



> Return address PO Box 320, 1110 AH Diemen

To the Minister of Health, Welfare and Sport
P.O. Box 20350
2500 EJ THE HAGUE

2025010699

Date 28 May 2025
Subject Advice on trastuzumab-deruxtecan (Enhertu®)

National Health Care Institute

Examination, Development
and Medicinal Products
Medicinal Products Team

Willem Dudokhof 1
1112 ZA Diemen
PO Box 320
1110 AH Diemen
www.zorginstituutnederland.nl
info@zinl.nl

T +31 (0)20 797 85 55

Contact

K. Watson
warcg@zinl.nl

Our reference

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Dear Ms Agema,

The National Health Care Institute is hereby advising you about including trastuzumab-deruxtecan (Enhertu®) in the health care package for the treatment of adult patients with non-resectable or metastatic HER2-low breast cancer who have previously received chemotherapy for the metastatic disease or whose disease has recurred during adjuvant chemotherapy or within 6 months of completing it. The reason for this advice was the placement of this medicine in the lock procedure for expensive medicinal products. The National Health Care Institute recommends that trastuzumab-deruxtecan also be included in the basic health care package for this new indication, provided that the price can be reduced substantially (by over 68%) after successful price negotiations.

On 15 February 2023, the National Health Care Institute issued a positive recommendation to your ministerial predecessor on including trastuzumab-deruxtecan (Enhertu®) in the basic health care package for treating adult patients with non-resectable or metastatic HER2-positive breast cancer who have previously received one or more treatments based on anti-HER2 therapies.¹ Since 11 April 2024, trastuzumab-deruxtecan (Enhertu®) has been reimbursable when used for this indication.²

Disorder

Every year, 18,000 women and 165 men in the Netherlands are told they have breast cancer. In stages 3 and 4, the tumour cannot be removed surgically. Recovery is then no longer possible. It is then only possible to limit the growth and further spread of the tumour with medicinal products. The focus then shifts to prolonging life, symptom control and the highest possible quality of life. The use of medicinal products is determined by specific characteristics of the exterior of the breast cancer cells. If there are more HER2 protrusions there than normal, the tumour is said to be HER2-positive (HER2+)³; if not, it is HER2-negative (HER2-). Thanks in part to improved HER2 diagnostics, it has now been established that

¹ See our letter dated 15 February 2023 (ref. 2023003942).

² See Government Gazette 2024, 12285 (10 April 2024)

³ HER: *human epidermal growth factor receptor*. In HER2-positive breast cancer, there are too many HER2 protrusions on the breast cancer cells, resulting in them growing faster than normal and multiplying uncontrollably.

HER2 protrusions are still present in HER2-negative tumours.⁴ Of 100 tumours that would previously have been described as HER2-negative, 60 to 65 would now be described as 'HER2-low' and 20 to 25 as 'HER2-ultralow'. In 10 to 15, there would genuinely be no HER2 protrusions present: 'HER2-null'. Depending on the presence of these and other protrusions, treatment consists of chemotherapy, anti-hormonal therapy, immunotherapy or a combination thereof.

National Health Care Institute
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28 May 2025

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Licensed indication

Trastuzumab-deruxtecan as a monotherapy is indicated for treating adult patients with non-resectable or metastatic HER2-low breast cancer who have previously received chemotherapy for the metastatic disease or whose disease has recurred during adjuvant chemotherapy or within 6 months of completing it.

Claim by the marketing authorisation holder

Trastuzumab-deruxtecan (Enhertu®) has added value for the licensed indication compared to the standard treatment with chemotherapy.

Package advice

The National Health Care Institute has determined that trastuzumab-deruxtecan meets the criterion of 'established medical science and medical practice'. In terms of overall survival (OS), trastuzumab-deruxtecan has added value over current standard chemotherapy treatment in adult patients with non-resectable or metastatic HER2-low breast cancer who have previously received chemotherapy for the metastatic disease or whose disease has recurred during adjuvant chemotherapy or within 6 months of completing it. The results of the pharmacoeconomic analysis are sufficient in terms of their quality for a decision to be made. As such, the National Health Care Institute recommends that you also include trastuzumab-deruxtecan in the basic health care package for this new indication, provided that the price can be reduced substantially (by over 68%) after successful price negotiations. Price negotiations should explicitly take account of probable indication extensions as well as the fact that quality of life has been measured but data on that aspect has not been published.

