NCPE Assessment Summary

Trastuzumab deruxtecan (Enhertu®)

HTA ID: 25039

09 September 2026

Applicant: AstraZeneca Pharmaceuticals (Ireland) DAC on behalf of Daiichi Sankyo Ireland Ltd

Trastuzumab deruxtecan as monotherapy for the treatment of adult patients with unresectable or metastatic hormone receptor-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of trastuzumab deruxtecan (Enhertu®) as monotherapy for the treatment of adult patients with unresectable or metastatic hormone receptor-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment.

Following assessment of the Applicant's submission, the NCPE recommends that trastuzumab deruxtecan (Enhertu®) not be considered for reimbursement, for this indication, unless cost-effectiveness can be improved relative to existing treatments*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (AstraZeneca Pharmaceuticals [Ireland] DAC on behalf of Daiichi Sankyo Ireland Ltd) Health Technology Assessment of trastuzumab deruxtecan (Enhertu®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In April 2026, AstraZeneca Pharmaceuticals (Ireland) DAC on behalf of Daiichi Sankyo Ireland Ltd jointly submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of trastuzumab deruxtecan (Enhertu®) as monotherapy for the treatment of adult patients with unresectable or metastatic hormone receptor-positive, human epidermal growth receptor 2 (HER2)-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment. This aligns with the therapeutic indication in the Summary of Product Characteristics (SmPC) for HER2-low and HER2-ultralow breast cancer. AstraZeneca Pharmaceuticals (Ireland) DAC on behalf of Daiichi Sankyo Ireland Ltd is seeking reimbursement of trastuzumab deruxtecan on the Oncology Drug Management System.

HER2 is responsible for the regulation of cell growth. Trastuzumab deruxtecan is a HER2-targeted antibody-drug conjugate that binds to tumours with HER2 protein overexpression causing DNA damage to the cancer cells and apoptotic cell death. Trastuzumab deruxtecan should be administered intravenously at a dose of 5.4mg/kg once every three weeks. Treatment with trastuzumab deruxtecan is recommended until disease progression or unacceptable toxicity.

The current standard of care for patients with unresectable or metastatic hormone receptor-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment is capecitabine monotherapy or paclitaxel monotherapy.

1. Comparative effectiveness of trastuzumab deruxtecan

The clinical trial programme informing this submission includes DESTINY-Breast06 (DB-06), a phase III, active-controlled, open-label trial. DB-06 compared the efficacy and safety of trastuzumab deruxtecan to investigator's choice chemotherapy (i.e. capecitabine, paclitaxel, nab-paclitaxel) in participants with hormone-receptor positive, HER2-low or HER2-ultralow advanced or metastatic breast cancer. In total, 866 participants were randomised 1:1, including 713 and 152 participants with HER2-low and HER2-ultralow breast cancer,

respectively.

The primary and key secondary endpoint were progression free survival (PFS) by blind independent central review (BICR) and overall survival (OS) in the subgroup of participants with HER2-low breast cancer, respectively. At interim analysis 1 (data cut off 18 March 2024, median follow-up 18 months), compared to investigator's choice chemotherapy, trastuzumab deruxtecan resulted in statistically significant improvements in PFS (hazard ratio [HR] 0.62; 95% confidence interval [CI] 0.52 to 0.75) but not OS (HR 0.83; 95% CI 0.66 to 1.05). Median PFS and OS in the trastuzumab deruxtecan arm were 13.2 months (95% CI 11.4 to 15.2) and 28.9 months (95% CI 25.7 to 33.7), respectively, compared to 8.1 months (95% CI 7.0, 9.0) and 27.1 months (95% CI 23.5, 29.9) in the investigator's choice chemotherapy arm. In the subgroup of participants with HER2-ultralow breast cancer, exploratory analyses showed numerically greater PFS and OS in the trastuzumab deruxtecan arm. Statistical significance was not tested in the HER2-ultralow subgroup.

Quality-of-life outcomes were reported in the full intention-to-treat (ITT) trial population. The ITT population includes both the HER2-low and HER2-ultralow subgroups. Trastuzumab deruxtecan resulted in significantly improved pain, insomnia, skin mucosis symptoms, arm symptoms, endocrine therapy symptoms, and breast symptoms compared to investigator's choice chemotherapy. Gastrointestinal symptoms (nausea/vomiting, appetite loss, constipation) and endocrine sexual symptoms were significantly worse in participants receiving trastuzumab deruxtecan. Given the open-label nature of the trial, these patient-reported quality of life outcomes are highly uncertain.

