NCPE Technical Summary

Olaparib (Lynparza®)

HTA ID: 22065

24 September 2024

Applicant: AstraZeneca

Olaparib as monotherapy or in combination with endocrine therapy for the adjuvant treatment of adults with germline *BRCA1/2*-mutations who have HER2-negative high risk breast cancer previously treated with neoadjuvant or adjuvant chemotherapy.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of olaparib (Lynparza®) as monotherapy or in combination with endocrine therapy for the adjuvant treatment of adults with germline *BRCA1/2*-mutations who have HER2-negative high risk breast cancer previously treated with neoadjuvant or adjuvant chemotherapy.

Following assessment of the Applicant's submission, the NCPE recommends that olaparib (Lynparza®) 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) Health Technology Assessment of olaparib (Lynparza®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes 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, the Applicant (AstraZeneca) submitted a dossier which investigated the clinical effectiveness, cost-effectiveness and budget impact of olaparib (Lynparza®) as monotherapy or in combination with endocrine therapy for the adjuvant treatment of adults with germline *BRCA1/2*-mutations (g*BRCA*m) who have human epidermal growth factor receptor 2 (HER2)-negative high risk breast cancer previously treated with neoadjuvant or adjuvant chemotherapy. The Applicant is seeking reimbursement of olaparib, for this indication, under the High Tech Drug Arrangement.

Olaparib is a poly-ADP-ribose polymerase (PARP) inhibitor. The recommended dose is 300mg orally twice daily. For this indication it is recommended that patients are treated for up to one year, or until disease progression, or unacceptable toxicity, whichever occurs first. Olaparib may be given as monotherapy, or in combination with endocrine therapy in hormone-receptor (HR)-positive disease.

The Applicant anticipates that olaparib will be used according to its licensed indication (as stated above). In line with the current standard of care (SoC) in Ireland, the proposed comparator is 'watch and wait'.

1. Comparative effectiveness of olaparib (Lynparza®)

The clinical evidence, supporting the regulatory approval of olaparib, comes from the ongoing OlympiA trial. OlympiA is a phase III, double-blind, randomised controlled trial (RCT) designed to evaluate the safety and efficacy of olaparib (n=921) versus placebo (n=915). Background adjuvant endocrine therapy was also received by the vast majority (90%) of patients with HR-positive disease. The trial enrolled adults with HER2-negative early breast cancer with a g*BRCA*m and high risk clinicopathological factors who had received prior treatment with neoadjuvant or adjuvant chemotherapy. Initially, only patients with HR-negative, HER2-negative (triple negative) breast cancer (TNBC) were enrolled. A protocol amendment, approximately 18-months after study start, widened the inclusion criteria to include HR-positive disease. Overall, approximately 18% of patients had HR-positive disease i.e. were HR-positive, HER2-negative (HR+/HER2-), with the remaining 82% having TNBC. Treatment was continued until confirmation of disease recurrence or unacceptable toxicity, up to a maximum of one-year. The primary endpoint was investigator-assessed invasive

disease-free survival (iDFS), (a composite endpoint of non-metastatic and metastatic recurrence, and death without recurrence), with overall survival (OS) measured as a key secondary endpoint.

The first interim analysis (DCO1) was conducted in March 2020 (median follow-up 2.5 years) and included the primary iDFS analysis. A second interim analysis (DCO2) was conducted in July 2021 (median follow-up 3.5 years). Both data cuts provided the clinical basis supporting regulatory approval. At DCO2, hazard ratios of 0.63 (95% confidence interval [CI] 0.50 to 0.78) and 0.68 (95% CI 0.50 to 0.91) were observed for iDFS and OS, respectively. Median iDFS and OS were not reached in either treatment arm. Limitations of the OlympiA trial include the immaturity of the trial data (18.6% iDFS and 10% OS events had occurred at DCO2), over-representation of TNBC in the trial population compared to the patient population in Ireland, and imbalances in subsequent treatments which may confound assessment of OS.

