**Dabrafenib/trametinib (Tafinlar®/Mekinist®) for the adjuvant treatment of adult patients with stage III melanoma**

Summary of recommendations by *Zorginstituut Nederland* (National Health Care Institute, the Netherlands) dated 28 August 2019

*Zorginstituut Nederland* carried out an assessment of the medicinal product dabrafenib/trametinib (Tafinlar®/Mekinist®) and concluded as follows.

*Zorginstituut Nederland* has completed its assessment of dabrafenib (Tafinlar®) in combination with trametinib (Mekinist®) for the adjuvant treatment of adults with stage III melanoma. Based on our assessment, we advise the Minister of Health, Welfare and Sport (VWS) not to include this combination treatment in the basic package. This letter sheds light on our conclusion.

The Minister of VWS placed dabrafenib in combination with trametinib for the said indication in the so-called *waiting room* (*'sluis'*) for expensive drugs. The combination has already been included in the standard package for non-operable, metastatic melanoma. The *Zorginstituut* has assessed the combination treatment based on the four package criteria[1] effectiveness,[2] cost-effectiveness,[3] necessity and feasibility*,* The *Zorginstituut* looks at whether new care should be included in the insured package. We do this both from a scientific perspective and from the perspective of societal support, while also paying attention to aspects relating to efficiency and transparency. The *Zorginstituut* was advised by two independent committees: the Scientific Advisory Board (WAR) which examines data against the criterion of established medical science and medical practice and determines the cost-effectiveness, and the Insured Package Advisory Committee (ACP) which considers societal aspects. We also consulted relevant parties during the assessment process.

**Integral consideration of the package criteria and package advice**
Based on initial results, we can state that dabrafenib in combination with trametinib complies with the legal criterion 'established medical science and medical practice' for the proposed indication, being adjuvant treatment after complete resection of stage III melanoma with a BRAF V600E/V600K mutation in adult patients with ECOG 0-1 status and a lymph-node metastasis of >1 mm. About half of the patients with a melanoma have a BRAF-V-600 mutation.

This adjuvant treatment is given in addition to surgical treatment to reduce the risk of the cancer returning. The Dutch guidelines on melanoma (2016) advise not to give systemic adjuvant treatment, but to wait and see. Currently,the BOM Committee advises to give adjuvant treatment with dabrafenib/trametinib for stage III melanoma with a BRAF-V600E or BRAF-V600K mutation. The same applies to adjuvant treatment with the immunotherapies nivolumab (Opdivo®) for stages IIIB and IIIC melanoma, and pembrolizumab (Keytruda®) for stage III melanoma. Nivolumab and pembrolizumab are reimbursed for this indication based on the financial arrangement that the Minister of VWS has agreed for these products. The specialists have indicated that, in practice, preference will be given

[1] Package Management in Practice 3 (2013). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

[2] Assessment of Established Medical Science and Medical Practice: updated version (2015). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

[3] Cost-effectiveness report (2015). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

to this immunotherapy (for 90-95% of the patients).

The treatment costs of dabrafenib/trametinib are almost €97,000.00 per patient, per treatment, based on the manufacturer's asking price. The use of dabrafenib plus trametinib for the said indication will result in additional costs that we estimate – with a wide margin – at between €6 and €28 million in the third year after inclusion in the standard package. This wide margin reflects the level of uncertainty about market penetration at the cost of immunotherapy. The lower margin is based on the opinion of the specialists.

The cost-effectiveness analysis supplied by the manufacturer is of insufficient quality, despite the fact that the manufacturer was given – and took advantage of – the opportunity to address this shortcoming. As a result, the *Zorginstituut* is unable to realistically estimate the cost-effectiveness, and unable to inform the Minister of VWS what price reduction is needed to reach an acceptable cost-effectiveness.
Unfortunately, the *Zorginstituut* is unable to advise the Minister regarding any price negotiation. Both we and the Minister feel that such a negotiation is essential, because reimbursing dabrafenib/trametinib at the manufacturer's current asking price would lead to an implicit and unwanted displacement of more cost-effective care. At population level, this will result in loss of health.

The *Zorginstituut* therefore advises the Minister of VWS, in light of the advice of the WAR and the ACP, not to include the combination dabrafenib/trametinib in the standard package. The *Zorginstituut* is well aware that the outcome of our assessment will be disappointing for patients and their specialists. We therefore invite the manufacturer to provide better evidence of the (cost-) effectiveness. Then, assessing from the perspective of the standard package, which is funded from collective premiums, the *Zorginstituut* will be able to realistically assess the costs and benefits of treating patients with stage III melanoma.

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*The original text of this excerpt from advice of Zorginstituut Nederland was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's advice.*
*Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.*