Cost-effectiveness of olaparib (Lynparza®) in combination with bevacizumab for the maintenance treatment of adults with advanced (FIGO stages III and IV) 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 in combination with bevacizumab, and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a *BRCA1/2* mutation and/or genomic stability.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of olaparib in combination with bevacizumab. Following assessment of the Applicant's submission, the NCPE recommends that olaparib in combination with bevacizumab be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

The HSE asked the NCPE to carry out an evaluation of the Applicant's (AstraZeneca) Health Technology Assessment of olaparib in combination with bevacizumab. 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 **January 2023**

Summary

In February 2022, AstraZeneca submitted a dossier examining the clinical effectiveness, cost-effectiveness and budget impact of olaparib in combination with bevacizumab (ola + bev) for the first-line maintenance treatment of adults with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of platinum-based chemotherapy (in combination with bevacizumab) and whose cancer is associated with homologous recombination deficiency (HRD) positive status. HRD-positive disease includes all cancers with a mutation in a *BRCA* gene (BRCAm) and/or those with genomic instability. Therefore, *BRCA*m disease constitutes a sub-group of HRD-positive disease. HRD testing is not currently routine in Ireland, however *BRCA*m testing is. A marketing authorisation (MA) was granted by the European Medicines Agency (EMA) for ola + bev in November 2020.

Olaparib is a poly-ADP-ribose polymerase (PARP) inhibitor. The recommended dose for this indication (in combination with bevacizumab) is 300mg orally twice daily. The dose of bevacizumab is 15mg/kg intravenously once every 21 days. Individuals can continue olaparib until radiological disease progression, unacceptable toxicity or for up to two years if there is no radiological evidence of disease. Individuals can continue olaparib beyond two years if they have evidence of disease but may derive further benefit from olaparib. When used with olaparib, individuals receive bevacizumab for a maximum of 15 months (including the periods given with chemotherapy and as maintenance). The Applicant is seeking reimbursement under the High-Tech Drug Arrangement.

Treatment options, in current practice, (in this indication), include bevacizumab (for individuals who have received bevacizumab as part of their initial platinum-based treatment), and olaparib (for individuals with a *BRCA*m, regardless of prior bevacizumab use). Consequently, the Applicant considered bevacizumab as the main comparator in the population with HRD-positive disease, with olaparib considered for the sub-population with *BRCA*m disease. A full Health Technology Assessment of niraparib as first-line maintenance treatment, regardless of HRD and *BRCA* status and prior bevacizumab use, has been completed by the NCPE and reimbursement is currently under consideration by the HSE. Given that HRD testing is not currently routine in Ireland, the

NCPE consider that niraparib is a potentially relevant comparator. However, niraparib is not considered within this assessment.

1. Comparative effectiveness of olaparib plus bevacizumab

PAOLA-1 trial

Direct comparative evidence for the effectiveness of ola + bev versus bevacizumab (as maintenance treatment in advanced ovarian, fallopian tube or primary peritoneal cancer which is in response following completion of first-line platinum-based chemotherapy administered in combination with bevacizumab) is available from the PAOLA-1, double-blind randomised controlled trial. Clinical data from a pre-specified subgroup of individuals, with HRD-positive disease (which includes a further sub-population with *BRCA*m disease) provided the pivotal clinical evidence in the EMA MA approval for ola + bev as first-line maintenance in HRD-positive disease.

Individuals were randomised 2:1 to olaparib 300mg orally twice daily (population with HRD-positive disease: n=255) or placebo (population with HRD-positive disease: n=132). Bevacizumab, 15mg/kg intravenously once every 21 days, was concurrently prescribed to all trial participants. Individuals were treated with olaparib until disease progression or unacceptable toxicity, for a maximum of two years. Bevacizumab was administered for a maximum of 15 months, including cycles received as part of first-line platinum-based chemotherapy. Individuals receiving placebo in combination with bevacizumab (pbo + bev) were not allowed to cross over to ola + bev. The primary endpoint was progression-free survival (PFS) as assessed by the Investigator. Secondary endpoints included overall survival (OS), second progression-free survival (PFS2), time to first and second subsequent treatments, health-related quality of life (HRQoL) outcomes (including EQ-5D-5L) and safety outcomes. Results from three data-cuts were available; DCO1 (March 2019), DCO2 (March 2020) and DCO3 (March 2022). Effectiveness results are presented here for DCO3, unless otherwise stated, with a median follow-up of 61.7 months for the ola + bev group and 61.9 months for the pbo + bev group.

