Cost-effectiveness of niraparib (Zejula®) for first-line maintenance treatment of adults with advanced epithelial (FIGO stages III and IV) high-grade 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 niraparib (Zejula®). Following assessment of the Applicant's submission, the NCPE recommends that niraparib (Zejula®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

The HSE asked the NCPE to carry out an assessment of the Applicant's (GlaxoSmithKline) Health Technology Assessment of niraparib (Zejula®). 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 **September 2022**

Summary

In October 2021, GlaxoSmithKline (Ireland) Ltd submitted a dossier examining the clinical effectiveness, cost-effectiveness and budget impact of niraparib as first-line maintenance treatment for adults with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete [CR] or partial [PR]) following completion of first-line platinum-based chemotherapy. A marketing authorisation (MA) was granted by the European Medicines Agency (EMA) for niraparib for this indication in October 2020.

Niraparib is a poly-ADP-ribose polymerase (PARP) inhibitor. The recommended dose, for first-line maintenance treatment, is 200mg (two 100mg capsules) taken orally once daily. A dose of 300mg (three 100mg capsules) is recommended for individuals weighing 77kg or more and with a baseline platelet count of at least 150,000/µL. Treatment with niraparib should be continued until disease progression or toxicity. The Applicant is seeking reimbursement under the High-Tech Drug Arrangement.

In Ireland, olaparib is reimbursed for the maintenance treatment of adults with advanced (FIGO stages III and IV), *BRCA1/2*-mutated (*BRCA*mut) 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. A 'watch and wait' approach (also known as routine surveillance [RS]) is taken in patients who do not have a *BRCA*mut. A cost-utility analysis was presented for the total licensed population (i.e., all patients regardless of *BRCA* mutation status), with RS as the comparator. A cost-minimisation analysis was also presented for the comparison with olaparib in the sub-population with *BRCA*mut disease. A submission for olaparib in combination with bevacizumab as first-line maintenance treatment in the sub-population with homologous-recombination deficiency positive (HRDpos) status was submitted to the NCPE in February 2022. As such, olaparib in combination with bevacizumab may be a comparator in the future for this sub-population; this is not considered within this assessment.

1. Comparative effectiveness of niraparib (Zejula®)

Direct comparative evidence for the effectiveness of niraparib versus placebo (considered as a proxy for RS) in adults with advanced 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, is available from the ongoing PRIMA double-blind randomised controlled trial. PRIMA provided the pivotal clinical evidence in the EMA MA approval for niraparib as first-line maintenance.

Individuals were randomised in a 2:1 ratio to receive niraparib orally once daily (n=487) or placebo (n=246). At the time of study initiation, all subjects in the niraparib arm received a dose of 300mg once daily niraparib. Due to high numbers of dose reductions caused by adverse events, an individualised starting dose of niraparib was introduced, such that individuals could receive a starting dose of 300mg or 200mg once daily based on body weight and platelet count. The individualised starting dose from PRIMA was used to inform the MA for niraparib (see above). Individuals received treatment until disease progression, or unacceptable toxicity, for a maximum of three years. Individuals receiving placebo were not allowed to cross over to niraparib treatment during the trial. The primary endpoint was progression-free survival (PFS) based on blinded independent central review. Secondary endpoints included overall survival (OS), time to first subsequent treatment, second progression-free survival (PFS2), health-related quality of life (HRQoL) outcomes (including EQ-5D-5L) and safety outcomes. The intention-to-treat (ITT) population was the primary population for all efficacy analyses.

At the primary efficacy analysis (median follow-up 13.8 months), median PFS was 13.8 months in individuals receiving niraparib and 8.2 months in individuals receiving placebo; hazard ratio (HR) = 0.62 (95% CI 0.50 to 0.76). In the interim analysis of OS, data for median OS were very immature ((10.8%); HR = 0.70 (95% CI 0.44 to 1.11)). HRQoL scores indicated that, overall, niraparib was not detrimental to HRQoL. The Review Group has concerns regarding the immaturity of the trial data, together with potential confounding in long-term outcomes introduced by multiple lines of subsequent treatments (including PARP inhibitors). There are also concerns that the initial fixed starting dose of 300mg once daily may have resulted in an overestimation of the efficacy of niraparib. It is also noted that the

three-year niraparib treatment cap is not in line with the marketing licence (which does not include a treatment cap).

