Cost-effectiveness of olaparib (Lynparza®) for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) *BRCA1/2*-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of olaparib (Lynparza®). Following assessment of the Applicant's submission, the NCPE recommends that olaparib (Lynparza®) for this indication not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.

The HSE asked the NCPE to carry out an assessment of the Applicant's (AstraZeneca) economic dossier on the cost effectiveness 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.

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

National Centre for Pharmacoeconomics **March 2020**

Summary

Olaparib has received a number of different licences, including extensions, which are detailed here. This assessment considers the cost effectiveness of the specific *BRCA* mutated group who have responded to first-line platinum-based chemotherapy.

In October 2019, AstraZeneca submitted a dossier examining the cost-effectiveness of olaparib tablets for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) *BRCA1/2*-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete [CR] or partial [PR]) following completion of first-line platinum-based chemotherapy. Olaparib was granted marketing authorisation by the European Commission for this indication in June 2019. This was an extension to the previous marketing authorisation, granted in May 2018, for olaparib tablets for maintenance treatment of adult patients with platinum-sensitive relapsed (PSR) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (CR or PR) to platinum-based chemotherapy. The capsule formulation of olaparib was granted marketing authorisation in December 2014 for the maintenance treatment of adult patients with PSR *BRCA* mutated (germline and/or somatic) high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (CR or PR) to platinum-based chemotherapy. It should be noted that the extended indication is for olaparib tablets only. Orphan designation for olaparib was removed in March 2018.

The recommended dose for olaparib tablets, for the indication under consideration here, is 300mg (two 150mg tablets) taken orally twice daily. Treatment with olaparib tablets is continued until radiological disease progression or for up to two years if there is no radiological evidence of disease. Patients with evidence of disease at two years, who, in the opinion of the treating physician, can derive further benefit from continuous treatment, can be treated beyond two years. The Applicant is seeking reimbursement under the High-Tech Drug Arrangement. Olaparib is a potent PARP-1, -2 and -3 inhibitor (ATC code: L01XX46).

There is no treatment currently reimbursed in Ireland for the indication under consideration here. The main comparator in the cost-effectiveness analysis is a 'watch and wait' approach (placebo may be considered as a proxy). Bevacizumab is prescribed for this indication in Ireland. Therefore, a comparison against bevacizumab was considered but not found to be feasible.

1. Comparative effectiveness of olaparib

Direct comparative evidence for the effectiveness of olaparib versus placebo in adult patients, with newly diagnosed advanced (FIGO stages III and IV) *BRCA1/2*-mutated (germline or somatic) high-grade serous or endometrioid epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (CR or PR) following completion of first-platinum-based chemotherapy, is available from the ongoing (not recruiting) SOLO1 double-blind randomised controlled trial.

Patients were randomised in a 2:1 ratio to receive olaparib 300mg twice daily (n=260) or placebo (n=131). The primary endpoint was progression-free survival (PFS) based on investigator assessment. Secondary endpoints included overall survival (OS), PFS2 (defined as second progression), time to first subsequent treatment (TFST), time to second subsequent treatment (TSST), time to discontinuation of treatment (TTD), and adverse events (AEs). Health related quality of life (HRQoL) measures were also collected using the Functional Assessment of Cancer Therapy–Ovarian Cancer (FACT-O) and EQ-5D-5L questionnaires. Median follow-up was 40.7 months for patients receiving olaparib and 41.2 months for patients receiving placebo.

Median PFS was not reached in patients receiving olaparib and was 13.8 months (95% CI 11.1 to 18.2) in patients receiving placebo; HR = 0.30 (95% CI 0.23 to 0.41). Median PFS2 was not reached in patients receiving olaparib and was 41.9 months (95% CI 36.5 to 47.9) in patients receiving placebo; HR = 0.50 (95% CI 0.35 to 0.72). Median OS was not reached in either treatment arm; HR = 0.95 (95% CI 0.60 to 1.53). PFS, PFS2 and OS data were immature. HRQoL scores did not indicate a clinically meaningful difference between the treatment arms. The Review Group has concerns regarding the immaturity of the clinical

effectiveness data, such that robust conclusions regarding the relative benefit of olaparib compared to placebo cannot be made.

2. Safety of olaparib

The safety population included all patients who received at least one dose of study drug. Median treatment duration was 24.6 months in patients receiving olaparib and 13.9 months in patients receiving placebo.

AEs were more common in patients receiving olaparib (any 98.5%; grade ≥3 39.2%) compared to those receiving placebo (any 92.3%; grade ≥3 18.5%). The most commonly reported grade 3-4 AEs in patients receiving olaparib were anaemia (22% vs 2% in patients receiving placebo) and neutropenia (9% vs 5% in patients receiving placebo). Acute myeloid leukaemia occurred in three (1.2%) patients receiving olaparib and none receiving placebo. All cases of AML occurred more than 30 days after the end of olaparib treatment. Pneumonitis or interstitial lung disease occurred in five (1.9%) of the patients receiving olaparib and no patients receiving placebo.

