.8 months.

There is some uncertainty in the budget impact about the number of patients who will actually be treated with lenvatinib in combination with pembrolizumab, the current market distribution of treatment options for advanced renal cell carcinoma, the market penetration of lenvatinib in combination with pembrolizumab, the duration of the treatment with lenvatinib in combination with pembrolizumab and of the comparative treatments.

The cost of lenvatinib in combination with pembrolizumab for the above indication is € 2.1 million in the third year after the marketing authorization procedure. The market introduction of lenvatinib in combination with pembrolizumab is associated with an additional cost of approximately € 135,000 in the third year after substitution of the treatment with axitinib in combination with pembrolizumab and cabozantinib in combination with nivolumab. These estimates do not include any administration costs.
The National Health Care Institute cannot determine the actual amount of the additional costs because financial arrangements have been made for pembrolizumab, nivolumab and ipilimumab, which means that the actual price is lower than the list price used in the budget impact analysis.

Cost-effectiveness

The National Health Care Institute concludes that there is an added value compared to sunitinib, but due to the similarities in effectiveness of lenvatinib in combination with pembrolizumab to the already reimbursed treatment combinations of cabozantinib in combination with nivolumab, pembrolizumab in combination with axitinib and nivolumab in combination ipilimumab, a similar value is concluded. Since treatment with one of the combination treatments is currently the first choice in the treatment regimen for these patients and only patients contraindicated for immunotherapy are treated with sunitinib, a cost-effectiveness analysis is not warranted.

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Package advice

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There is an equal value in relation to these medicinal products that are already being reimbursed and there is no indication that one combination is preferable to the other. The National Health Care Institute would like to point out that the Insured Package Advisory Committee has advised them in general terms that the price for a treatment should be reduced when several medicinal products are available for the same indication. In addition, 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