For the population with HRD-positive disease, median PFS was 46.9 months with ola + bev versus 17.6 months with pbo + bev; median OS was 75.2 months versus 57.3 months respectively. In the sub-population with *BRCA*m disease, median PFS (DCO2) was 44.7 months with ola + bev

versus 22.0 months with pbo + bev; OS data was immature. HRQoL data were available from DCO1 only; clinically meaningful differences between ola + bev and pbo + bev on HRQoL were not observed. The Review Group has concerns that HRD status, although pre-specified, was determined post randomisation. Also, the survival data are immature and confounding in long-term outcomes may have been introduced by the multiple lines of subsequent treatments.

Indirect comparative evidence

In the absence of direct evidence for the comparison of ola + bev with olaparib in the population with *BRCA*m disease, an unanchored population-adjusted direct comparison (PAIC) was performed. The PAIC utilised data from PAOLA-1 (sub-group of the HRD-positive population with *BRCA*m disease) and SOLO-1. SOLO-1 is a placebo-controlled, randomised trial of olaparib first-line maintenance treatment in individuals with *BRCA*m disease. Ola + bev was associated with a numerical, but non-significant increase in PFS versus olaparib. The Review Group identified the following key issues and uncertainties with the PAIC. The inability to adjust for differences in prior bevacizumab between PALOA-1 and SOLO-1 means that any analyses reflect the comparison of the overall treatment schema rather than a comparison of ola + bev maintenance with olaparib maintenance. Furthermore, the PAIC could not address imbalances in several baseline characteristics between the two trials, or assess long-term outcomes i.e., PFS2 and OS. NCPE consider the outputs of the PAIC to be uncertain, however they were not directly used in the cost-effectiveness analysis.

2. Safety of olaparib plus bevacizumab

Safety data, from DCO2 (PAOLA-1), were used to inform the cost-effectiveness analysis. The safety population included all individuals who received at least one dose of study treatment, regardless of their HRD status (ola + bev: n= 535, pbo + bev: n=267). Median treatment exposure was 17.3 months for ola + bev and 15.6 months for pbo + bev.

Treatment emergent adverse events (AEs) were more common in individuals receiving ola + bev (99.3%) compared to pbo + bev (95.9%). Treatment related AEs were more common with ola + bev (88.0% versus 63.7%). The most reported grade 3 or above AEs with ola + bev were hypertension (18.7% versus 30.7% with pbo + bev), anaemia (17.6% versus 0.4%), lymphopenia (6.9% versus 1.1%) and fatigue (5.2% versus 1.5%). Hypertension was reported as a serious AE

(SAE) in 9.0% and 13.1% of the respective arms. Anaemia was reported as an SAE in 6.4% and 0.4% of the respective arms.

The safety profile of ola + bev is generally consistent with the safety profile of the individual therapies.

3. Cost effectiveness of olaparib plus bevacizumab

Methods

A cost-utility analysis was implemented using a four-state, partitioned survival, cost-effectiveness model, with a cycle length of one month and a 50-year (lifetime) horizon. A half cycle correction was applied. For each treatment regimen, a hypothetical patient cohort enters the model in the progression-free (PF) health state and are at risk of progression (PD1) or death without progression. After first progression, individuals are at risk of secondary progression (PD2) or death. From the PD2 health state individuals are at risk of death. Individuals in the PD1 and PD2 health states can receive subsequent lines of treatment for recurrent disease.

An "area under the curve" approach was used to estimate the number of individuals in the PF, PD1 and PD2 health states, using extrapolated survival curves fitted to trial data. Clinical data for ola + bev and bevacizumab were obtained from the PAOLA-1 trial. DCO3 informed the clinical inputs for the HRD-positive population, with DCO2 used for ola + bev in the *BRCA*m sub-population. Clinical data for olaparib were obtained from the SOLO-1 trial. The key effectiveness inputs in the cost-effectiveness model were PFS, PFS2, OS and time to treatment discontinuation. A parametric mixture survival model (PMM) approach was implemented in the extrapolation of PFS from PAOLA-1, to account for long-term survivors. It was assumed that individuals remaining progression-free at five-years were long-term survivors. For the comparison of ola + bev versus olaparib in the *BRCA*m sub-population, a modified PMM approach was used to extrapolate the individual PFS patient data used to inform the PAIC. Parametric survival distributions were fitted to PFS2 and OS data.

