Cost-effectiveness of olaparib (Lynparza®) as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy

The 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®) not be considered for reimbursement unless 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.

The HSE asked the National Centre for Pharmacoeconomics (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.

National Centre for Pharmacoeconomics **February 2020**

Summary

In June 2019, AstraZeneca submitted a dossier examining the cost-effectiveness of olaparib tablets as a monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed (PSR) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete [CR] or partial [PR]) to platinum-based chemotherapy, (i.e. all patients regardless of *BRCA* mutation status). Olaparib was granted marketing authorisation by the European Commission for this indication in May 2018. This was an extension to the previous marketing authorisation, granted in December 2014, for the capsule formulation of olaparib as monotherapy for the maintenance treatment of adult patients with PSR relapsed *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 and does not include the capsule formulation. Furthermore, the requirement for tumours to be serous in origin has also been removed from the extended indication for olaparib tablets. 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. The recommended dose for olaparib capsules, as monotherapy for the maintenance treatment of adult patients with PSR relapsed *BRCA*-mutated high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer, is 400mg (eight 50mg capsules) taken orally twice daily. For both tablets and capsules treatment should be continued until disease progression. Olaparib capsules are currently reimbursed under the High-Tech Drug Arrangement and the Applicant is seeking reimbursement of olaparib tablets. Olaparib is a potent PARP-1, -2 and -3 inhibitor (ATC code: L01XX46).

Three cost-effectiveness analyses were presented; one for the intention to treat (ITT) population and two sub-group analyses for patients with a deleterious *BRCA* mutation (*BRCA*m) and for those without a *BRCA* mutation (non-*BRCA*m). Niraparib and a 'watch and wait' approach were chosen as the comparators for all three cohorts.

1. **Comparative effectiveness of olaparib**

Two randomised controlled trials provide direct evidence for the efficacy of olaparib versus placebo (may be considered a proxy for a 'watch and wait' approach) in patients with PSR, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (CR or PR) to platinum-based chemotherapy. Study 19 was the pivotal phase II trial, including patients with *BRCA*m and non-*BRCA*m status, that supported the EMA approval of olaparib capsules in patients with *BRCA*m PSR high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer. SOLO2 was the phase III trial, including patients with *BRCA*m (germline and/or somatic) that supported the change in the EMA marketing authorisation to support use of olaparib tablets in patients with PSR, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer regardless of *BRCA* mutation status. In their evaluation report the CHMP concluded that the extrapolation of efficacy results obtained with the capsule formulation to tablet formulation was reasonably supported by the pharmacokinetic data (Study 24 was a Phase I formulation comparison study of the comparative bioavailability of olaparib capsules and tablets) and that Study 19 data support the indication in patients regardless of *BRCA* mutation status.

In Study 19, patients were randomly assigned 1:1 to olaparib capsules (n=136) 400mg orally twice daily or placebo (n=129). Knowledge of a patient's *BRCA* mutation status was not required for inclusion in Study 19 but was determined retrospectively. Statistical analyses were conducted on the ITT population and also in the subgroups with *BRCA*m and non-*BRCA*m status. Patients in SOLO2 were randomly assigned 2:1 to olaparib tablets (n=196) 300mg orally twice daily or placebo (n=99). SOLO2 provided data for patients with *BRCA*m only. The primary endpoint, in both trials, was progression-free survival (PFS) as assessed by investigator (INV). Secondary endpoints in Study 19 included; overall survival (OS) and adverse events (AEs). The EMA requested three additional *post hoc* exploratory analyses of treatment effect: time to discontinuation of study treatment (TTD), time to first subsequent treatment (TFST) and time to second subsequent treatment (TSST). Secondary endpoint analyses in SOLO2 included; time from randomisation to second progression (PFS2), TTD, TFST, TSST, OS and AEs. Health related quality of life (HRQoL) measures were also collected in both trials, using the EQ-5D-5L (SOLO2) and FACT-O (Study 19 and SOLO2). Median

follow-up was 5.6 months for PFS in Study 19 and 78 months for all other endpoints. In SOLO2 patient median follow-up was 22 months for all endpoints.

The clinical effectiveness results were as follows:

Study 19

ITT cohort (i.e. Patients with BRCAm status and patients with non-BRCAm status; n=265)

- Median PFS; olaparib = 8.4 months (95% CI 7.4 to 11.5), placebo = 4.8 months (95% CI 4.0 to 5.5), HR = 0.35 (95% CI 0.25 to 0.49).
- Median OS; olaparib = 29.8 months (95% CI 26.9 to 35.7), placebo = 27.8 months (95% CI 24.9 to 33.7), HR = 0.73 (95% CI 0.55 to 0.95).

