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

The NCPE has issued a recommendation regarding the use of olaparib for this indication. The NCPE does not recommend reimbursement of olaparib.

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to evaluate the manufacturer's (AstraZeneca) economic dossier on the cost effectiveness of olaparib. 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 that the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examine all the evidence that 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 **December 2015**

Summary

AstraZeneca submitted a dossier for olaparib (Lynparza®) in August 2015. Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed BRCA mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum based chemotherapy. Olaparib is a member of a new drug class of human poly (ADP-ribose) polymerase enzyme (PARP) inhibitors.

1. Comparative Effectiveness

- There are no existing therapies licensed, or administered, as maintenance therapy i.e. after chemotherapy, to prolong remission in platinum sensitive relapsed (PSR) ovarian cancer patients, therefore the chosen comparator is best supportive care (described as a 'watch and wait' approach and not alternative chemotherapy).
- The evidence submitted to support efficacy was a multi-centre, randomised, double-blind, placebo-controlled phase II trial (Study 19). The trial recruited patients with high grade serous, recurrent ovarian or fallopian-tube cancer or primary peritoneal cancer. Patients had completed at least two courses of platinum-based chemotherapy. The cancer was required to be platinum-sensitive (an objective response to the penultimate platinum-based regimen of more than six months) and the most recent regimen must have induced an objective response. Patients were required to commence study treatment within eight weeks of their previous platinum-based regimen. The trial included a pre-planned retrospective analysis of outcomes by BRCA status (BRCAm population). The primary endpoint was PFS (progression-free survival) based on investigator assessment. Secondary efficacy endpoints included OS (overall survival), HRQoL (health related quality of life), and disease related symptoms. Three additional post-hoc exploratory analyses of treatment effect; time to first subsequent treatment (FST), time to treatment discontinuation (TTD) and time to second subsequent treatment (SST) were also performed. Patients in the placebo arm were allowed to cross-over to olaparib following disease progression.
- The unadjusted median OS (52% maturity) was 34.9 months for olaparib

versus 31.9 months for placebo, HR=0.73 (95% CI 0.45, 1.17). The median OS for placebo was 26.6 months once adjusted for crossover, HR=0.52 (95% CI 0.28, 0.97). The median PFS was 11.2 months for olaparib versus 4.3 months for placebo, HR=0.18 (95% CI 0.11, 0.31). The median time to FST was 15.6 months for olaparib versus 6.2 months for placebo, HR=0.33 (95% CI 0.22, 0.50). The median time to SST was 23.8 months for olaparib versus 15.2 months for placebo, HR=0.44 (95% CI 0.29, 0.67).

- The NCPE has a number of concerns regarding the methodology of the main clinical trial (Study 19) and the robustness of any clinical treatment effects observed. These concerns included small sample size, patient cross-over, potential bias introduced by investigator assessed outcomes, post-hoc analyses of outcomes and the immaturity of OS data.

2. Safety

- The most commonly reported adverse events occurring with greater frequency in olaparib patients in the clinical trial in both the full population and BRCAm subpopulations were nausea, fatigue, vomiting and anaemia. In addition diarrhoea was more frequently reported with olaparib than placebo in the BRCAm population.
- As of the data cut-off date, 56.6% of the full population and 50% of BRCAm patients receiving olaparib and 60.2% of full population and 54.8% of BRCAm patients receiving placebo were reported to have died whilst on treatment. The majority of deaths were due to ovarian cancer.
- There is also a small risk for the development of AML/Myelodysplastic Syndrome in patients treated with olaparib, as three patients in Study 19 receiving olaparib treatment were diagnosed with or had laboratory abnormalities suggestive of MDS or AML. In addition, one patient was diagnosed with Myelodysplastic Syndrome in the placebo arm.

3. Cost-Effectiveness analysis

- A cost utility analysis comparing olaparib with placebo was submitted by the company. The perspective of the HSE (payer) was presented.
- The model was a multi-state cost-utility semi-Markov model incorporating four health states: progression-free, first subsequent treatment (FST),

second subsequent treatment (SST) and death. The progression free health state was further partitioned into patients on and off therapy. The time horizon was 15 years (reflecting a life-time horizon), with monthly cycles.

- Health benefit was measured in quality adjusted life years (QALYs). Utilities identified in the model included health state utilities and utility decrements for AEs. Utility values for the PF state were predicted by mapping HRQoL data collected in the trial using published algorithms. Utility estimates for the FST and SST health states were obtained from a trial (OVA-301) of trabectedin plus pegylated liposomal doxorubicin in patients with partially PSR ovarian cancer. The NCPE has concerns regarding the methods used to estimate utilities in the progression free health state and the generalisability of the data from the OVA-301 trial to the FST and SST health states.
- Costs included drug acquisition, BRCA mutation testing, health state costs, and costs associated with end-of-life care and adverse events.
- The main efficacy outcomes used in the model were OS, time to FST, time to SST and time to treatment discontinuation (TTD), based on parametric survival curves fitted to patient level data from Study 19.

Results

- The incremental cost due to treatment with olaparib versus placebo was €93,447 for a QALY gain of 0.84 and a life-year gain of 1.10 years, resulting in an ICER of €111,248 per QALY and an ICER of €84,908 per life-year.

Sensitivity analysis

- The following parameters were included as part of the one-way sensitivity analysis: costs, utilities and clinical data. The cost utility results were most sensitive to utility weights attributable to the progression free health state (especially for patients on treatment), monthly cost of olaparib and discount rates.
- Several scenario analyses were performed. The cost utility results were most sensitive to: no adjustment for PARP inhibitor use in the placebo arm post progression, increasing the olaparib dosing intensity, changing extrapolation from log-normal to generalised gamma for time to FST and using the independent survival model for TTD. In all cases the ICER per QALY increased.

- The probability of cost effectiveness at a threshold of €45,000 per QALY was estimated at 0.2%.

4. Budget Impact Analysis

The projected cumulative gross budget impact, based on company estimates of market share, is €4.86 million over the first 5 years: €0.28 million (year 1), €0.87 million (year 2), €1.17 million (year 3), €1.33 million (year 4) and €1.21 million (year 5).

5. Conclusion

Olaparib is licenced as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed BRCA mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum based chemotherapy.

The NCPE do not consider the evidence used to support the cost effectiveness of olaparib, for the above indication, to be robust and that the case for cost effectiveness has not been proven, therefore reimbursement of olaparib (Lynparza®) is not recommended at the current price.