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To the State Secretary of
Health, Welfare and Sport
PO Box 20350
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2021047153

Date 17 December 2021
Subject Package advice ipilimumab (Yervoy®) in combination with nivolumab (Opdivo®) for the treatment of inoperable malign pleural mesothelioma

National Health Care Institute
Care
Medicinal Products

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Our reference
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Dear Mr Blokhuis,

The National Health Care Institute advises you on ipilimumab (Yervoy®) in combination with nivolumab (Opdivo®) as first-line treatment for inoperable malignant pleural mesothelioma. The reason for this advice was that ipilimumab was being placed in the so-called 'lock procedure' for expensive medicinal products.

The National Health Care Institute has concluded that ipilimumab in combination with nivolumab meets the statutory criterion of 'established medical science and medical practice' for the indication mentioned. Ipilimumab combination with nivolumab is an effective treatment in which a distinction must be made between the effectiveness of the different tumour-histological types: the combination mentioned has a clear added value for patients with the non-epithelioid tumour-histological type compared to chemotherapy. However, no apparent added value of the combination treatment for patients with the epithelioid tumour-histological type has been demonstrated compared to the current treatment, which means that no more than an equal value can be concluded for this group.
However, the combination of ipilimumab with nivolumab involves a significant additional cost for the health care insurance package. There are considerations for negotiating prices. We advise you to include ipilimumab in combination with nivolumab in the health insurance package after successful price negotiations.

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 takes into account that the health care is paid from joint premiums. We weigh the information from a scientific point of view, as well as in terms of public support, and we consider the efficiency and transparency aspects.

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The National Health Care Institute has assessed ipilimumab in combination with nivolumab for the indication mentioned 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 cost-effectiveness, and the Insured Package Advisory Committee for the appraisal. We also consulted stakeholders during the assessment process.

Established medical science and medical practice
The effectiveness of ipilimumab (Yervoy®) in combination with nivolumab (Opdivo®) as first-line treatment for inoperable malignant pleural mesothelioma has been studied in one open-label, randomised, controlled study (CheckMate-743). The results show that the combination of medicinal products has a clinically relevant effect on overall survival compared to chemotherapy (pemetrexed in combination with platinum). The median overall survival of the entire study population was 18.07 months (95% CI: 16.82; 21.45) in the ipilimumab/nivolumab arm and 14.09 months (95% CI: 12.45; 16.23) in the control group. This results in an absolute increase in survival of 4.0 months and a relative impact estimate (Hazard Ratio: HR) of 0.74 (95% CI: 0.61-0.89). This survival gain of 4.0 months 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).

In the Checkmate-743 study mentioned above, a pre-defined subgroup analysis of patients with a non-epithelioid tumour-histological subtype (22% of the study population) shows the effect of ipilimumab in combination with nivolumab in relation to chemotherapy convincingly (median survival of 18.89 months vs. 8.80 months with an HR of 0.46 with a 95% CI: 0.31; 0.70). This means that the combination mentioned above provides a longer overall survival than with a chemotherapy treatment. For patients with an epithelioid tumour-histological subtype (78% of the study population), it is uncertain whether the difference in survival is clinically relevant (median survival of 18.73 months vs. 16.23 months with an HR of 0.85 with a 95% CI: 0.68-1.06). This means that for this subgroup, it is uncertain whether a longer overall survival is achieved with the above combination compared to chemotherapy. The effect throughout the whole study population is largely borne by the 22% of patients with the non-epithelioid subtype in which a large effect on survival was measured. This is to be traced to the fact that patients with an epithelioid tumour type respond much better to chemotherapy than patients with a non-epithelioid tumour type.

Common undesirable effects caused by the treatment with ipilimumab in combination with nivolumab are diarrhoea, fatigue, dyspnoea, nausea and reduced appetite. In the treatment with ipilimumab in combination with nivolumab, more intervention-related adverse events occurred and more patients withdrew from treatment than was the case for patients treated with chemotherapy. This is partly explained by the longer treatment time of ipilimumab in combination with nivolumab.