Subgroup with BRCAm status (n=136)

- Median PFS; olaparib = 11.2 months (95% CI 8.3 to not reached (NR)), placebo = 4.3 months (95% CI 3.0 to 5.4), HR = 0.18 (95% CI 0.10 to 0.31).
- Median OS; olaparib = 34.9 months (95% CI 29.2 to 54.6), placebo = 30.2 months (95% CI 23.1 to 40.7), HR = 0.62 (95% CI 0.42 to 0.93).

Subgroup with non-BRCAm status (n=118)

- Median PFS; olaparib = 7.4 months (95% CI 5.5 to 10.3), placebo = 5.5 months (95% CI 3.7 to 5.6), HR = 0.54 (95%CI 0.34 to 0.85).
- Median OS; olaparib = 24.5 months (95% CI 19.8 to 35.0), placebo = 26.6 months (95% CI 23.1 to 32.5), HR = 0.84 (95%CI 0.57 to 1.25).

SOLO2

ITT cohort (i.e. patients with BRCAm status; n=295)

- Median PFS; olaparib = 19.1 months (95% CI 16.3 to 25.7, placebo = 5.5 months (95% CI 5.2 to 5.8), HR = 0.30 (95% CI 0.22 to 0.41).
- Median OS; olaparib = NR, placebo = NR, HR = 0.80 (95% CI 0.50 to 1.31).

HRQoL scores indicated similar patient reported scores between arms in both Study 19 and SOLO2.

The Review Group had concerns that while SOLO2 assesses the formulation of interest (tablet) it only includes a subgroup (patients with *BRCA*m status) of the population of interest. Further, many key outcomes in the trial are immature. Study 19 provides more mature data for all outcomes in the relevant population, but for the capsule formulation (which is not licensed for the extended indication). Consequently, definitive long-term data for olaparib tablets must be inferred from data obtained for capsules. There are also concerns that the treatment effect described in the subgroups with *BRCA*m and with non-*BRCA*m were based on exploratory post-hoc analyses of Study 19 and are therefore susceptible to bias. There were additional concerns regarding OS. While OS data in Study 19 were relatively mature, the trial was not powered to show an OS benefit. OS data in SOLO2 were immature with median OS not reached in either treatment arm. Consequently, robust direct evidence of OS benefit with olaparib tablets is not available. Updated OS data from SOLO2 is anticipated in late 2020.

In the absence of direct head-to-head evidence comparing olaparib and the PARP inhibitor niraparib, the Applicant explored the feasibility of conducting network meta-analyses (NMAs) using Study 19 and SOLO2 and a trial of niraparib versus placebo in patients with PSR, high-grade serous or predominantly serous ovarian, fallopian tube or primary peritoneal cancer (ENGOT-OV16/NOVA). Separate NMAs were performed for the cohorts with *BRCA*m status and non-*BRCA*m status. Several issues were identified in terms of differences in patient populations, prior therapies, methodologies of assessing PFS, definition and maturity of PFS and maturity of OS between the three trials and the Applicant did not deem a robust formal comparison feasible. Therefore, naive comparisons using extrapolated survival data from the olaparib arms of Study 19, SOLO2 and ENGOT-OV16/NOVA were used in the cost-effectiveness model. The Review Group does not consider the issues regarding the feasibility of the NMAs sufficient to preclude their use and considers NMAs, including all relevant evidence, would provide more robust estimates of the relative treatment effect of olaparib and niraparib than a naive comparison. The Review Group considers the use of the naïve comparison to be associated with a high level of uncertainty.

2. Safety of olaparib (Lynparza®)

Safety data were reported for the ITT population of Study 19 as the pattern of AEs observed in the subgroups with *BRCA*m status and non-*BRCA*m status was consistent with that observed for the ITT population. Study 19 provided over 6.5 years of long-term follow-up data for olaparib capsules. SOLO2 provided safety data for olaparib tablets for 22 months of follow-up. In both trials the safety population included all patients who had received at least one dose of study drug.

AEs were more common in patients receiving olaparib than placebo; Study 19 any grade 97.1% vs. 93.0% respectively, grade ≥3 43.4% vs. 21.9%, and SOLO2 any grade 98.5% vs. 94.9, grade ≥3 36.9% vs. 18.2%.