Health state utility values were applied to the PF, PD1 and PD2 health states. Non-treatment specific values were used. Event-specific values were included for grade 3 and above AEs. Health state utility values were informed by EQ-5D-5L data (mapped to EQ-5D-3L) from PAOLA-1 for the

population with HRD-positive disease and SOLO-1 for the sub-population with *BRCA*m disease. Age-related utility decrements were included.

The Review Group considers that relevant costs were included in the cost-effectiveness analysis. Costs were included for drug acquisition (including administration where appropriate), disease management, subsequent treatment, routine care and monitoring, end-of-life care, HRD and *BRCA* testing and the management of AEs.

Results

Analyses presented in this document are based on the list prices of the intervention and comparators. Results of the Applicant's base case analyses are presented in Table 1. The Review Group identified concerns with the estimates of OS and efficacy in the cost-effectiveness analysis, due to immature data and short-term follow-up in PAOLA-1. The Review Group conducted an exploratory analysis based on more conservative long-term survival estimates for the HRD-positive population. The results of the NCPE exploratory analysis are also presented in Table 1.

Table 1: Deterministic pairwise analyses*

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Applicant base case analysis					
HRD-positive population					
Ola + bev	169,317	6.46			
Bevacizumab	130,608	4.39	38,709	2.07	18,667
*BRCA*m sub-population					
Ola + bev	190,006	8.02			
Olaparib	168,061	7.75	21,945	0.27	80,340
NCPE exploratory analysis					
HRD-positive population					
Ola + bev	167,517	5.85			
Bevacizumab	130,582	4.38	36,935	1.46	25,221

bev: bevacizumab; ***BRCAm:*** *BRCA* mutated; **HRD:** homologous repair deficiency; **ICER:** incremental cost-effectiveness ratio; **ola:** olaparib; **QALY:** quality adjusted life year

*Total costs and QALYS presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable.

Sensitivity analysis

Mean probabilistic ICERs were aligned with the respective deterministic ICERs. In the NCPE exploratory analysis, ola + bev had a 93.5% probability of cost-effectiveness, versus bevacizumab, at the €45,000 per QALY threshold in the HRD-positive population. There was a

37.5% probability of cost-effectiveness at the €20,000 per QALY threshold. In the Applicant base case, ola + bev had 98.0% and 55.5% probability of cost-effectiveness, versus bevacizumab, at the €45,000 per QALY and €20,000 per QALY thresholds, respectively. For the comparison with olaparib in the *BRCA*m population, ola + bev had 23.1% and 5.3% probability of cost-effectiveness at the €45,000 per QALY and €20,000 per QALY thresholds, respectively.

Deterministic sensitivity analysis, indicate that the main drivers of cost-effectiveness, for all analyses, were the OS distribution and discount rates. The comparison with bevacizumab was also sensitive to proportion of individuals assumed to receive subsequent PARP inhibitors. The comparison with olaparib was also sensitive to assumptions surrounding PFS extrapolation.

4. Budget impact of olaparib plus bevacizumab

The price-to-wholesaler of olaparib is €2,507.00 for a pack of 56 x 100mg or a pack of 56 x 150mg tablets. The price-to-wholesaler for a 400mg vial of bevacizumab is €725.72 (reflecting the maximum acceptable biosimilar price). The annual per-patient drug acquisition cost of olaparib is €66,314 (assuming 100% dose intensity) and €36,854 (including VAT) for bevacizumab, including all relevant fees, mark-ups and rebates. Olaparib is an oral treatment, therefore VAT is not applicable. The budget impact assumed that most individuals receiving ola + bev would cease treatment with olaparib at two-years, with the cost of bevacizumab applied in the first year of treatment only.

The Applicant estimated that, in Ireland, eight individuals with HRD-positive disease would be treated with ola + bev in year 1, rising to 57 in year 5. The Applicant also presented a net drug budget impact assuming ola + bev will displace olaparib in individuals with *BRCA*m disease and bevacizumab in the remaining HRD-positive population.

The cumulative five-year gross drug budget impact for ola + bev was estimated to be €14.1 million (€13.4 million excluding VAT). The cumulative five-year net drug budget impact was estimated to be €9.2 million (€9.0 million excluding VAT).

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 in combination with bevacizumab 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.*