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Our reference
2020021411

Date 02 June 2020
Subject Package advice dabrafenib/trametinib

Dear Mr van Rijn,

National Health Care Institute has completed the reassessment of the pharmaco-economic analysis of dabrafenib in combination with trametinib (Tafinlar®/Mekinist®) in the adjuvant treatment of adult patients with stage III melanoma. Based on this reassessment, we recommend that you include this combination treatment in the basic package after a price negotiation. In this letter, we explain our advice.

History
You have placed dabrafenib in combination with trametinib in the package lock for expensive medicinal products for the indication 'adjuvant treatment after full surgical treatment of stage III melanoma with a BRAF V600E/\/600K mutation in adult patients with ECOG status 0-1 and lymph node metastasis >1 mm'. On 28 August 2019, we sent you an initial advisory report on this combination therapy. At that time, the National Health Care Institute recommended you not to include dabrafenib/trametinib in the package. Although the combination met the legal criterion of 'established medical science and medical practice', the National Health Care Institute could not provide advice on potential price negotiation. The cost-effectiveness analysis provided by the manufacturer was of insufficient methodological quality. As a result, the National Health Care Institute could not provide a realistic estimate of the cost-effectiveness.

Reassessment
In the meantime, the marketing authorisation holder has provided a new pharmaco-economic analysis. On this basis, the National Health Care Institute concludes, after consulting the Scientific Advisory Board, that the analysis is now sufficient and suitable to make a realistic assessment of the cost-effectiveness. At a reference value of 50,000 euro/QALY that is applicable to the burden of disease, the adjuvant treatment with dabrafenib/trametinib is cost-effective compared to 'wait-and-see (placebo). Until recently, there was no pharmaceutical treatment for patients in an adjuvant setting. The ICER will probably be between €13,127 and €23,967.

The treatment costs of dabrafenib/trametinib are almost € 97,000,- per patient per treatment, based on the manufacturer's asking price. Applying dabrafenib and

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trametinib for the indication mentioned above will mean additional costs estimated at €6-28 million in the third year after inclusion in the package. This broad estimate reflects the uncertainty about market penetration in relation to immunotherapy. The lower limit of the estimate is the opinion of the occupational group.

Package advice
The National Health Care Institute considers it important that the combination of dabrafenib/trametinib for the assessed indication is rapidly made available on the basis of this reassessment. It is an effective therapy that could provide a solution for some of the patients with a contraindication for immunotherapy (5-10%). The National Health Care Institute advises you to negotiate the price of this combination therapy because in this case, the reference value used for cost-effectiveness is too high for a number of reasons.

In view of the uncertainty about survival gains, the negotiation could consider options such as pay-for-performance and pay-for-proof. We would like to indicate two uncertainties:
Firstly, it is still unclear whether the treatment will lead to survival gains, compared to a wait-and-see approach. Secondly, the occupational group has access to other substances recently made available (immunotherapy with nivolumab or pembrolizumab) to treat the majority of this patient group (90-95%). It is still unclear whether this combination therapy is more effective than these two adjuvant treatments. Other considerations are related to the competitive landscape. Several new products are expected shortly and a large part of the investments may be considered to have already been recovered by the manufacturer, because both of the combined medicinal products are already on the market for other indications.

Appropriateness
The occupational group has a melanoma register (DMTR) that collects all data, ensuring that the treatment results can also be monitored in the longer term and reported to the National Health Care Institute. We will actively ask for this from the management of the melanoma register. We will discuss these treatment outcomes further with the occupational group, in light of the use of the medicinal products within the treatment landscape of melanoma treatment applicable at the time.

Evaluation
If the combination therapy dabrafenib/trametinib is included in the insured package, the National Health Care Institute will actively monitor the use as described above in the section on appropriateness.
We will inform you about our findings no later than 2023.
In the context of the treatment landscape, the National Health Care Institute takes the following points into consideration:
- The initial estimate of the number of patients compared to the actual number treated;
- The cost development compared to the original estimate.
- The use of agreements on appropriateness.

If this monitoring yields signals that deviate strongly from the current estimates, this may give the National Health Care Institute cause to discuss the use of the

medicinal product or the reassessment of dabrafenib/trametinib with the occupational group.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board

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