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Our reference
2020038453

Date 24 September 2020
Subject Package advice trastuzumab-emtansine (Kadcyla®) in adjuvant treatment of adult patients with HER-2 positive breast cancer in an early stage

Dear Ms van Ark,

Zorginstituut Nederland advises you about trastuzumab-emtansine (Kadcyla®) in adjuvant treatment of adult patients with HER2-positive breast cancer in an early stage, who have invasive residual disease after a taxane-based and HER2-focused neoadjuvant treatment. The reason for this advice was the placing of the said medicinal product in the so-called 'package lock' for expensive medications.

The Zorginstituut assessed trastuzumab-emtansine on the basis of the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity and feasibility. Through this letter, I would like to inform you about the result of the full weighting of these package criteria.
Zorginstituut Nederland has concluded that, in the above indication, trastuzumab-emtansine (Kadcyla®) meets the legal criterion 'current level of knowledge and practice'. This is an effective medicinal product, but there are arguments to advise you to negotiate the prices.

I will explain the advice below.

General

At your request, the Zorginstituut assesses whether new care should be part of the insured package. The Zorginstituut bases its decision on the point of view of the basic insured package paid from joint premiums. The Zorginstituut is advised by two independent committees: the Scientific Advisory Council (WAR) for the scientific and practical assessment of the data and the determination of the cost-effectiveness, and the Package Advisory Committee (ACP) for the social assessment. The Zorginstituut has also consulted interested parties during the assessment process.

Integral package criteria weighting

[1] Real-world package management 3 (2013). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl

[2] Current state of science and practice assessment: updated version (2015). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

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

In a randomised study (KATHERINE study) trastuzumab-emtansine was compared with trastuzumab, which is the current standard treatment. The effect is significant (the hazard ratio (HR) was 0.50 [95% confidence interval 0.39 – 0.64). This treatment effect is statistically significant and also clinically relevant according to the PASKWIL criteria that the Oncological Medicines Assessment Committee (BOM) has adopted for clinical effects.
It is however too early to use the data from the KATHERINE study to make any statement about the effect of trastuzumab-emtansine on overall survival. The immaturity of the data is sufficient reason for the BOM committee to deem its positive recommendation about trastuzumab-emtansine to be provisional at this stage. The EMA has required the marketing authorisation holder to provide additional data on overall survival by 2024 at the latest. The BOM committee will also assess the mature survival data and, if necessary, amend its advice.

The quality of life was specifically lower *during* treatment with trastuzumab-emtansine. This corresponds to the higher toxicity profile of trastuzumab-emtansine compared to the standard treatment trastuzumab. However, most of the undesirable effects were mild and transient.

The fixed treatment time of trastuzumab-emtansine is 14 cycles, except in the case of recurrence or serious toxicity. Applying trastuzumab-emtansine for the indication mentioned above will mean additional costs estimated at €16.4 million in the third year after inclusion in the package. Trastuzumab-emtansine is already being used in later stages for the treatment of the indication being discussed here. The use of trastuzumab-emtansine at an earlier stage of treatment for this indication therefore leads to a shift in the costs. In the future, savings may be made by preventing disease progression, but at the present time this is difficult to estimate.

The Zorginstituut concludes that the incremental cost-effectiveness ratio (ICER) of trastuzumab-emtansine compared to comparative treatment with trastuzumab is between €496 and €4,252 per QALY. This range is based on the different extrapolations of the survival gains of the trastuzumab-emtansine, which are uncertain. The effect of the chosen extrapolation is limited because the ICER range is well below the reference value of €20,000 per QALY and therefore trastuzumab-emtansine is cost-effective compared to trastuzumab.

Health care insurers have indicated to the Zorginstituut that they have negotiated very high discounts for trastuzumab and trastuzumab biosimilars. These discounts are not public. That is why the Zorginstituut has not been able to take this into account in the determination of the budget impact and the cost-effectiveness. Zorginstituut realises that the additional costs and cost-effectiveness can be higher and less favourable than estimated, respectively.

Package advice
Like the BOM committee, the Zorginstituut sees trastuzumab-emtansine as a medicinal product with potential for the above indication. The Zorginstituut will review its advice when the data on overall survival become available if the provisional positive advice of the BOM committee becomes a negative advice.

Bearing in mind that the additional costs and cost-effectiveness are in fact less favourable than estimated, the Zorginstituut advises you to include trastuzumab-

emtansine in the basic insured package only after successful price negotiations to achieve a socially acceptable price. The Zorginstituut advises you to let the health care insurers inform you about the amount of the discounts stipulated.

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Appropriateness
Prior to the start of trastuzumab-emtansine for the indication mentioned above, patients must be identified as HER2-positive and having invasive residual disease following a taxane-based and HER2-focused neoadjuvant treatment. The maximum duration of treatment is 14 cycles; in case of recurrent disease and/or in case of non-treatable toxicity, treatment should be discontinued. The Zorginstituut is confident that the occupational group will use trastuzumab-emtansine effectively.

Evaluation
If trastuzumab-emtansine is admitted to the health insurance package, the Zorginstituut will actively monitor the use of trastuzumab-emtansine. We will inform you about our findings no later than 2024.

In the context of the treatment landscape, the Zorginstituut 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 cost estimate;
- The link between tumour characteristics and the use of trastuzumab-emtansine;
- The place of trastuzumab-emtansine in the treatment arsenal of the occupational group, based on the final advice of the BOM committee.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board