We have explained the preparation of this package advice below.

General

At your request, the National Health Care Institute assesses whether new care should be part of the standard health care package, from the perspective of the health care package paid from joint premiums. We consider this both in scientific terms and in terms of public support, weighing up aspects such as efficiency and transparency. The National Health Care Institute assessed trastuzumab-deruxtecan on the basis of the four package criteria⁵: effectiveness⁶, cost-effectiveness⁷, necessity⁸ and feasibility⁹.

⁴ See our report entitled (in translation) 'Exploratory analysis of HER2-low diagnostics' (25 March 2025)

⁵ 'Real-world insured package management 3' (2023). National Health Care Institute, Diemen (NL). Via www.zorginstituutnederland.nl.

⁶ Assessment of the established medical science and medical practice, 2023, National Health Care Institute, Diemen (NL) Via www.zorginstituutnederland.nl.

⁷ 'Healthcare cost-effectiveness assessment framework' (2024) National Health Care Institute, Diemen (NL). Via www.zorginstituutnederland.nl.

⁸ Necessity is related to the medical need due to the severity of a disease for the patient (burden of disease) and the need for the specific aspect to be insured. See report number 4 on real-world insured package management (2023).

The Scientific Advisory Board (WAR) advises the National Health Care Institute about the scientific support and the conclusion of the assessment. If there are risks regarding the accessibility and affordability, the assessment of the package criterion of effectiveness (established medical science and medical practice) will be placed in the wider social context of the four package criteria. The Insured Package Advisory Committee (ACP) advises the Executive Board of the National Health Care Institute in this regard. This social weighting results in the package advice. The various stakeholders will be consulted during the process.

National Health Care Institute
Examination, Development and Medicinal Products
Medicinal Products Team

Date
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Comprehensive weighting of package criteria

Effectiveness and established medical science and medical practice

Trastuzumab-deruxtecan has been studied in one phase-3 trial (DESTINY-Breast04) in 557 patients with metastatic HER2-low breast cancer against chemotherapy (as per the attending physician's choice). Patients were identified as HER2-low using the Ventana test (ultraView). The composition and characteristics of the study population matched the Dutch patient population. Treatment with trastuzumab-deruxtecan resulted in a clinically relevant improvement in overall survival of 6.6 months. This favourable effect of trastuzumab-deruxtecan meets the 2023 'PASKWIL' criteria (palliative, adjuvant, specific side effects, quality of life, impact of treatment and level of evidence) used by the Dutch oncology occupational group for issuing positive recommendations for palliative treatment. Although over 92% of patients treated with trastuzumab-deruxtecan had completed questionnaires about it during the study, no results were published on the effect of trastuzumab-deruxtecan on their quality of life.¹⁰

The number of severe adverse effects related to the intervention was similar in patients treated with trastuzumab-deruxtecan and with chemotherapy. However, twice as many patients treated with trastuzumab-deruxtecan discontinued treatment as those treated with chemotherapy; this was clinically relevant.

The National Health Care Institute concludes that trastuzumab-deruxtecan complies with established medical science and medical practice for the licensed indication.

Cost-effectiveness

The National Health Care Institute concludes that the pharmacoeconomic analysis is sufficiently high-quality. Although the outcomes can be used in decision-making, they are uncertain because of the lack of data about the effect of trastuzumab-deruxtecan on quality of life, the uncertainty about the long-term effect on overall survival, and the uncertainty about the nationwide standardisation and reliability of the tests used (or due to be used) in the Netherlands to determine HER2-low status. Using tests other than the Ventana test (ultraView) may have cost-effectiveness implications. There could potentially be other patients classified as HER2-low who would not have been given that

⁹ The feasibility criterion deals with whether it is feasible or tenable to include a specific type of care in the basic health care package. It is mainly a test of a number of implementation aspects, such as the healthcare organisation, the support base, ethical and legal aspects, budget impact, etc. See report number 4 on real-world insured package management (2023).

¹⁰ This was also the case for the indication that trastuzumab-deruxtecan is currently being reimbursed for (since April 2024).

classification with the Ventana test (ultraView), and vice versa¹¹.