In the absence of direct head-to-head evidence for the comparison with olaparib in the sub-population with a *BRCA*mut, the Applicant performed a feasibility assessment of an indirect treatment comparison (ITC) using data from PRIMA (sub-population with a *BRCA*mut) and SOLO-1. SOLO-1 is a placebo-controlled, randomised trial of olaparib as first-line maintenance treatment in individuals with a *BRCA*mut. The Applicant considered that an ITC was not feasible and as such, the cost-effectiveness analysis with olaparib was limited to a cost-minimisation approach and a side-by-side naïve comparison. The Review Group considers that an approach comprising an ITC and cost-effectiveness analysis, with all limitations and uncertainties highlighted, would be preferable to a cost-minimisation approach.

2. Safety of niraparib (Zejula®)

The safety analysis included data from the PRIMA trial. The safety population included all patients who received at least one dose of study treatment. Median treatment exposure was 11.1 months for individuals receiving niraparib and 8.3 months for individuals receiving placebo.

Treatment emergent adverse events (TEAEs) were more common in individuals receiving niraparib (98.8%) compared to those receiving placebo (91.8%). The most reported grade 3 or above TEAEs in individuals receiving niraparib were anaemia (31.0% versus 1.6% with placebo), thrombocytopenia (28.7% versus 0.4%), platelet count decreased (13.0% versus 0%), neutropenia (12.8% versus 1.2%), neutrophil count decreased (7.6% versus 0%) and hypertension (6.0% versus 1.2%). Serious TEAEs, occurring in at least 5% of individuals receiving niraparib, included thrombocytopenia (12.2%) and anaemia (5.6%), no individuals receiving placebo reported serious TEAEs of thrombocytopenia or anaemia.

3. Cost effectiveness of niraparib (Zejula®)

Methods

A cost-utility analysis was implemented using a three-state, partitioned survival, cost-effectiveness model, for the comparison with RS, with a cycle length of one month and a 39-year (lifetime) horizon. A half cycle correction was applied. For each treatment regimen, a hypothetical patient cohort enters the model in the progression-free disease (PFD) health state; here individuals may be on or off first-line maintenance treatment. Individuals remain in the PFD health state until they experience disease progression, where they move to the progressed disease (PD) health state, or death without progression. Individuals in the PD health state can receive second-line subsequent treatments. From the PD health state, individuals are also at risk of death.

An "area under the curve" approach was used to estimate the number of individuals in the PFD and PD health states, using extrapolated survival curves fitted to PRIMA data. The key effectiveness inputs in the cost-effectiveness model were PFS, OS and time to treatment discontinuation (TTD). The population defined in the EMA label (MA-population), whilst based solely on PRIMA, is broader than the ITT population in the PRIMA trial. Individuals with stage III disease, and no visible residual disease after primary cytoreductive/debulking surgery were excluded from PRIMA. An adjustment based on external trial data was applied to the PFS curves to reflect the entire MA-population. The Applicant considered the analysis using the MA-population as their base case. A scenario analysis was presented using the PRIMA ITT population. Conventional methods were used to parameterise OS data from the RS arm from PRIMA. The niraparib OS data from PRIMA were immature. Therefore, an incremental mean PFS:mean OS relationship between niraparib and RS of 1:2 (based on the relationship observed in the second-line setting) was assumed. An adapted version of the cost-utility model was used for the cost-minimisation analysis of niraparib versus olaparib in the sub-population with a *BRCA*mut. Clinical data for the cost-minimisation analysis were derived from the sub-population with a *BRCA*mut from PRIMA, with equal efficacy assumed between niraparib and olaparib. Overall, the Review Group considers the assumption of equal effectiveness to be reasonable, despite concerns with the cost-minimisation approach.

Health state utility values were applied to the PFD and PD health states; the same values were used regardless of treatment. Event specific utility values were included for grade 3 and above TEAEs. Health state utility values were informed by EQ-5D-5L data (mapped to EQ-5D-3L) from PRIMA.