The most commonly reported grade 3-4 AEs in the olaparib arm in Study 19 were fatigue (8.1% vs 3.1% in the placebo group), anaemia (5.9% vs 0.8%), neutropenia (3.7% vs 0.8%) and abdominal pain (2.2% vs 3.1%). The only serious AE reported in more than two patients in either treatment group was anaemia (2.2% in the olaparib group vs 0% in the placebo group). The most commonly reported grade 3-4 AEs in the olaparib arm in SOLO2 were anaemia (19.5% vs. 2.0% placebo), abdominal pain (2.6% vs. 3.0%) and asthenia (3.1% vs. 2.0%). The most common serious AEs reported in the olaparib group in SOLO2 were anaemia (3.6% vs. 0% in the placebo group), abdominal pain (1.5% vs. 0%) and intestinal obstruction (1.5% vs. 1.0%).

The Applicant performed a set of indirect treatment comparisons to compare the safety of PARP inhibitor maintenance therapy, including olaparib and niraparib, in PSR ovarian cancer. Olaparib tablets were predicted to have a better safety profile than niraparib in patients with a *BRCA*m status. These results were mirrored for olaparib capsules in patients with a non-*BRCA*m status. Haematological and cardiovascular adverse effects were more frequent with niraparib than olaparib. In addition, greater discontinuity of treatment was observed in patients treated with niraparib compared to olaparib.

3. Cost effectiveness of olaparib (Lynparza®)

Methods

The cost-effectiveness was assessed using a three-state partitioned survival cost-utility model with a cycle length of one month and a 20-year time horizon, with a half-cycle correction applied. All patients enter the model in the progression free health state and remain there until experiencing progressive disease (where they move to the progressive disease health state). Death was the absorbing state. Costs of disease management, utilities and risks of death all differ between the progression free and progressive disease health states. The partitioned survival approach uses the "area under the curve" approach, where the number of patients in each health state at a given time is taken directly from survival curves fitted to clinical trial data. The model explored the use of both standard parametric and spline-based models, with spline-based models predominantly selected for the base case.

Study 19 was used to inform clinical data for olaparib and the comparison with a 'watch and wait' approach in the model base case, with ENGOT-OV16/NOVA used to inform niraparib data. Separate models were presented for the ITT population and the subgroups with *BRCA*m and non-*BRCA*m status for both comparisons. It should be noted that the prevalence of patients with *BRCA*m status in Study 19 (approximately 50%) does not reflect real world prevalence, where 10-15% of cases of ovarian cancer would occur in patients with germline BRCA mutations, plus approximately 5-6% of patients with tumours harbouring somatic BRCA mutations. Consequently, ICERs derived from the ITT population may not be reflective of the Irish population. The key effectiveness inputs in the model were PFS, time to treatment discontinuation (TTD) and OS. As the data were more mature only clinical effectiveness data from Study 19 were used in the model base case, implicitly assuming equivalence between the tablet and capsule formulations. Due to the immaturity of PFS data in Study 19, TTD was used as a proxy in the model for the comparison of olaparib to a 'watch and wait' approach.

Utilities identified in the model included health state utilities and utility decrements for AEs. The same health state utility values were used, regardless of *BRCA* status, for all treatment arms and were sourced from SOLO2. The Review Group considers that all relevant costs were included in the model. Costs were included for drug acquisition, *BRCA* mutation

testing, management, AEs, subsequent treatment and terminal care. Irish cost data were used where possible.

The Review Group identified several key issues and uncertainties with the economic model. There are concerns with the exclusion of the SOLO2 clinical-effectiveness data from the cost-effectiveness analysis, together with concerns around the choice of survival distributions used to extrapolate clinical outcomes.

Results

Due to uncertainty in the assumptions used in the economic model the Review Group suggested several changes based on plausible alternative assumptions, which included using the outputs from the NMA in the comparison with niraparib. However, model functionality did not allow the user to input all the outputs from the NMA. Instead, the Applicant used the HR for PFS from the NMA using SOLO2 in the subgroup with *BRCA*m status and the HR for PFS from Study 19 for the subgroup with non-*BRCA*m status to derive the NCPE alternative base case. The Review Group has concerns that the model remains subject to uncertainty regarding the relative clinical- and cost-effectiveness of olaparib and niraparib. Therefore, the Review Group considers that the results are not robust, thus making it difficult to draw definitive conclusions regarding this comparison.

The NCPE alternative ICERs (Table 1) and the Applicant base case ICERs (Table 2) are shown.