The marketing authorisation holder has calculated an ICER of €190,476 per QALY gained for trastuzumab-deruxtecan in comparison with chemotherapy. Given the high degree of uncertainty about the long-term effect of trastuzumab-deruxtecan on overall survival, the National Health Care Institute considers this too optimistic. The National Health Care Institute considers an ICER of at least €219,803 per QALY gained to be more plausible in the above context. Based on this ICER, the price would have to come down by at least 68% to stay within the reference figure of €80,000. These calculations are based on the list prices of the medicinal products, as listed in the pharmacoeconomic report.

National Health Care Institute
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Medicinal Products Team

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Budget impact

The overall treatment costs per patient are estimated at €95,203 on average for trastuzumab-deruxtecan, compared to €3,411 for chemotherapy. The occupational group expects that chemotherapy will rapidly be fully substituted by trastuzumab-deruxtecan. In year 3 after inclusion in the basic health care package, the National Health Care Institute estimates that 475 patients per year will be eligible for treatment with trastuzumab-deruxtecan. The budget impact in year 3 is estimated at €40.6 million.

In particular, there is uncertainty about the number of patients with HER2-low breast cancer and the market penetration. As with the cost-effectiveness calculations, allowance should be made here for the fact that the calculations rely on HER2 classification using the tests currently available for this in the Netherlands. Using tests other than the Ventana test (ultraView) for determining the HER2-low status may affect the number of patients diagnosed as HER2-low. It is then not possible to rule out that other patients may then be classified as HER2-low to those in the DESTINY-Breast04 study¹². The additional costs of reliably classifying HER2-low patients are estimated by the National Health Care Institute to be relatively modest, at €240,200 in year 3.

Social weighting

The Insured Package Advisory Committee (ACP) sees the importance of trastuzumab-deruxtecan also becoming available for the licensed indication. However, it recommends that trastuzumab-deruxtecan should only be included in the basic health care package at a socially acceptable price. Given that this is an expansion of the indication, that further such expansions are expected in the foreseeable future and that sales of this medicinal product worldwide are already high¹³, the Committee believes that the price should come down by much more than 68% after negotiations. The fact that the quality of life has been assessed but no data has been published on that is an important consideration for the Committee. Especially in the final phases of life, the quality of life weighs heavily in patients' decisions whether or not to undergo yet another treatment with serious adverse effects. Given the large budgetary impact and the ever-changing treatment landscape, the Committee believes that a financial arrangement with a throughput time of up to two years would be appropriate.

Final conclusion

Trastuzumab-deruxtecan (Enhertu®) complies with established medical science

¹¹ In terms of patient numbers, there could therefore be more or fewer.

¹² In terms of patient numbers, there could therefore be more or fewer.

¹³ According to the marketing authorisation holder, global sales in 2024 were about USD 3.5 billion.

and medical practice in the treatment of adult patients with non-resectable or metastatic HER2-low breast cancer who have previously received chemotherapy for the metastatic disease or whose disease has recurred during adjuvant chemotherapy or within 6 months of completing it.

The National Health Care Institute advises you to include trastuzumab-deruxtecan in the basic health care package for this new indication. When doing so, the National Health Care Institute believes that a price discount of substantially more than 68% would be justified. Price negotiations should explicitly take account of probable indication extensions¹⁴ as well as the fact that quality of life has been measured but data on that aspect has not been published.

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Appropriate care

Finally, if a decision to reimburse is made, it is essential that treatment with trastuzumab-deruxtecan must be equally accessible to all patients with HER2-low breast cancer in the Netherlands, based on nationally uniform and reliable HER2-low diagnostics. To ensure this, in collaboration with and at the request of the National Health Care Institute, the Diagnostics Assessment Committee (cieBOD) issued a formal advisory report (guideline) in mid-April 2025 on national standardisation of HER2-low diagnostics that it then published on its website¹⁵.

We trust that this letter will have provided you with the information you need. The assessment reports have been added as annexes (pharmacotherapeutic report, budget impact analysis, pharmacoeconomic report and exploratory analysis of HER2-low diagnostics).

Yours sincerely,

M.J. Janssen
Chair of the Executive Board

¹⁴ In early April 2025, the European Commission also approved trastuzumab-deruxtecan for application in 'HER2-ultralow breast cancer'. Previously, the CHMP issued a positive recommendation for applying the drug in an "HER2-positive form of stomach cancer" and a "form of lung cancer with an HER2-activating mutation".

¹⁵ See <https://pathologie.nl/ciebod/>