2. Safety of olaparib (Lynparza®)

Overall, the safety data from OlympiA were consistent with the known safety profile of olaparib. All-grade adverse events (AEs) were reported in 91.8% of patients receiving olaparib and 83.8% receiving placebo. The most frequently reported AEs with olaparib were gastrointestinal (nausea, vomiting, and diarrhoea), nervous system disorders (headache, dysgeusia and dizziness), infections and infestations (neutrophil count decreased, and white blood cell decreased), fatigue, anaemia, and decreased appetite. The majority of AEs were Grade 1 or 2 in severity. The olaparib SmPC carries special warnings for haematological toxicity, myelodysplastic syndrome/acute myeloid leukaemia, venous thromboembolic events and pneumonitis.

3. Cost effectiveness of olaparib (Lynparza®)

Separate cost-effectiveness analyses were presented for the populations with TNBC and HR+/HER2- disease. Although patients can be considered high risk irrespective of histological subtype, risk of recurrence has been demonstrated to differ between patients with TNBC and HR+/HER2- disease. The difference in risk between the patient populations is expected to impact long-term costs and health outcomes.

Methods

A cost-utility analysis using a semi-Markov transition model developed in Microsoft Excel® was submitted by the Applicant. The model included five mutually exclusive health states: 'disease-free', 'non-metastatic recurrence', 'early onset metastatic recurrence', 'late onset metastatic recurrence' and 'death.' The model assumed a cycle length of one-month and a lifetime horizon. A half-cycle correction was applied. The same model structure was used for the populations with TNBC and HR+/HER2- status. Transition probabilities were based on the intention-to-treat (ITT) population. The exception to this is the use of TNBC specific data in the modelling of iDFS in this population.

To derive transition probabilities from the 'disease-free' health state, parametric survival models were fitted to iDFS Kaplan-Meier (KM) data from OlympiA and extrapolated for each treatment arm separately, with the placebo arm considered a proxy for SoC ('watch and wait'). The subgroup analyses represented differences in the risk of recurrence between TNBC and HR+/HER2- disease. The extrapolated curves chosen by the Applicant indicated that the hazard rate for olaparib will eventually become higher than SoC. However, the Applicant did not believe that this was a plausible assumption and therefore olaparib iDFS hazard rates were adjusted such that they were always lower than or equal to SoC. The Review Group considered that a reduction in the hazard rate for SoC once a number of patients in that cohort have already relapsed was plausible and therefore believed that this adjustment was inappropriate. To inform the transitions to 'non-metastatic recurrence' a conditional probability for non-metastatic recurrence (derived from iDFS event types in OlympiA) was applied to the iDFS survival curves. Patients that developed a metastatic recurrence in the first two-years entered the 'early onset metastatic recurrence' health state, with those developing a metastatic recurrence after two years entering the 'late onset recurrence' health state. Transitions from 'disease-free' to the 'death' health state were based on general population mortality with an adjustment to reflect excess mortality in the population with g*BRCA*m.

Transition probabilities from the 'non-metastatic recurrence' and 'early onset metastatic recurrence' health states were derived by fitting parametric survival models to KM data from OlympiA. The same distributions were used for each population. No clinical benefit was assumed for olaparib in the transitions from the 'non-metastatic recurrence' health state.

Separate survival curves were used for the transition from the 'early onset recurrence' health state for each treatment.

Transition probabilities from 'late onset metastatic recurrence' to death were modelled using data external to the OlympiA trial, to reflect the benefits of different treatment options in the late metastatic recurrence setting.

Health-related quality of life utility estimates for the 'disease-free' health state were informed by the OlympiA trial. It was assumed that patients in the 'non-metastatic recurrence' health state would have the same utility as those in the 'disease-free' health state. Due to a paucity of data in the metastatic setting from the OlympiA trial, estimates were informed by the available literature. Health state utility values were adjusted for age, and disutilities were included for AEs.

Direct medical costs were included for drug acquisition (including administration where appropriate), *BRCA* mutation testing, disease management including further surgery, radiotherapy and/or drug therapy for recurred disease, and AEs. A once-off end-of-life cost was applied. Irish costs were used where available.

