Cost-effectiveness of niraparib (Zejula®) as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous 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 niraparib (Zejula®). Following assessment of the applicant's submission, the NCPE recommends that niraparib (Zejula®) 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 (Tesaro, a GSK company) economic dossier on the cost effectiveness 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.

National Centre for Pharmacoeconomics **August 2019**

Summary

In January 2019, Tesaro, a GSK company, submitted a dossier examining the cost-effectiveness of niraparib for the below licensed indication. Niraparib was granted marketing authorisation by the European Commission in November 2017. The indication is as a monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed (PSR) high-grade serous ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response [CR] or partial response [PR]) to platinum-based chemotherapy.
Niraparib was granted orphan medicinal product designation for the indication of PSR high-grade serous ovarian cancer in August 2010, this was maintained at a review in October 2017.

The recommended dose is 300mg (three 100 mg hard capsules) taken orally once daily. A starting dose of 200 mg for patients weighing less than 58 kg may be considered. Treatment should be continued until disease progression. The Applicant is seeking reimbursement under the High-Tech Drug Arrangement (HT). Niraparib is a potent and selective PARP-1 and -2 inhibitor (ATC code: L01XX54).

Two separate cost-effectiveness analyses were presented; one for patients with a deleterious germline *BRCA* mutation (g*BRCA*mut) and one for those without (non-g*BRCA*mut). Olaparib and routine surveillance were chosen as comparators for the population with g*BRCA*mut and routine surveillance for the population with non-g*BRCA*mut. Olaparib is currently reimbursed in Ireland as maintenance monotherapy for adult patients with PSR *BRCA*-mutated (germline and/or somatic) high-grade serous ovarian, fallopian tube, or primary peritoneal cancer who are in response (CR or PR) to platinum-based chemotherapy. In May 2018, the indication of olaparib was extended to patients regardless of their *BRCA* mutation status, therefore the NCPE Review Group considers that olaparib is also a potential comparator in the population with non-g*BRCA*mut disease.

1. Comparative effectiveness of niraparib

The only direct evidence available for the efficacy of niraparib is from the international, multicentre, randomised, double-blind, ENGOT-OV16/NOVA trial to assess the efficacy, safety and tolerability of maintenance therapy with niraparib versus placebo (may be considered a proxy for routine surveillance) in patients with PSR, high-grade serous or predominantly serous ovarian, fallopian tube, or primary peritoneal cancer who had previously received at least two platinum-based regimens. The trial was designed to include two separate patient cohorts, with statistical analysis conducted on each group separately: patients with a germline *BRCA* mutation (g*BRCA*mut cohort) (n=203) and those without (non-g*BRCA*mut cohort) (n=350). The primary endpoint was progression-free survival (PFS) as assessed by independent review committee. Secondary endpoints included time to first subsequent treatment time to second subsequent treatment, chemotherapy-free interval, time to second objective disease progression (PFS2), and overall survival (OS). Health related quality of life (HRQoL) measures were also collected using the EQ-5D-5L and Fact Ovarian Cancer Symptoms Index (FOSI). Median follow-up was 16.4 months in the cohort with g*BRCA*mut disease and 17.5 months in the cohort with non-g*BRCA*mut disease.

For the cohort with g*BRCA*mut disease, the median independently assessed PFS was 21.0 months (95% CI 12.9 to NE) in the niraparib arm (n=138) and 5.5 months (95% CI 3.8 to 7.2) in the placebo arm (n=65); HR = 0.27 (95% CI 0.17 to 0.41). For the cohort with non-g*BRCA*mut disease, the independently assessed median PFS was 9.3 months (95% CI 7.2 to 11.25) in the niraparib arm (n=234) and 3.9 months (95% CI 3.7 to 5.5) in the placebo arm (n=116); HR = 0.45 (95% CI 0.34 to 0.61). At the time of database lock 17% of patients had died and median OS had not been reached in either treatment arm: g*BRCA*mut cohort HR = 0.91 (95% CI 0.36 to 2.28), non-g*BRCA*mut cohort HR = 0.74 (95% CI 0.45 to 1.20). HRQoL scores indicated similar patient reported scores in both treatment arms in both cohorts. The NCPE review team has concerns with the immaturity of the OS data; conclusions regarding the extent to which the observed PFS benefit translates to benefit in OS cannot be made. The difference in median PFS2 between the niraparib and placebo arms appears to be much smaller than for PFS suggesting that PFS benefit may not be maintained over the long term. There are also concerns that independent assessment of PFS was not performed

concurrently with that of the trial investigators assessment. Patients discontinued treatment based on investigator assessment which may have an impact on OS, given that some patients may be treated beyond progression and others stopped early.