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[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

The National Health Care Institute concluded that ipilimumab, in combination with nivolumab as first-line treatment for inoperable malignant pleural mesothelioma, meets the established medical science and medical practice for the entire study population. The National Health Care Institute has established that this combination has a clear added value for patients with the non-epithelioid tumour-histological type, compared to chemotherapy. However, no apparent added value of the combination treatment for patients with the epithelioid tumour-histological type has been demonstrated compared to the current treatment, which means that no more than an equal value can be concluded for this group.

Budget impact
The application of ipilimumab in combination with nivolumab as first line treatment for inoperable malignant pleural mesothelioma will be accompanied by costs estimated at €16.8 million in the third year after inclusion in the package. This regards 393 patients in the third year. The distribution of the two histological tumour types in the Netherlands may differ from the available clinical data from the Checkmate-743 study.

Cost-effectiveness
Because an added value, compared to standard treatment, could only be concluded for patients with the non-epithelioid tumour-histological type, a cost-effectiveness analysis was only performed for this subgroup.

The cost-effectiveness analysis provided by the marketing authorisation holder is of sufficient methodological quality. The ICER is €69,047 per QALY compared to standard treatment. At a reference value of €80,000 per QALY, ipilimumab in combination with nivolumab is cost-effective compared to chemotherapy in patients with the non-epithelioid tumour-histological type.

Other considerations
No apparent added value of ipilimumab in combination with nivolumab for patients with the epithelioid tumour-histological type has been demonstrated compared to the current treatment, which means that no more than an equal value can be concluded for this group. The current standard treatment consists of chemotherapy; the National Health Care Institute has calculated that the average total treatment costs of this are €10,994.74. The total average treatment costs of ipilimumab in combination with nivolumab are €95,446.26 per patient, of which €35,299 is related to ipilimumab. In view of the equal value, the price of the combination of ipilimumab and nivolumab may not exceed that of the current treatment. The National Health Care Institute also advises the physicians' association to make informed choices. The patient's disease burden must also be considered. Treatment with ipilimumab in combination with nivolumab is continued until disease progression or unacceptable toxicity, or a maximum of 2 years while chemotherapy treatment is stopped after a maximum of 6 cycles of 3 weeks. The shorter treatment time for chemotherapy can be an advantage, from the point of view of ease of use. The expert opinion of the NVALT SAGA section also states that patients who experience favourable results from immune therapy have to visit the hospital for treatment more often and for longer. Because of the centralisation of immune-therapeutic care, the burden of a longer travel time will be important for some patients, and possibly even a reason to refrain from it. In addition, ipilimumab in combination with nivolumab is already being

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reimbursed for the indications melanoma and advanced renal cell carcinoma. The National Health Care Institute has also assessed the combination for the indication non-small cell lung cancer. At the time of drafting this package advice, the negotiations for a lung cancer indication were still ongoing. A further extension of indication has recently been approved for the indication of colorectal carcinoma. The National Health Care Institute will assess ipilimumab in combination with nivolumab for this extension of indication, since ipilimumab has been placed in the lock procedure for expensive medicinal products.

Package advice
The National Health Care Institute advises you to include ipilimumab in combination with nivolumab in the health insurance package for the entire indication.

We also recommend that you negotiate prices for the ipilimumab with nivolumab combination on the basis of the following considerations:

- Due to the conclusion of equal value for patients with an epithelioid tumour type, ipilimumab in combination with nivolumab cannot cost more than chemotherapy for this patient group.
- Even though the cost-effectiveness for the group of patients with the non-epithelioid tumour type is beneficial, price negotiation is still recommended, given that ipilimumab in combination with nivolumab is already reimbursed for several indications. This means that the marketing authorisation holder has already been largely compensated for the efforts they have had to make to market the product.

Appropriateness
The treatment of ipilimumab in combination with nivolumab is centralized.
The National Health Care Institute does not expect any relevant risks regarding appropriate use.

Evaluation
If ipilimumab, in combination with nivolumab, for inoperable pleural mesothelioma is added to the health insurance package, the National Health Care Institute will monitor the use of the combination mentioned. The two histological tumour types will be split. We will inform you about our findings no later than 2025.
In the context of the treatment landscape, the National Health Care Institute considers the following:

- the initial estimate of the number of patients compared to the actual number treated;
- the cost development compared to the original estimate.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board