The Review Group identified several limitations with the cost-effectiveness analysis. The immaturity of the trial data and short duration of follow-up relative to the model time horizon results in considerable uncertainty in the survival extrapolations derived from the OlympiA trial. Furthermore, the low patient numbers used to derive transitions from the 'non-metastatic recurrence' health state, and the adjustment of iDFS hazards for olaparib to not exceed those of SoC, add additional uncertainty to these estimates. Finally, the ITT population is dominated by the TNBC subgroup and as such the cost-effectiveness results for the population with HR+/HER2- status are very uncertain.

Results

Due to uncertainty in the cost-effectiveness model, the Review Group removed the adjustment of iDFS hazards for olaparib to not exceed SoC in an NCPE-adjusted base case. The results of the Applicant's base case, and the NCPE-adjusted, deterministic cost-effectiveness analyses are presented in Table 1 for the population with TNBC status and Table 2 for the population with HR+/HER2- status.

Table 1: Incremental cost -effectiveness results (population with TNBC status)

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Applicant base case analysis[a]					
Olaparib	78,806	13.54	-	-	
Watch and wait	32,237	12.48	46,568	1.05	44,240
NCPE-adjusted analysis[b]					
Olaparib	79,667	13.43	-	-	
Watch and wait	32,237	12.48	47,430	0.95	50,186

ICER: incremental cost-effectiveness ratio; **QALY:** quality adjusted life year
[a] Corresponding probabilistic ICER using 5,000 iterations = €42,644/QALY
[b] Corresponding probabilistic ICER using 5,000 iterations = €46,186/QALY
Total costs and QALYS presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable

Table 2: Incremental cost -effectiveness results (population with HR+/HER2- status)

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Applicant base case analysis[a]					
Olaparib	111,632	11.80	-	-	
Watch and wait	58,601	10.88	53,031	0.92	57,916
NCPE-adjusted analysis[b]					
Olaparib	111,876	11.79	-	-	
Watch and wait	58,601	10.88	53,275	0.90	58,945

ICER: incremental cost-effectiveness ratio; **QALY:** quality adjusted life year
[a] Corresponding probabilistic ICER using 5,000 iterations = €53,267/QALY
[b] Corresponding probabilistic ICER using 5,000 iterations = €53,903/QALY
Total costs and QALYS presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable

The Review Group also calculated a weighted ICER for the full, licensed population based on the proportions of patients with HR+/HER2- and TNBC status assumed in the budget impact model (BIM) (i.e. 85.6% HR+/HER2- and 14.4% TNBC). This resulted in an NCPE-adjusted ICER of €57,634 per QALY.

Sensitivity analysis

Mean probabilistic ICERs were aligned with deterministic ICERs. Sensitivity analyses indicated that the main drivers of cost-effectiveness in the Applicant base case related to the choice of survival distributions for iDFS and also the utility values.

A price-ICER analysis, under the NCPE-adjusted base case assumptions, based on the full, licensed population (with HR+/HER2- and TNBC proportions based on those used in the BIM) indicates that reductions in the olaparib price-to-wholesaler (PtW) of approximately 30% and 70% are required to meet the €45,000 per QALY and €20,000 per QALY thresholds, respectively.

4. Budget impact of olaparib (Lynparza®)

The PtW of olaparib is €2,445.81 for a pack of 56 x 150mg tablets. The total cost per patient per treatment course (assuming a mean treatment duration of 294.4 days, based on the OlympiA trial) is about €51,775, including all relevant fees, mark ups and rebates. Note: VAT is not applicable to oral treatments.

The Applicant submitted a BIM. Many of the inputs are uncertain and there is therefore considerable uncertainty associated with budget impact estimates. The Applicant estimated that 198 patients would receive treatment over five years. The Applicant's estimated five-year cumulative gross budget impact for olaparib is €10.4 million. Reimbursement of olaparib for this indication is not expected to result in cost offsets due to the displacement of other drugs. Therefore, the net drug budget impact is the same as the gross drug budget impact.

5. Patient Organisation Submission

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

6. Conclusion

The NCPE recommends that olaparib be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*. Olaparib 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+/HER2- 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.