NCPE Assessment

Technical Summary

Trastuzumab deruxtecan (Enhertu®)

HTA ID: 23011

30th September 2024

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 HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

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 HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

Following assessment of the Applicant's submission, the NCPE recommends that trastuzumab deruxtecan (Enhertu®) be considered for reimbursement, for this indication, if 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 September 2023, AstraZeneca Pharmaceuticals (Ireland) DAC, on behalf of Daiichi Sankyo Ireland Ltd submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of trastuzumab deruxtecan (Enhertu®) for the treatment of adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-low breast cancer (BC) who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy. Reimbursement of trastuzumab deruxtecan is sought on the Oncology Drugs Management Scheme.

Trastuzumab deruxtecan is a HER2-targeted antibody-drug conjugate which binds to HER2 expressed on the surface of certain tumour cells causing DNA damage and apoptotic cell death. The recommended dose is 5.4mg/kg administered via intravenous infusion once every three weeks (21 days) until disease progression or unacceptable toxicity. The current standard of care for the treatment of this patient population in Ireland is treatment of physician's choice (TPC) in the form of single-agent chemotherapy, most commonly including eribulin, capecitabine, nab-paclitaxel, gemcitabine and paclitaxel.

1. Comparative effectiveness of trastuzumab deruxtecan

The efficacy and safety of trastuzumab deruxtecan is assessed in Destiny Breast-04 (DB-04), an ongoing phase III, active-controlled, open-label trial. DB-04 compares the safety and efficacy of trastuzumab deruxtecan to TPC in patients with HER2-low unresectable or metastatic BC. In total, 557 patients were randomised 2:1, including 494 patients with hormone receptor-positive (HR+) BC and 63 patients with HR-negative (HR-neg) BC.

The primary end point was progression-free survival (PFS) in the cohort with HR+ status. Key secondary end points included PFS among the Full Analysis Set (FAS), overall survival (OS) in cohort with HR+ status, and OS in the FAS [data cut off (DCO) 01 March 2023, median follow-up 32 months]. In the cohort with HR+ status, median PFS was statistically significantly longer in subjects treated with trastuzumab deruxtecan (10.1 months) compared to TPC (5.4 months), hazard ratio (HR) 0.51 (95% confidence interval (CI), 0.40 - 0.64; p<0.001). In the

FAS, median PFS was statistically significantly longer in the trastuzumab deruxtecan arm (9.9 months) compared to TPC (5.1 months), HR 0.50 (95% CI, 0.40, 0.63; p<0.001). Median OS in the FAS was 22.9 months and 16.8 months in the trastuzumab deruxtecan and TPC arms, respectively (HR: 0.69, 95% CI 0.55, 0.86). Limitations of DB-04 include the open label design and the limited HR-neg sample size, which was included in the study for exploratory purposes only.

2. Safety of trastuzumab deruxtecan

The most common adverse event (AE) in the safety dataset included nausea, fatigue and increased transaminases. The incidence of grade ≥3 AEs was 54.4% and 67.4% in the trastuzumab deruxtecan and TPC arms, respectively. The most common grade ≥3 AEs were neutropenia, anaemia and fatigue. Serious AEs were reported by 29.1% and 25.6% of patients in the trastuzumab deruxtecan and TPC arms, respectively. The Summary of Product Characteristics carries safety warnings for interstitial lung disease/pneumonitis; neutropenia; left ventricular ejection fraction decrease; and embryo-foetal toxicity. Use of trastuzumab deruxtecan is cautioned in patients with moderate and severe hepatic impairment (due to limited safety data).

3. Cost effectiveness of trastuzumab deruxtecan

The Applicant's base case analysis compared the cost-effectiveness of trastuzumab deruxtecan to TPC in the full licensed population (i.e. patients with HR+ and HR-neg HER2-low BC). Direct evidence was derived from the DB-04 trial.

Methods

A three health-state partitioned survival model was submitted by the Applicant, including three mutually exclusive health states: PFS, progressed disease and dead. The treatment effects captured by the model were the delay of disease progression and death. The key inputs of PFS, OS and time-to-treatment discontinuation (TTD) were modelled using time-to-event data from the DB-04 trial FAS. In each cycle, patients accrue quality adjusted life years (QALYs) and incur costs based on the utilities and costs specified for the health-state occupied, the relevant treatment arm, and the time on treatment. Health-related quality of life (HRQoL) utility values were derived directly from EQ-5D-5L data measured during the DB-04 trial, and mapped to the EQ-5D-3L value set. Treatment-specific utility values,

