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To the Minister of Health, Welfare and Sport  
PO Box 20350  
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2022007846

Date 14 March 2022  
Subject Package advice cabozantinib in combination with nivolumab  
(Cabometyx®/Opdivo®)

**National Health Care  
Institute**

Care  
Medicinal Products

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**Contact**

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**Our reference**

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Dear Mr Kuipers,

The National Health Care Institute advises you on the assessment of cabozantinib in combination with nivolumab (Cabometyx®/Opdivo®) as first line treatment for adult patients with advanced renal cell carcinoma. The reason for this advice is that cabozantinib in combination with nivolumab is being placed in the lock procedure for expensive medicinal products.

The National Health Care Institute has concluded that cabozantinib in combination with nivolumab as first line treatment for adult patients with advanced renal cell carcinoma complies with the legal criterion of 'established medical science and medical practice'. The National Health Care Institute has established that the therapeutic value of this medicinal product is comparable to the value of the already reimbursed medicinal products pembrolizumab in combination with axitinib; in patients with an intermediate or unfavourable prognosis, the therapeutic value is also comparable to the value of nivolumab in combination with ipilimumab. All of these combination treatments have a clinically relevant effect on overall survival, compared to treatment with sunitinib.

The National Health Care Institute advises you to include cabozantinib in combination with nivolumab in the 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 pembrolizumab in combination with axitinib 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 medicinal products are available for the same indication.

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 care package from the point of view of the standard health insurance 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 cabozantinib in combination with nivolumab on the basis of the four package criteria<sup>1</sup>: effectiveness<sup>2</sup>, cost-effectiveness<sup>3</sup>, necessity and feasibility. 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.

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### **Integral weighting of package criteria**

#### *Established medical science and medical practice*

Cabozantinib in combination with nivolumab was studied in the randomized CHECKMATE 9-ER study. In this study, the treatment with cabozantinib and nivolumab was directly compared to sunitinib. On the basis of this study, it can be concluded that cabozantinib in combination with nivolumab, compared to sunitinib, has a clinically relevant effect on progression-free survival and is likely to have a clinically relevant effect on overall survival. Treatment with cabozantinib in combination with nivolumab resulted in a 40% lower risk of death compared to sunitinib (Hazard Ratio [HR] 0.60 (95% CI 0.44 to 0.82)). The median progression-free survival rate increased significantly by 8.3 months (HR 0.51 (95% CI 0.41 to 0.64)). The relative effect estimation meets the PASKWIL criteria for a clinically relevant effect.

In addition, cabozantinib in combination with nivolumab was indirectly compared, using a network meta-analysis, to pembrolizumab in combination with axitinib and nivolumab in combination with ipilimumab. For the comparison with nivolumab in combination with ipilimumab, only the effectiveness in patients with an intermediate or unfavourable prognosis was considered, since this combination is not registered for patients with a favourable prognosis. In this indirect comparison between cabozantinib in combination with nivolumab, pembrolizumab in combination with axitinib and nivolumab in combination with ipilimumab, no clinically relevant difference was found in overall survival and progression-free survival between the different treatments.

Compared to nivolumab in combination with ipilimumab, the use of cabozantinib in combination with nivolumab causes more severe intervention-related undesirable effects. No clinically relevant difference in the occurrence of severe intervention-related undesirable effects has been found compared to sunitinib and pembrolizumab in combination with axitinib. In addition, compared with the other treatments, relatively few patients discontinue the treatment due to intervention-related undesirable effects. In relation to the desirable effects, the National Health Care Institute therefore considers the undesirable effects to be acceptable.

Cabozantinib in combination with nivolumab has an added therapeutic value compared to sunitinib and has an equal therapeutic value compared to pembrolizumab in combination with axitinib (all risk groups) and nivolumab in combination with ipilimumab (intermediate or unfavourable prognosis).

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<sup>1</sup> Real-world package management 3 (2013). National Health Care Institute, Diemen. Via [www.zorginstituutnederland.nl](http://www.zorginstituutnederland.nl)

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

<sup>3</sup> Cost-effectiveness report (2015). National Health Care Institute, Diemen. Via [www.zorginstituutnederland.nl](http://www.zorginstituutnederland.nl)

### *Budget impact*

It is expected that 41 patients will have been treated with cabozantinib in combination with nivolumab 3 years after inclusion in the package. Treatment with cabozantinib in combination with nivolumab as first line treatment for adult patients with advanced renal cell carcinoma costs an average of €157,145 per patient based on a median treatment period of 14.3 months. The estimated costs are €3 million in the third year after inclusion in the package. If partial substitution of pembrolizumab in combination with axitinib is taken into account, the additional costs of cabozantinib in combination with nivolumab are estimated at €0.5 million in the third year after inclusion in the package, based on the list price of the combinations already available. These estimates do not include any administration costs.

The inclusion of cabozantinib in combination with nivolumab in the reimbursed package therefore comes with additional 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.

### *Cost-effectiveness*

Because of the similarities in effectiveness (equal therapeutic value) of cabozantinib in combination with nivolumab in relation to the already reimbursed treatment combinations of pembrolizumab in combination with axitinib and nivolumab in combination with ipilimumab, a cost-effectiveness analysis is not relevant in this case.

### **Package advice**

The National Health Care Institute advises you to include cabozantinib in combination with nivolumab in the health care package for the indication mentioned above, provided that the net price after successful price negotiations with the marketing authorisation holder is not higher than the net price of the existing treatment with pembrolizumab in combination with axitinib or nivolumab in combination with ipilimumab. Since there is an equal value compared to these already reimbursed medicinal products, and there are no indications that one medicinal product is preferable to another, we advise you to take the net price of pembrolizumab in combination with axitinib or nivolumab in combination with ipilimumab into account during the price negotiations. We would like to point out that the Insured Package Advisory Committee has advised the National Health Care Institute in general terms that the price for a treatment should be reduced when several medicinal products are available for the same indication.

Yours sincerely,

Sjaak Wijma  
*Chair of the Executive Board*

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