DB-06 provided direct comparative evidence for trastuzumab deruxtecan compared to investigator's choice chemotherapy (capecitabine, paclitaxel, nab-paclitaxel). As capecitabine and paclitaxel are the key comparators, no indirect treatment comparisons were required.

2. Safety of trastuzumab deruxtecan

In DB-06, more participants in the trastuzumab deruxtecan arm experienced adverse events (AEs) leading to treatment discontinuation (14%) than in the investigator's choice chemotherapy arm (9%). All but one common drug-related AE (occurring in ≥ 20% of participants in either arm) were reported with numerically increased frequency for

trastuzumab deruxtecan compared to investigator's choice chemotherapy. Palmar-plantar erythrodysesthesia syndrome was more common in participants receiving investigator's choice chemotherapy (35%) than trastuzumab deruxtecan (1%). The most common drug-related AEs in participants receiving trastuzumab deruxtecan were nausea (66%), alopecia (45%), anaemia (27%), vomiting (27%), and fatigue (25%). Two participants died whilst receiving trastuzumab deruxtecan, during DB-06, due to interstitial lung disease (ILD). The Summary of Product Characteristics (SmPC) stipulates that patients should be monitored for signs and symptoms of ILD/pneumonitis.

3. Cost effectiveness of trastuzumab deruxtecan

The Applicant's base case analysis compared the cost-effectiveness of trastuzumab deruxtecan to investigator's choice chemotherapy in the full licensed population. Direct evidence was derived from the ITT population from the DB-06 trial (data cut off 18 March 2024).

Methods

The Applicant submitted a cohort level partitioned-survival model including three mutually exclusive health states; progression-free (PF), progressed disease (PD) and death. These states capture PFS and OS which were primary and secondary endpoints of the DB-06 trial, respectively. All patients enter the model in the PF state and receive treatment with either trastuzumab deruxtecan or investigator's choice chemotherapy (assumed to be capecitabine and paclitaxel in equal 50% shares). In each three-week model cycle, patients either remain in their current state, transition from the PF state to the PD state, or transition from the PF or PD states to the death state. OS and PFS are modelled using parametric distributions fitted to time-to-event data from the DB-06 trial. In each cycle, patients accrue quality-adjusted life years (QALYs). Health-related quality of life (HRQoL) utility values were derived directly from EQ-5D-5L data measured during the DB-06 trial and mapped to the EQ-5D-3L value set. Treatment-specific utility scores were implemented by the Applicant for both the PF and PD health states, with higher utility values assumed for trastuzumab deruxtecan than investigator's choice chemotherapy. The model included drug acquisition, administration and AE costs associated with each treatment. Other healthcare resource costs included ward nurse and medical oncologist costs, scans and subsequent anti-cancer treatments. A once-off end-of-life cost was applied. The Review Group identified limitations in the Applicant's

analysis which were addressed through changes in the NCPE adjusted base case. Key changes included: 1) the choice of OS extrapolation curves in the trastuzumab deruxtecan and investigator's choice chemotherapy arms; 2) treatment waning was applied; 3) HRQoL utilities were adjusted in the PF and PD health states to account for the potential bias introduced by the open-label design and the lack of evidence for a differential utility between treatments in the PD state; 4) the assumed proportion of patients receiving subsequent treatment with trastuzumab deruxtecan were aligned to empirical DB-06 trial data for both arms to maintain internal consistency between modelled costs and observed survival benefit in the model. This differed from the Applicant base case, which assumed a much higher proportion of subsequent treatment with trastuzumab deruxtecan in the investigator's choice chemotherapy arm. Therefore, the Applicant base case, inflated comparator costs without assigning a corresponding increase in survival and likely biased results in favour of the intervention.

Results

The results of the Applicant's base case deterministic cost-effectiveness analysis are presented in Table 1. Respective results of the NCPE adjusted base case are presented in Table 2. The probabilities of cost-effectiveness, for trastuzumab deruxtecan versus investigator's choice chemotherapy, in the Applicant and NCPE adjusted base case was 0% at both incremental cost-effectiveness ratio (ICER) thresholds of €20,000/QALY and €45,000/QALY.