In the absence of direct head-to-head evidence comparing niraparib and olaparib, the Applicant explored the feasibility of conducting an indirect treatment comparison using two trials of olaparib vs. placebo (Study 19 and SOLO-2) and ENGOT-OV16/NOVA. Several issues were identified in terms of differences in study designs, methodologies of assessing PFS and patient populations between the three trials and the Applicant did not deem a robust formal comparison possible. Therefore, equal efficacy of niraparib and olaparib, in the g*BRCA*mut cohort, was assumed in the cost-effectiveness model. The NCPE Review Group does not consider the issues regarding the feasibility of an indirect treatment comparison sufficient to preclude its use and considers an adjusted indirect treatment comparison would have been preferable. However, further analysis by the Review Group indicates that the assumption presented by the applicant is sufficiently conservative, notwithstanding the high level of uncertainty.

2. Safety of niraparib

Safety data for the two cohorts (g*BRCA*mut and non-g*BRCA*mut) were analysed together. Median treatment duration was 9.9 months for patients on niraparib and 7.0 months for patients on placebo patients. The safety population included all patients who had received at least one dose of study drug.

Adverse events were more common in patients on niraparib (any 100%; grade ≥3 74.1%) compared to those on placebo (any 95.5%; grade ≥3 22.9%). The most commonly reported grade 3-4 adverse events in patients in the niraparib arm were; thrombocytopenia events (33.8% vs. 0.6% for placebo), anaemia (25.3% vs. 0%), neutropenia events (19.6% vs. 1.7%), hypertension (8.2% vs. 2.2%), fatigue (8.2% vs. 0.6%), nausea (3.0% vs. 1.1%) and vomiting (1.9% vs. 0.6%). Serious adverse events were reported in 30.0% of the patients in the niraparib arm and 15.1% of those in the placebo arm. The most common serious adverse events were thrombocytopenia events (niraparib 11% vs. placebo 0%) and anaemia events (niraparib 4% vs. placebo 0%).

3. Cost effectiveness of niraparib

Methods

The cost-effectiveness was assessed using a cost-utility model over a lifetime horizon of 40 years. The economic model compares niraparib with routine surveillance in both patient populations, and with olaparib in the g*BRCA*mut cohort. The key effectiveness inputs in the model were PFS, OS and time on maintenance treatment. Mean PFS and OS were estimated to characterise the clinical benefits of each treatment. Upon commencement of maintenance treatment, patients enter the model in the progression-free disease health state. Patients transition to the progressed disease health state after the mean PFS time point; this is derived from the ENGOT-OV16/NOVA trial. Patients then remain in the progressed disease health state for a mean period of time calculated as the difference between mean OS and mean PFS. Mean OS is derived from Study 19 for routine surveillance Niraparib OS benefit is extrapolated from niraparib PFS benefit assuming a 2:1 ratio in the Applicant's base case model. Equal efficacy of niraparib and olaparib was assumed in the gBRCAmut cohort. Utility values for niraparib and routine surveillance were obtained from ENGOT-OV16/NOVA and values for olaparib were sourced from the olaparib NICE TA381. Costs and QALYs for each treatment were accumulated based on the mean time spent in the progression free and progressed disease health states.

The Review Group considers that all relevant costs are included in the model. Costs were included for drug acquisition and administration, monitoring, adverse events and terminal care costs. Irish cost data were used where possible.

The NCPE Review Group identified several key issues and uncertainties with the economic model. There are concerns that the model is oversimplified, failing to model outcomes over time and that the means-based approach does not account for treatment cycle specific costs. There are also concerns regarding the reliability and validity of the extrapolation of OS from PFS, the assumption of equal efficacy of niraparib and olaparib in terms of OS, the application of a 20-year cap on PFS and time on maintenance treatment, the use of

treatment specific utilities derived from differing data sources and the choice of survival distributions for PFS.

