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To the Minister of Medical Care and Sport  
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2021028621

Date 11 August 2021  
Subject Package advice ipilimumab (Yervoy®) in combination with nivolumab (Opdivo®) for the treatment of non-small cell lung cancer.

**National Health Care Institute**

Care  
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**Our reference**

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Dear Ms van Ark,

The National Health Care Institute is hereby advising you about ipilimumab (Yervoy®) in combination with nivolumab (Opdivo®) and two cycles of platinum-based chemotherapy as primary care treatment for metastatic non-small cell lung cancer (NSCLC) in adults without a sensitising EGFR mutation or ALK translocation. The reason for this advice was that ipilimumab was being placed in the so-called 'package lock' for expensive medicinal products.

The National Health Care Institute has concluded that ipilimumab in combination with nivolumab and two cycles of platinum-containing chemotherapy meets the statutory criterion of 'established medical science and medical practice' for the indication mentioned. The National Health Care Institute has determined that the therapeutic value of this combination is equal to the value of existing combinations of immunotherapy with chemotherapy. All of these treatment options significantly prolong patients' lives. However, the combination of ipilimumab with nivolumab and two cycles of platinum-containing chemotherapy involves a significant additional cost for the package. We advise you not to include the new combination in the package, unless price negotiations with the Marketing authorisation holder (MAH) successfully deliver a net price that does not exceed that of the existing combinations.

**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. We take into consideration the degree of certainty that this will be achieved, both in the scientific sense, as well as in terms of public support, and we consider the efficiency and transparency aspects.

The National Health Care Institute has assessed ipilimumab in combination with nivolumab and two cycles of platinum-containing chemotherapy for the indication mentioned 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 by the Scientific Advisory Board (WAR) for the review of data according to established medical science and medical practice. We also consulted stakeholders during the assessment process.

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

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

The effectiveness of ipilimumab (Yervoy®) in combination with nivolumab (Opdivo®) and two cycles of platinum-containing chemotherapy in the treatment of metastatic NSCLC has been investigated in one open-label, randomised, controlled study (CheckMate-9LA). The results show that the combination of medicinal products has a beneficial effect on overall survival compared to four cycles of platinum-containing chemotherapy. The median overall survival was 15.6 months (95% CI: 13.9-20.0) in the ipilimumab/nivolumab/chemotherapy arm and 10.9 months (95% CI: 9.5-12.6) in the control group. These results give a relative effect estimate (hazard ratio) of 0.66 (95% CI: 0.55-0.80). This survival gain meets the Oncological Medicines Assessment Committee's (BOM) PASKWIL criteria (palliative, adjuvant, specific side effects, quality of life, impact of treatment and level of evidence).

The CheckMate-9LA study compared the combination of medicinal products mentioned with chemotherapy. However, the standard treatment for the indication mentioned no longer consists of chemotherapy, but of immunotherapy in combination with chemotherapy. At the moment, primary care treatment with chemotherapy alone is only appropriate for patients with a contraindication for immunotherapy. Therefore, for the assessment of ipilimumab in combination with nivolumab and two cycles of platinum-based chemotherapy, we have used indirect comparisons with pre-existing combinations of immunotherapy with platinum-containing chemotherapy: pembrolizumab in combination with platinum-containing chemotherapy, atezolizumab in combination with platinum-containing chemotherapy, and atezolizumab in combination with bevacizumab and platinum-containing chemotherapy.

However, differences in study design, patient characteristics, outcome measures and duration of follow-up make indirect comparisons difficult. Nevertheless, the National Health Care Institute has determined that the beneficial effect on overall survival of ipilimumab (Yervoy®) in combination with nivolumab (Opdivo®) and two cycles of platinum-containing chemotherapy is clinically relevant. The various treatment options all have similar adverse effects. We therefore conclude that the assessed combination is an effective therapy, and that its effect is comparable to that of existing treatment options. These treatment options significantly prolong lives.

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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)

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Therefore, ipilimumab in combination with nivolumab and two cycles of platinum-containing chemotherapy in metastatic NSCLC in adults without a sensitising EGFR mutation or ALK translocation regardless of PD-L1 status or tumour histology is in line with established medical science and medical practice. The treatment also has equal therapeutic value to pembrolizumab in combination with 4 cycles of chemotherapy, atezolizumab in combination with 4-6 cycles of chemotherapy, and atezolizumab in combination with bevacizumab and 4-6 cycles of chemotherapy.

*Budget impact*

The application of ipilimumab in combination with nivolumab and two cycles of platinum-containing chemotherapy in the primary care treatment of metastatic NSCLC in adults without a sensitising EGFR mutation or ALK translocation will be associated with costs estimated at €4.7 to €11 million in the third year after inclusion in the package, depending on market penetration (15-35% in the third year after inclusion in the package).

We based our estimate of the costs involved on the standard list prices of ipilimumab and nivolumab. However, the actual costs are probably lower than this, as a financial arrangement has already been concluded for all current and future indications for nivolumab. In addition, a financial arrangement has been concluded for the two medicinal products in the existing combinations, pembrolizumab and atezolizumab. As a result, the actual prices of each of the treatments mentioned are lower than the standard list prices. All of these arrangements are confidential, so their effect on the budget impact analysis is unclear.

*Cost-effectiveness*

The National Health Care Institute did not perform a cost-effectiveness analysis. This was due to similarities between the effectiveness (equal therapeutic value) of ipilimumab in combination with nivolumab and two cycles of platinum-containing chemotherapy, and the combinations of medicinal products with which this combination was compared.

*Other considerations*

Indications for the combination of ipilimumab and nivolumab have recently been extended. The National Health Care Institute will assess this combination of medicinal products for these indication extensions as well. This is due to the fact that ipilimumab has been placed in the so-called 'package lock' for expensive medicinal products. These indication extensions are expected to produce further increases in the total cost of medicinal products, when these are included in the health insurance package.

**Final conclusion**

The National Health Care Institute advises you not to include ipilimumab in combination with nivolumab and two cycles of platinum-containing chemotherapy in the health insurance package, unless negotiations with the Marketing authorisation holder (MAH) result in a lower price. We advise you to take into account the existing discounts for pembrolizumab and atezolizumab: the net price of ipilimumab in combination with nivolumab and two cycles of platinum-containing chemotherapy should not exceed the net prices of pembrolizumab and atezolizumab, both in combination with chemotherapy. We also advise you to take the recently introduced indication extensions into account as well.

Yours sincerely,

Sjaak Wijma  
*Chair of the Executive Board*

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