Table 1 NCPE alternative base case analysis

Treatment	Incremental Costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Comparison to a 'Watch and wait' approach			
ITT	112,363	0.94	119,431
*BRCA*m	124,192	1.18	105,540
Non-*BRCA*m	137,953	0.76	181,650
Comparison to niraparib			
ITT	32,516	0.84	38,893
*BRCA*m	100,928	2.41	41,895
Non-*BRCA*m	69,323	0.65	106,409

*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. *BRCA*m = *BRCA* mutation; ICER = incremental cost-effectiveness ratio; ITT = intention to treat; QALYs = quality adjusted life years; non-*BRCA*m = non-*BRCA* mutation.

Table 2 Applicant base case analysis

Treatment	Incremental Costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Comparison to a 'Watch and wait' approach			
ITT	105,990	0.94	112,657
*BRCA*m	117,120	1.18	99,530
Non-*BRCA*m	130,356	0.76	171,646
Comparison to niraparib			
ITT	32,397	0.84	38,751
*BRCA*m	-19,567	1.17	Olaparib dominates
Non-*BRCA*m	63,155	0.63	99,818

*The Review Group identified a number of errors in the submitted model, which were rectified to produce the results shown. Figures in the table are rounded, and so calculations will not be directly replicable. *BRCA*m = *BRCA* mutation; ICER = incremental cost-effectiveness ratio; ITT = intention to treat; QALYs = quality adjusted life years; non-*BRCA*m = non-*BRCA* mutation.

Sensitivity analysis

In the main, respective probabilistic and deterministic ICERs were generally comparable.

The probability of cost-effectiveness at a threshold of €45,000 per QALY was 0.1% for the ITT population and the subgroup with non-*BRCA*m status and 0.6% for the subgroup with *BRCA*m status for the comparison to a 'watch and wait' approach and 54.0%, 52.3% and 14.0% for the ITT population, and the subgroups with *BRCA*m and non-*BRCA*m status respectively for the niraparib comparison. At a threshold of €20,000 per QALY, the probability of cost-effectiveness was 0% for the ITT population and both sub-groups with the comparison to a 'watch and wait' approach and 18.9%, 2.1% and 2.5% for the ITT population, and the subgroups with *BRCA*m and non-*BRCA*m status respectively for the niraparib comparison.

The Review Group notes that the choice of survival distribution for OS was a major driver of the economic model for all comparisons. For the NCPE alternative model for olaparib versus comparison to a 'watch and wait' approach, the ICERs ranged from €111,521 to €187,969 per QALY in the ITT population, €105,540 to €150,885 per QALY in the subgroup with *BRCA*m status and €181,650 to €366,926 per QALY in the subgroup with non-*BRCA*m status, depending on the choice of distribution. For the niraparib comparison, the ICERs ranged from €29,817 per QALY to olaparib being dominated in the ITT population, €38,608 per QALY to olaparib being dominated in the subgroup with *BRCA*m status and €66,821 per QALY to olaparib being dominated in the subgroup with non-*BRCA*m status, depending on the choice of distribution.

4. Budget impact of olaparib (Lynparza®)

The price to wholesaler of olaparib is €2,507.00 for a pack of 56 x 150mg tablets. The mean annual drug acquisition costs of olaparib, including all relevant fees, mark-ups and rebates is estimated as €67,785 per-patient; assuming a 100% dosing intensity. In the budget impact model mean treatment duration was estimated from the ITT population of Study 19, resulting in an average total treatment cost per patient of €167,656.

The Applicant estimated that 29 patients would begin treatment with olaparib in year 1, increasing to 32 beginning treatment in year 5. However, it was noted that these numbers include 12 to 13 patients with *BRCA*m status who would be treated with currently reimbursed olaparib capsules. The gross budget impact was estimated to be €1,981,347 in year 1, increasing to €5,231,867 in year 5 for the ITT population. The projected cumulative 5-year gross budget impact, including drug acquisition costs only, was €21.3 million for the ITT population (€8.6 million for the subgroup with *BRCA*m status and €12.7 million for the subgroup with non-*BRCA*m status).

The Applicant also presented a net drug budget impact subtracting the costs of olaparib capsules, currently reimbursed as monotherapy for the maintenance treatment of adult patients with PSR relapsed *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, from the gross budget impact. This resulted in a cumulative 5-year net budget impact of €12.8 million.

5. **State if any patient submissions were received, and name submitting organisations.**

No patient submissions were received in support of the application

6. **Conclusion**

The NCPE recommends that olaparib (Lynparza®) not be considered for reimbursement unless 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.