The Review Group considers that relevant costs were included in the model. Costs were included for drug acquisition (including administration where appropriate), disease management, subsequent treatment, routine care and monitoring, end-of-life care, and the management of TEAEs. Irish cost data were used where possible.

Results

Due to uncertainty in the assumptions used in the cost-effectiveness model, the Review Group suggested several changes to the Applicant base case based on plausible alternative assumptions. These included the use of the PRIMA ITT population data, a conservative incremental mean PFS: mean OS ratio of 1:1, and the removal of duration of treatment caps for niraparib and olaparib. The Applicant incremental cost-effectiveness ratios (ICERs) are shown in Table 1 and the NCPE-adjusted ICERs are shown in Table 2.

Table 1: Deterministic Applicant base case analysis*,^

Treatment	Total costs (€)	Total QALYS	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
MA population					
Niraparib	145,754	6.29			
RS	48,974	2.89	96,780	3.39	28,515
ITT population					
Niraparib	122,135	4.64			
RS	53,159	2.87	68,975	1.77	39,076
***BRCA*mut population**					
Niraparib	158,149	4.31			
Olaparib	157,244	4.31	905	-	-

***BRCA*mut:** *BRCA* mutated; **ICER:** incremental cost effectiveness ratio; **ITT:** intention-to-treat; **MA:** marketing authorisation; **QALY:** quality adjusted life year; **RS:** routine surveillance

*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

^Commercial-in-confidence patient access schemes are in place for niraparib and olaparib for currently reimbursed indications; these are not included in these analyses.

Table 2: Deterministic NCPE adjusted base case analysis *,^

Treatment	Total costs (€)	Total QALYS	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
ITT population					
Niraparib	116,271	3.75			
RS	53,159	4.74	63,112	0.75	84,671
***BRCA*mut population**					
Niraparib	182,332	3.55			
Olaparib	212,030	3.55	-29,699‡	-	-

ICER: incremental cost effectiveness ratio; **QALY:** quality adjusted life year; **RS:** routine surveillance

*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

^Commercial-in-confidence patient access schemes are in place for niraparib and olaparib for currently reimbursed indications; these are not included in these analyses.

‡Olaparib is more expensive than niraparib.

The probability of niraparib being cost-effective versus RS was 11.2% at a threshold of €45,000 per QALY, decreasing to 0% for a threshold of €20,000 per QALY, using the NCPE-adjusted base case.

Deterministic sensitivity analyses for the comparison with RS, indicated that the cost-effectiveness model was most sensitive to the PFS distribution and the incremental mean PFS:mean OS ratio. The MA-population cost-effectiveness analysis was also sensitive to the adjustment applied to the ITT PFS curves.

4. Budget impact of niraparib (Zejula®)

The price to wholesaler of niraparib (Zejula®) is €5,008.45 for a pack of 56 x 100mg capsules. The annual per-patient drug acquisition cost of niraparib, including all relevant fees, mark-ups and rebates is €59,144.66 (based on weighted mean dose from PRIMA).

The Applicant estimated that, in Ireland, seven individuals would be treated with niraparib in year 1, rising to 41 in year 5. The Applicant also presented a net drug budget impact assuming niraparib will displace olaparib in the population with a *BRCA*mut. The five-year gross and net drug budget impacts are presented in Table 3. Commercial-in-confidence patient access schemes are in place for niraparib and olaparib for currently reimbursed indications; these are not included in these analyses.

Table 3: Drug budget impact of niraparib*,^,‡

Population	Year 1	Year 2	Year 3	Year 4	Year 5	5-year cumulative
Gross drug-budget impact (€)	423,676	1,180,223	1,650,861	2,033,806	2,418,242	7,706,809
Net drug-budget impact (€)†	332,067	866,706	1,197,610	1,475,661	1,754,437	5,626,480

*Including all relevant fees and rebates.
^Commercial-in-confidence patient access schemes are in place for niraparib and olaparib for currently reimbursed indications; these are not included in these analyses.
‡Niraparib is an oral treatment, therefore VAT is not applicable.
†Assumes niraparib will displace olaparib in the first-line setting only.

5. Patient submission

No patient organisation submission was received during the course of this assessment.

6. Conclusion

Following assessment of the Applicant submission, the NCPE recommends that niraparib (Zejula®) 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.*