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Our reference
2023003942

Date 15 February 2023
Subject Advice on trastuzumab-deruxtecan (Enhertu®)

Dear Mr. Kuipers,

The National Health Care Institute advises you about the admission of trastuzumab-deruxtecan (Enhertu®) to the health insurance package for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior treatments based on anti-HER2 therapies. The reason for this advice was the placing of this medicinal product in the lock procedure for expensive medications.

Trastuzumab-deruxtecan meets the established medical science and medical practice for this indication. In terms of progression-free survival (PFS), it has a therapeutic added value compared to the current standard treatment trastuzumab-emtansine. The effect on overall survival (OS) could not yet be reliably determined but the direction of the effect is positive. As such, the National Health Care Institute advises you to include trastuzumab-deruxtecan in the health insurance package for the specified indication. The results of the pharmaco-economic analysis, although of sufficient methodological quality for decision-making, are uncertain due to the lack of data concerning the effect of trastuzumab-deruxtecan on OS and quality of life. Based on the conservative estimate of cost-effectiveness, the National Health Care Institute believes that a discount of at least 45% is justified. In the negotiations, we advise to take into account a possible indication expansion.[1] In addition, the National Health Care Institute suggests that you ask the National Health Care Institute for a reassessment prior to price renegotiations when mature OS data are available. I will explain this advice below.

General

At your request, the National Health Care Institute assesses whether new care should be part of the standard health insurance package from the perspective of the health insurance package from joint premiums. We consider these both in the scientific sense and in terms of public support, and also review the aspects of efficiency and transparency. The National Health Care Institute assessed trastuzumab-deruxtecan on the basis of the four package criteria[2]: effectiveness[3],

[1] On 15 December 2022, the CHMP gave a positive advice for the use of TD in HER2-low breast cancer and in case of an HER2-positive form of stomach cancer.

[2] Real-world package management 3 (2013). National Health Care Institute, Diemen

[3] Established medical science and medical practice assessment: updated version (2015). National Health Care

cost-effectiveness[4], necessity and feasibility. The National Health Care Institute is advised by its Scientific Advisory Board (WAR) for advice on established medical science and medical practice and on cost-effectiveness; and by the Insured Package Advisory Committee for the social assessment. Stakeholders were also consulted during the assessment process.

Comprehensive weighting of package criteria

Established medical science and medical practice

Trastuzumab-deruxtecan was investigated in one directly controlled open-label, randomized phase III multi-centre study (*DESTINY-Breast03*). The primary endpoint was progression-free survival (PFS). The first interim analysis showed that the PFS increased substantially from 6.8 months for treatment with trastuzumab-emtansine to 15.5 months for treatment with trastuzumab-deruxtecan. This effect is clinically relevant (HR 0.28; 95% CI: 0.22 – 0.37; p < 0.001). The absolute difference in median PFS could not be established because it had not yet been reached for trastuzumab-deruxtecan.[5] The effect on overall survival (OS) could not be reliably determined at the time of the first interim analysis, but the direction of the effect is positive. The effects meet the PASKWIL criteria applied by oncologists for positive treatment advice. The side effects of trastuzumab-deruxtecan are generally reversible and clinically manageable. Severe intervention-related undesirable effects occurred more often during treatment with trastuzumab-deruxtecan than during treatment with trastuzumab-emtansine (10.9% vs. 6.1%). However, this difference may be related to the open-label setting of the study. It is in part therefore (still) uncertain whether this difference is clinically relevant. Given the desirable effects, the National Health Care Institute therefore considers the undesirable effects to be acceptable.
On the basis of these findings, the National Health Care Institute has concluded that trastuzumab-deruxtecan for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior treatments based on anti-HER2 therapies, has added value compared to trastuzumab-emtansine. Trastuzumab-deruxtecan is, therefore, in line with established medical science and medical practice.

Budget impact

The average total treatment costs per patient are estimated at €312,857 for trastuzumab-deruxtecan, compared to €71,499 for trastuzumab-emtansine. The physicians' association expects that trastuzumab-emtansine will be rapidly substituted by trastuzumab-deruxtecan. The National Health Care Institute estimates that after inclusion in the health insurance package 243 – 609 patients per year will be eligible for treatment with trastuzumab-deruxtecan. This results in an estimated budget impact of €106 million in year 3.

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[4] Cost-effectiveness report (2015). National Health Care Institute, Diemen.

[5] In the second interim analysis of the DESTINY-Breast03 study, published online on 7 December 2022 by *The Lancet*, the median PFS for trastuzumab-deruxtecan was available: 28.8 months (95% CI: 22.4 – 37.9) versus the median PFS for trastuzumab-emtansine (6.8 months; 95% CI: 5.6 – 8.2).

Cost-effectiveness
The results of the pharmaco-economic analysis, although of sufficient methodological quality for decision-making, are uncertain due to the lack of data concerning the effect of trastuzumab-deruxtecan on OS and quality of life. According to the marketing authorisation holder, the ICER is €146,296 per gained QALY for trastuzumab-deruxtecan compared to trastuzumab-emtansine. In view of the great uncertainty about trastuzumab-deruxtecan's long-term effect on OS, the National Health Care Institute finds this estimate optimistic. Based on a scenario analysis, the National Health Care Institute considers an ICER of at least €167,116 more likely in this context. The number of life years gained is 6.09 with trastuzumab-deruxtecan and 3.84 with trastuzumab-emtansine. Comparatively, trastuzumab-deruxtecan yields 2.25 life years gained. The incremental gain in QALYs for trastuzumab-deruxtecan compared to trastuzumab-emtansine is 1.70 QALY per patient. Due to the high burden of disease, a reference value of €80,000 per QALYs gained is applied. Based on an ICER of €167,116 per QALY gained, the price of trastuzumab-deruxtecan should decrease by at least 45% to stay below the reference value.

Final conclusion

Trastuzumab-deruxtecan (Enhertu®) meets the established medical science and medical practice for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior treatments based on anti-HER2 therapies. In terms of PFS, it has therapeutic added value compared to trastuzumab-emtansine, the current standard treatment.

The National Health Care Institute advises you to include trastuzumab-deruxtecan in the health insurance package for the specified indication. Based on a conservative estimate of cost-effectiveness, the National Health Care Institute advises a discount of at least 45%. In the negotiations, the expansion of the indication for the treatment of patients with 'HER2-low breast cancer' should be considered.

Finally, the National Health Care Institute suggests that you ask the National Health Care Institute for a reassessment prior to price renegotiations if/when mature OS data are made available.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board