Table 1 Applicant base case incremental cost-effectiveness results [a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
ICC	77,449	2.17	-	-	-
T-DXd [b]	155,761	2.62	78,312	0.45	174,293

ICC: Investigator's choice of chemotherapy; **PAS**: patient access scheme; **T-DXd**: trastuzumab deruxtecan

[a] Corresponding probabilistic ICER using 1,000 iterations =€179,811/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount of 4% applied to costs and outcomes.

[b] A commercial in confidence PAS been proposed for T-DXd and is not included in this table.

Table 2: NCPE adjusted base case incremental cost-effectiveness results [a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
ICC	64,985	1.85	-	-	-
T-Dxd [b]	154,745	2.13	89,760	0.28	322,899

ICER: Incremental cost effectiveness ratio; **ICC**: Investigator's choice of chemotherapy; **PAS**: patient access scheme; **QALY**: quality adjusted life year; **T-DXd**: trastuzumab deruxtecan

[a] Corresponding probabilistic ICER using 1,000 iterations =€316,951/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount of 4% applied to costs and outcomes.
[b] A commercial in confidence PAS been proposed for T-DXd and is not included in this table.

A Price-ICER analysis, conducted using the NCPE adjusted base case, indicated that an 81.43% and 87.95% reduction in the price to wholesaler of trastuzumab deruxtecan was required to meet the €45,000/QALY and €20,000/QALY threshold, respectively.

4. Budget impact of trastuzumab deruxtecan

The price to wholesaler for trastuzumab deruxtecan is €1,500 per 100mg vial. The estimated cost of trastuzumab deruxtecan per patient per treatment course is €139,635 including VAT. A treatment duration of 14.42 months was assumed, derived from the gamma distribution for time-to-treatment discontinuation (TTD) in the cost-effectiveness model. The Applicant assumed 50% wastage (i.e., that half of trastuzumab deruxtecan vials would be shared in clinical practice).

The Applicant's submission is for trastuzumab deruxtecan after at least one endocrine therapy in the metastatic setting, in line with the SmPC. Trastuzumab deruxtecan is currently reimbursed in Ireland in a later-line treatment setting, i.e., for patients with HER2-low breast cancer who have received prior chemotherapy in the metastatic setting (HTA ID 23011). It is anticipated that if trastuzumab deruxtecan is reimbursed for the indication under consideration in this submission, then this would reduce the use of trastuzumab deruxtecan in later treatment lines. The Applicant has incorporated cost offsets in their budget impact analysis by reducing the number of patients with HER2-low breast cancer expected to receive treatment in third and later lines. The final number of patients estimated by the Applicant to be newly eligible for treatment in year one was 84, increasing to 110 by year five.

The estimated five-year cumulative gross drug budget impact is €31.30 million (including VAT). The estimated five-year cumulative net drug budget impact is €19.72 million (including VAT). Many of the budget impact model (BIM) inputs are uncertain and there is considerable uncertainty associated with the budget impact estimates. The Applicant estimated that trastuzumab deruxtecan would have a market share of 40% in year one, increasing to 50% by year five. Clinical opinion to the Applicant indicated that market shares may be as high as

80% for trastuzumab deruxtecan. In the scenario where the market share is increased to 80% in all years, the resulting five-year cumulative net drug budget impact is an estimated €48.6 million, including VAT.

5. Patient Organisation Submission

A patient organisation submission was received from UCAN Ireland (United Cancer Advocates Network). This submission will form part of the information that the HSE considers when making their drug funding decision.

6. Conclusion

The NCPE recommends that trastuzumab deruxtecan not be considered, for this indication, unless cost effectiveness can be improved relative to existing treatments*.

Trastuzumab deruxtecan demonstrated a PFS benefit in the DB-06 trial, however no statistically significant OS or HRQoL benefit was observed. Trastuzumab deruxtecan is considerably more expensive than the current standard of care and is associated with a substantial and highly uncertain five-year cumulative net drug budget impact.

*Next steps: The NCPE Assessment Report and recommendation and Patient Organisation submission, will be considered by the HSE when making their decision on reimbursement, while also having regard to the criteria specified in the Health Pricing and Supply of Medical Goods Act 2013.

Further information on this process may be found here.