3. Cost effectiveness of olaparib (Lynparza®)

Methods

The cost-effectiveness was assessed using a four-state partitioned survival cost-utility model with a cycle length of one month and a 50-year time horizon, with a half-cycle correction applied. All patients enter the model in the progression-free health state (PFS) and are at risk of progression (PD1) or death without progression. Patients that have progression are then at risk of secondary progression (PD2) or death. From the PD2 health state patients are at risk of death. The inclusion of the PD2 health state facilitates the inclusion of second-line PARP inhibitors. The key effectiveness inputs in the model were PFS, PFS2 and OS. To reflect long-term survival in the model, the survival rate for PFS, after a landmark of seven years, was set to equal all-cause mortality. The model consistently overpredicted median OS in the comparison with a 'watch and wait' approach. As relatively robust fits to SOLO1 data were observed for olaparib OS, a constant treatment effect was applied to the olaparib arm to generate results for the 'watch and wait' arm. As OS data were immature in SOLO1, the incremental difference was estimated from PFS2, accounting for subsequent PARP inhibitor

use. The Review Group had concerns regarding the immaturity of the PFS2 data from SOLO1 and the validity of assuming the relative difference observed in PFS2 translates to OS. There are also concerns regarding the assumption that any OS benefit would persist for the lifetime of the model when OS data from SOLO1 shows that the olaparib and placebo curves cross as approximately 45 months.

Utilities identified in the model included health state utilities and utility decrements for age and AEs. Health state utilities for the PFS and PD1 states were based on EQ-5D-5L data from SOLO1. EQ-5D 5L was mapped to EQ-5D 3L using the van Hout *et al.* cross walk algorithm. Utilities for PD2 were sourced from NICE TA381. The Review Group considers that relevant costs were included in the model. Costs were included for drug acquisition and administration, disease monitoring, AEs, end-of-life care and *BRCA* mutation testing (olaparib arm only). Irish cost data were used where possible.

Results

Due to uncertainty in the assumptions used in the economic model, the Review Group suggested several changes to the Applicant base case based on plausible alternative assumptions, including using a differing survival curve for PFS, PFS2 and OS, removal of the seven-year landmark, the use of Kaplan-Meier data for 36 months for OS and assuming no treatment effect on OS. The NCPE adjusted ICERs (Table 1) and the Applicant base case ICERs (Table 2) are shown.

Table 1: NCPE adjusted base case analysis*

Treatment	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)
Watch and wait			
Olaparib	72,961	0.97	75,289

QALY: Quality adjusted life year; **ICER:** Incremental Cost Effectiveness Ratio
*A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.

Table 2: Applicant base case ICERs*

Treatment	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)
Watch and wait			
Olaparib	65,063	2.28	28,571

QALY: Quality adjusted life year; **ICER:** Incremental Cost Effectiveness Ratio
*A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.

The Review Group has concerns that the NCPE adjusted base case remains subject to considerable uncertainty in assumptions surrounding the extrapolation of OS, including uncertainty introduced using trial data with limited follow-up to predict long-term survival. Therefore, the Review Group considers that the results are not robust, thus making it difficult to draw definitive conclusions regarding the cost-effectiveness of olaparib versus watch and wait.

Sensitivity analysis

The respective probabilistic and deterministic ICERs were comparable for the NCPE adjusted base case. The probability of cost-effectiveness for the NCPE adjusted base case at threshold of €45,000 per QALY was 40% decreasing to 3% for a threshold of €20,000.

The Review Group notes that scenario analyses altering the OS treatment effect covariate in the cost-effectiveness model result in substantially differing estimates of cost-effectiveness. Some plausible scenarios resulting in a 'watch and wait' approach dominating olaparib, i.e. olaparib becomes associated with higher costs and lower QALYs. Highlighting the substantial degree of uncertainty in the survival curves.

4. Budget impact of olaparib

The price to wholesaler of olaparib is €2,507.00 for a pack of 56 x 150mg tablets. The mean annual drug acquisition cost of olaparib, including all relevant fees, mark-ups and rebates is estimated as €67,785 per patient; assuming a 100% dosing intensity. Mean treatment duration was estimated from SOLO1, resulting in an average treatment cost per patient of €116,930.

The Applicant estimated that 19 patients would be treated with olaparib in year 1, rising to 20 in year 2, then dropping to 16 in year 5. The projected cumulative 5-year gross drug budget impact is €9.1 million.

The Applicant also presented a net budget impact assuming offsets for fewer patients receiving bevacizumab as first-line combination chemotherapy followed by bevacizumab maintenance. This resulted in a cumulative 5-year net drug budget impact of €4.0 million.

5. Patient submission

A patient organisation submission was received from Ovacare.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that olaparib (Lynparza®) for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) *BRCA1/2*-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in response (CR or PR) following completion of first-line platinum-based chemotherapy, not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

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