NCPE Assessment

Technical Summary

Trastuzumab deruxtecan (Enhertu®)

22050

12 December 2023

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-positive breast cancer who have received one or more prior anti-HER2-based regimens.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of trastuzumab deruxtecan (Enhertu®).

Following assessment of the Applicant's submission, the NCPE recommends that trastuzumab deruxtecan (Enhertu®) be considered for reimbursement 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 March 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)-positive breast cancer who have received one or more prior anti-HER2-based regimens. Reimbursement is sought on the Oncology Drugs Management System.

Trastuzumab deruxtecan is a HER2-targeted antibody-drug conjugate. The function of the antibody portion is to bind to HER2 expressed on the surface of certain tumour cells. After binding, the trastuzumab deruxtecan complex then undergoes internalisation and intracellular linker cleavage by lysosomal enzymes that are upregulated in cancer cells. Upon release, the membrane-permeable deruxtecan causes apoptotic cell death. The recommended dosage for trastuzumab deruxtecan is 5.4 mg/kg bodyweight as an intravenous (IV) infusion once every 21-day cycle. Treatment with trastuzumab deruxtecan should be continued until disease progression or unacceptable toxicity. Dose interruptions or dose reductions, due to adverse events (AEs) are permitted. The current standard of care for the treatment of this patient population, in Ireland, is trastuzumab emtansine.

1. Comparative effectiveness of trastuzumab deruxtecan

DESTINY-Breast03 is a phase III, international, open-label, randomised active-comparator controlled trial designed to evaluate the efficacy and safety of trastuzumab deruxtecan versus trastuzumab emtansine. The study recruited adult patients with HER2-positive, unresectable or metastatic breast cancer who had received prior treatment with trastuzumab and a taxane in the advanced or metastatic setting, or that had progressed within six months after neoadjuvant or adjuvant treatment with trastuzumab and a taxane. Patients were randomised (1:1), stratified by hormone receptor status, prior treatment with pertuzumab and history of visceral disease. The primary efficacy endpoint was independently assessed progression-free survival (PFS), and overall survival (OS) was a key secondary endpoint. Data presented in the submission pertained to the July 2022 data cut-off, which was the most recently available data at the time. At this time, the median

duration of study follow-up was 28.4 months for trastuzumab deruxtecan and 26.5 months for trastuzumab emtansine.

A total of 524 patients were randomized (trastuzumab deruxtecan n=261; trastuzumab emtansine =263). The median age of the study population was 54 years. Approximately 60% of patients were Asian; approximately 20% of the study population were European. In terms of previous treatment for metastatic disease, approximately half of participants had received one prior line of therapy, while a minority of patients (about 8%) had received five or more lines of treatment in this setting.

The 12-month PFS rates were 75.2% for trastuzumab deruxtecan and 33.9% for trastuzumab emtansine. The 24-month PFS rates were 53.7% and 26.4%, respectively. Median PFS was 28.8 months for trastuzumab deruxtecan and 6.8 months for trastuzumab emtansine (hazard ratio [HR] 0.33, 95% confidence interval [CI] 0.26 to 0.43). This was consistent across all groups included in the subgroup analysis, including subgroups stratified by number of prior lines of treatment in the metastatic setting. OS data were immature, and median OS was not reached in either treatment arm. The 12-month OS rates were 94.1% (95% CI 90.4 to 96.4) for trastuzumab deruxtecan and 86.0% (95% CI 81.1 to 89.8) for trastuzumab emtansine. The 24-month OS rates were 77.4% (95% CI 71.7 to 82.1) and 69.9% (95% CI 63.7 to 75.2), respectively.

Given the immaturity of the OS data, a benefit in terms of OS cannot be concluded. Additional results from later data cut-offs may help to establish this. However, in DESTINY-Breast03, patients randomized to trastuzumab emtansine could receive trastuzumab deruxtecan in the post-trial setting after discontinuation of study drug treatment. This may need to be considered in the interpretation of later data cut-offs.

2. Safety of **trastuzumab deruxtecan**

Safety data, informing the submission, was sourced mainly from DESTINY-Breast03. Treatment-emergent AEs were reported in 256 (99.6%) of those randomised to trastuzumab deruxtecan and 261 (95.4%) of those randomised to trastuzumab emtansine. The most frequently reported treatment-emergent AEs in those randomised to trastuzumab deruxtecan were gastrointestinal and haematological in nature. Compared to subjects receiving trastuzumab emtansine, those who received trastuzumab deruxtecan had a ≥10

percentage point higher incidence of the following treatment-emergent AEs: nausea, fatigue, vomiting, neutropenia, alopecia, constipation, anaemia, leukopenia, decreased appetite, diarrhoea, abdominal pain, stomatitis, and neutrophil count decreased. Interstitial lung disease/pneumonitis has previously been identified as an important AE associated with trastuzumab deruxtecan. A total of 39 (15.2%) patients in the trastuzumab deruxtecan arm and 8 (3.1%) patients in the trastuzumab emtansine arm reported drug-related interstitial lung disease (maximum observed Grade 3 severity). The observed frequency of left ventricular dysfunction was consistent with the known safety profile of trastuzumab-based drugs.