indicating a higher HRQoL utility for patients receiving trastuzumab deruxtecan compared with TPC, for patients in the same health state, were applied in the Applicant's base case. The model included drug acquisition, administration and AE costs associated with each treatment, in addition to other health-state specific healthcare resource costs. A once-off end-of-life cost was also applied. The Review Group identified a number of limitations in the Applicant's analysis, which were addressed through changes in the NCPE adjusted base case. Key changes included: 1) Using the mean body surface area derived from the European cohort of the DB-04 trial (which is expected to be more reflective of the Irish population); 2) Using the actual trastuzumab deruxtecan vial distribution from the European cohort of the DB-04 trial, rather than a mean body weight; 3) Choice of extrapolation curve for TTD; 4) Adjustment of the HRQoL utilities 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 progressed disease health state; 5) Assumption of 50% vial sharing; 6) Assumption of equivalent proportions of subsequent treatments in both arms [75.5%]. Costs and outcomes were discounted at an annual rate of 4%. The perspective of the analysis was that of the HSE.

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 TPC, in the NCPE adjusted base case was 0% at both incremental cost-effectiveness ratio (ICER) thresholds of €20,000/QALY and €45,000/QALY. A Price-ICER analysis, under the NCPE adjusted base case assumptions, indicates that a reduction of 69% and 82%, in the price-to-wholesaler (PtW) of trastuzumab deruxtecan, would be required to meet the €45,000/QALY and €20,000/QALY thresholds, respectively.

Table 1 Applicant base case incremental cost-effectiveness results (Full population) [a,b c]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
TPC	37,345	1.55	-	-	-
Trastuzumab deruxtecan	110,900	2.14	73,555	0.59	124,741

ICER: Incremental cost-effectiveness ratio; **QALY**: quality adjusted life year; **TPC**: Treatment of physician's choice.
[a] Corresponding probabilistic ICER using 1,000 iterations =€127,787/QALY. Total costs and QALYS presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable.
[b] A CIC PAS has been proposed for trastuzumab deruxtecan and is in place for eribulin (TPC), not included in this table.
[c] Additional subgroup comparisons were provided by the Applicant in patients with HR+ and HR-neg status. The ICER in the HR+ and HR-neg subgroups was €134,365/QALY and €82,025/QALY, respectively.

Table 21 NCPE adjusted base case incremental cost-effectiveness results (Full population) [a,b,c]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
TPC	40,036	1.59	-	-	-
Trastuzumab deruxtecan	122,482	2.12	82,446	0.53	153,730

ICER: incremental cost-effectiveness ratio; **NCPE**: National Centre for Pharmacoeconomics; **QALY**: quality adjusted life year; **TPC**: treatment of physician's choice.

[a] Corresponding probabilistic ICER using 1,000 iterations =€162,110/QALY. Total costs and QALYS presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable

[b] A CIC PAS has been proposed for trastuzumab deruxtecan and is in place for eribulin (TPC), not included in this table.

[c] Subgroup analysis, using NCPE-adjusted base case assumptions based on hormone-receptor status, was not conducted by the Review Group.

The Review Group identified considerable uncertainty in the long-term OS predictions in the model, which were supported in the base case by limited external data and variable clinical opinion. Additional scenario analyses were conducted, in which alternative extrapolation models were explored, to account for the possible overestimation of OS in the base case. In these scenarios, the ICER increased to €200,258/QALY.

4. Budget impact of trastuzumab deruxtecan

The PtW of trastuzumab deruxtecan is €1,650 per 100mg vial. The estimated cost of trastuzumab deruxtecan per-patient, per-treatment course is €125,134 including value added tax [VAT] (€99,998 excluding VAT), assuming a treatment duration of 11.26 months. This treatment duration was derived from the generalised gamma distribution for TTD in the cost-effectiveness model.

The Applicant estimated that 458 patients will receive treatment over five years. It is likely that the budget impact could be higher and due to the uncertainty associated with the inputs for the budget impact model, the Review Group made a number of key changes to align with the NCPE cost-effectiveness model. These related to body surface area , trastuzumab deruxtecan vial distribution and vial sharing. Additionally, the NCPE based the trastuzumab deruxtecan treatment duration on the predicted mean TTD from the NCPE adjusted base case model, and removed the Applicant's discontinuation rate of 16.20% for trastuzumab deruxtecan and TPC, as this is implicitly accounted for in the mean TTD. The NCPE adjusted five-year cumulative gross drug budget impact for trastuzumab deruxtecan is €47.4 million including VAT (€37.9 million excluding VAT). The estimated five-year

cumulative net drug budget impact is €42.8 million including VAT (€34.2 million excluding VAT).

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

6. Conclusion

The NCPE recommends that trastuzumab deruxtecan be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

Trastuzumab deruxtecan is considered to provide additional benefit to the target population compared with current standard of care, but is also associated with considerable additional costs. The magnitude of long-term benefit is uncertain due to the immaturity of the clinical trial data, particularly for the cohort with HR-neg status who were under-represented in the trial.

**This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013*