Results

Applicant base case

- For the niraparib versus olaparib comparison in the g*BRCA*mut population the applicant estimates an ICER of **€158,503** per QALY (incremental costs €30,221; incremental QALYs 0.191).
- For the niraparib versus routine surveillance comparison in the g*BRCA*mut population, the applicant estimates an ICER of **€42,632** per QALY (incremental costs €136,913; incremental QALYs 3.212).
- For the niraparib versus routine surveillance comparison in the non-g*BRCA*mut population, the applicant estimates an ICER of **€64,818** per QALY (incremental costs €112,524; incremental QALYs 1.736).

Due to uncertainty in the assumptions used in the economic model the NCPE suggested several changes based on plausible alternative assumptions. This gave the following results:

NCPE preferred base case

- For the niraparib versus olaparib comparison in the g*BRCA*mut population niraparib is **dominated** by olaparib (incremental costs €30,221; incremental QALYs 0).
- For the niraparib versus routine surveillance comparison in the g*BRCA*mut population, an ICER of **€114,229** per QALY is estimated (incremental costs €135,536; incremental QALYs 1.187).
- For the niraparib versus routine surveillance comparison in the non-g*BRCA*mut population, an ICER of **€240,773** per QALY is estimated (incremental costs €111,915; incremental QALYs 0.465).

Sensitivity analysis

The model did not contain functionality to run the probabilistic sensitivity analysis on the survival distributions for PFS. As such the NCPE Review Group is unable to present the probabilistic sensitivity analysis for the NCPE preferred base case, nor can the Review Group independently verify the suitability of the probabilistic sensitivity analysis for the Applicant's base case.

The NCPE Review Group notes that the choice of survival distribution for PFS is a major driver of the economic model versus routine surveillance, and there is substantial uncertainty surrounding the choice of distribution. For the NCPE preferred base case for niraparib versus routine surveillance, the ICER ranges from €78,477 per QALY to €196,401 per QALY for the gBRCAmut population and €125,934 per QALY to €342,910 per QALY for the non-gBRCAmut population, depending on the choice of survival distribution.

Overall, the NCPE Review Group considers that there is substantial uncertainty associated with this model. In particular, the NCPE Review Group requested a comparison of niraparib versus olaparib in the non-gBRCAmut patients; this was not provided.

4. Budget impact of niraparib

The price to wholesaler is €5,846 for a pack of 56 x 100 mg capsules. The mean annual drug acquisition costs of niraparib, including all relevant fees, mark-ups and rebates is estimated as €77,418 in year 1 and €70,356 in subsequent years in the g*BRCA*mut population and €84,373 in year 1 and €78,702 in subsequent years in the non-g*BRCA*mut population. The mean dose of niraparib received per 28-day treatment cycle is derived from the ENGOT-OV16/NOVA trial.

For the population with gBRCAmut, the Applicant estimates that there will be nine patients receiving niraparib in year 1, increasing to 53 in year 5. The projected gross budget impact, including drug acquisition costs only for niraparib, is €5.5 million over 5 years.

For the non-gBRCAmut population, based on company estimates of market share, the Applicant estimates that there will be 15 patients receiving niraparib in year 1, increasing to

87 in year 5. The projected gross budget impact, including drug acquisition costs only is €7.4 million over 5 years.
The combined gross budget impact for the populations with gBRCAmut and non-gBRCAmut is €12.9 million over 5 years.

A net budget impact was presented assuming niraparib would replace olaparib in the population with g*BRCA*mut. The cumulative net drug budget impact over 5-years is €1.4 million for this group. An additional net budget impact was performed including costs associated with routine surveillance administration, monitoring, resource, adverse events, subsequent chemotherapy and end-of-life costs. All costs were applied as per the cost-effectiveness model. The cumulative net drug budget impact over 5-years is: gBRCAmut vs. olaparib = €1.4 million, gBRCAmut vs. routine surveillance = €5.4 million and non-gBRCAmut vs. routine surveillance = €7.8 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

This treatment appears to be more effective in patients with gBRCAmut disease compared to patients with non-gBRCAmut disease and this is reflected in the cost effectiveness estimates. The NCPE recommends that niraparib (Zejula®) as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy, 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.*