The safety profile of trastuzumab deruxtecan is considered clinically significantly different from that observed with trastuzumab emtansine. However, the safety profile overall is considered acceptable and manageable by the European Medicines Agency. Interstitial lung disease is the most prominent AE associated with trastuzumab deruxtecan.

3. Cost effectiveness of **trastuzumab deruxtecan**

Methods

The Applicant used a partitioned-survival model comprising three health states: 'Progression free', 'Post progression' and an absorbing death state. The modelled population was aligned with the DESTINY-Breast03 study population, and were modelled over a lifetime horizon. The treatment effects captured by the model were the delay of disease progression and death. The key efficacy inputs to the model were PFS and OS, which were modelled using treatment group-specific parametric distributions fitted to time-to-event data from DESTINY-Breast03. In each cycle, patients accrued quality-adjusted life years (QALYs) and incurred costs based on the utilities and costs specified for the health-state occupied, the relevant treatment arm, and the time on treatment. Utilities were informed by health-related quality of life data from DESTINY-Breast03 and the literature.

The NCPE Review Group identified a number of concerns which were addressed in the NCPE-adjusted base case. These included:

- Using modelled population characteristics aligned with the population in Ireland, as opposed to the international DESTINY-Breast03 study population.

- Assuming no vial sharing, as opposed to 50% vial sharing assumed by the Applicant.
- Assuming the same proportion of patients who received trastuzumab deruxtecan and trastuzumab emtansine would receive subsequent treatment, if they experienced disease progression. The Applicant assumed patients who received trastuzumab deruxtecan were less likely to receive subsequent treatments.
- Using clinical opinion from clinicians in Ireland to reweight subsequent treatments given, as opposed to direct data the DESTINY-Breast03 trial data.

Results

Deterministic incremental cost-effectiveness ratios (ICERs) generated under the NCPE-adjusted base case and Applicant's base case model assumptions are presented in Tables 1 and 2, respectively.

Table 1: NCPE-adjusted base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Trastuzumab emtansine	193,302	2.708	-	-	-
Trastuzumab deruxtecan	333,166	3.966	139,865	1.258	111,193

QALY: quality-adjusted life year;
[a] Corresponding probabilistic ICER using 1,000 iterations = €112,800/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. The discount rate applied to costs and outcomes is 4%.

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

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Trastuzumab emtansine	226,025	2.708	-	-	-
Trastuzumab deruxtecan	315,684	3.966	89,659	1.258	71,279

QALY: quality-adjusted life year
[a] Corresponding probabilistic ICER using 1,000 iterations =€70,792/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. The discount rate applied to costs and outcomes is 4%.

Sensitivity analysis

Under the NCPE-adjusted base case, the probability of cost effectiveness was 0.0% at a willingness-to-pay thresholds of €20,000 per QALY and €45,000 per QALY. Under the Applicant's base case, the probabilities of cost effectiveness at the €20,000 per QALY and €45,000 per QALY thresholds were 1.2% and 13.4%, respectively. The scenario analyses which had the greatest impact on cost-effectiveness related to variation in the selected parametric distributions for PFS and OS. Both PFS and OS extrapolations are subject to considerable uncertainty, which is driven by the short duration of trial follow-up data. A price ICER analysis on the NCPE-adjusted base case demonstrated that 41.2% and 54.6%

price reductions on the price to wholesaler are required to achieve ICERs of €45,000 and €20,000 per QALY, respectively.

4. Budget impact of **trastuzumab deruxtecan**

The price-to-wholesaler of trastuzumab deruxtecan is €1,650 per 100 mg vial (pack size: one vial). Assuming a patient bodyweight of 73 kg and no vial sharing, the expected per-patient cost for 18.2 months treatment (median duration of treatment with trastuzumab deruxtecan in DESTINY-Breast03) is €199,676 including VAT (€159,566 excluding VAT).

The Applicant predicted 48 patients would receive treatment with trastuzumab deruxtecan in Year 1, increasing to 83 patients by Year 5. Under the Applicant's base case assumptions, the five-year cumulative gross drug budget impact was estimated at €59.4 million including VAT (€47.3 million excluding VAT), and the net drug budget impact was €42.9 million including VAT (€34.3 million excluding VAT). The NCPE-adjusted base case assumed a higher mean patient bodyweight, assumed no vial sharing and used mean (as opposed to median) treatment duration to estimate treatment costs. Under the NCPE-adjusted base case, the five-year cumulative gross drug budget impact was €66.5 million including VAT (€53.1 million excluding VAT), and the net drug budget impact was €40.5 million including VAT (€32.4 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 (Enhertu®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

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