NICE National Institute for Health and Care Excellence

TA620 Olaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer: committee discussion

Other supporting evidence

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1 Committee discussion

The appraisal committee considered evidence submitted by AstraZeneca and a review of this submission by the evidence review group (ERG). See the committee papers for TA620 for full details of the evidence.

Clinical need and current management

People with ovarian cancer have a high disease burden

1.1 The patient experts explained that relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer is a devastating condition. It is a huge emotional burden knowing that the disease can relapse at any time and there is no cure. People with a mutation in the BRCA1 or BRCA2 gene have the additional burden that members of their immediate family may also have the mutated gene. The clinical experts explained that survival rates and outcomes for ovarian cancer are worse in the UK than in other developed countries. This is likely to be because ovarian cancer is diagnosed at a later stage in the UK, and other countries have more radical surgical techniques and access to other drug treatments. The committee understood these factors and concluded that there is a high burden of disease for people with relapsed, platinum-sensitive ovarian cancer.

People with ovarian cancer would welcome wider availability of olaparib with a more convenient administration schedule

1.2 At the time of this appraisal NICE recommended olaparib (as capsules) for maintenance treatment of relapsed, platinum-sensitive, ovarian, fallopian tube and peritoneal cancer in people who have a BRCA mutation, after response to 3 or more courses of platinum-based chemotherapy (NICE's technology appraisal guidance on olaparib [TA381]). Olaparib capsules are only licensed for people with a BRCA mutation. The marketing authorisation for olaparib tablets covers a broader population. The tablets are licensed for adults with platinum-

sensitive, relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer whose disease has had a response (complete or partial) to platinum-based chemotherapy, irrespective of BRCA mutation status. This appraisal considered olaparib tablets which, according to the company, will eventually replace olaparib capsules. A patient expert explained that taking olaparib had changed her life because it had minimal side effects and allowed her to live a more normal life. The tablets are more convenient to take than the capsules, because only 4 tablets per day are needed instead of 16 capsules per day. Also, the tablets can be taken with or without food. The clinical experts explained that using olaparib earlier in the treatment pathway than recommended in TA381 is better because there is progressive loss of platinum sensitivity with repeated courses. Early treatment increases the chance of having a treatment response and prolonging the disease-free period. The committee concluded that wider availability of olaparib, to extend periods of remission and improve quality of life, would be greatly valued by patients and their families.

Clinical evidence

It is reasonable to assume that the tablet and capsule formulations of olaparib have similar efficacy

1.3 The committee noted that the results of an open-label, dose-finding study (study 24) showed that the 2 formulations of olaparib cannot be considered bioequivalent on a milligram-for-milligram basis. However, at the recommended dose, which is lower for the tablets than the capsules, they had similar pharmacokinetic, efficacy and tolerability profiles. The company supported this view and considered that the evidence showed the tablet formulation to be at least as clinically effective as the capsule formulation. The European public assessment report from the European Medicines Agency also stated that extrapolating efficacy results obtained with the capsule formulation to the tablet formulation was reasonably supported by pharmacokinetic data. Therefore the committee concluded that it was reasonable to assume that the tablet and capsule formulations have similar efficacy.

The clinical trials are generalisable to clinical practice but SOLO 2 is more relevant for people with a BRCA mutation

1.4 The clinical trial evidence came from 2 double-blind randomised placebo-controlled trials (study 19 and SOLO 2). Study 19 evaluated the efficacy and safety of olaparib capsules in people with platinum-sensitive relapsed ovarian cancer, irrespective of BRCA mutation status. BRCA mutation status was determined retrospectively. SOLO 2 assessed the efficacy and safety of olaparib tablets, and only included people with a BRCA mutation. At the second committee meeting, after deciding to limit its commercial arrangement to people with a BRCA mutation, the company proposed that SOLO 2 was more suitable for evaluating clinical and cost effectiveness in this population. It highlighted that in the subgroup of people with a BRCA mutation in study 19, which comprised 50% of the trial population, 60% of these people had had 3 or more courses of platinum before olaparib. This is higher than would be expected in clinical practice, and higher than in SOLO 2 (42%). The clinical expert at the second committee meeting stated that both trials were informative. However, because SOLO 2 was done more recently, they accepted that it probably better reflected current clinical practice, including in terms of the population's baseline level of previous treatment. The committee acknowledged this point. It concluded that:

- Study 19 had the advantage of mature overall survival data, but this was for a mixed population (that is, people with and without a BRCA mutation).
- SOLO 2 was more relevant for people with a BRCA mutation.

Olaparib improves progression-free survival compared with placebo but the benefit appears to be greater in the subgroup with a BRCA mutation

1.5 Investigator-assessed progression-free survival was the primary end point in both study 19 and SOLO 2. In study 19 there was a statistically significant improvement in progression-free survival in the overall population compared with placebo; 8.4 months with olaparib and 4.8 months with placebo, a difference of 3.6 months (hazard ratio [HR] 0.35, 95% confidence interval [CI] 0.25 to 0.49). However, radiological

assessments were not required after the primary data analysis, and therefore further mature data on progression-free survival were not available. The committee considered whether the results of the study 19 subgroup analysis by BRCA status provided any evidence that olaparib's effectiveness varies depending on BRCA status. For the group without a BRCA mutation, the difference in median progression-free survival between olaparib and placebo was 1.9 months (HR 0.54, 95% CI 0.34 to 0.85). For the group with a BRCA mutation, the difference was 6.9 months (HR 0.18, 95% CI 0.10 to 0.31). The committee noted that because the study 19 subgroup analysis was retrospective, the results should be considered with caution. In SOLO 2, which included only people with a BRCA mutation, there was a statistically significant benefit for olaparib compared with placebo, with a difference in median progression-free survival of 13.6 months (HR 0.30, 95% CI 0.22 to 0.41 at a median follow up of 22 months). The clinical experts explained that BRCA mutation status was a predictor of response to a PARP inhibitor, but was not the sole predictor. The committee concluded that olaparib improved progression-free survival irrespective of BRCA mutation status, and generally people with a BRCA mutation had greater benefit. However, the size of the difference in the benefit compared with the overall population was still uncertain. It also concluded that SOLO 2 provided the most reliable measure of relative effect for progression-free survival in people with a BRCA mutation, for the reasons outlined in section 1.4.

More people are alive after taking olaparib than after standard care

1.6 The only available mature overall survival data came from study 19. The data showed that at a median follow up of 6.5 years, median overall survival in the total population (people with and without a BRCA mutation) was 29.8 months with olaparib and 27.8 months with placebo (difference of 2.0 months, HR 0.73, 95% CI 0.55 to 0.95). The committee noted that the difference between olaparib and placebo was not statistically significant at the level set for the analysis ($p<0.0095$). However, 13.5% of people in the placebo group had PARP inhibitor treatment after progression, which could have reduced the size of any difference between olaparib and standard care. The clinical experts

explained that study 19 had identified a group of 'super-responders', many of whom were in remission without evidence of disease after 6 years (11% of people in the olaparib group and less than 1% in the placebo group). They explained that this very long-term response is more common in people with a BRCA mutation, but around 40% of people who have this response do not have a BRCA mutation. However, it is not possible to predict who will have such a response. The committee concluded that study 19 provided evidence that olaparib leads to clinically important improvements in overall survival in people with platinum-sensitive relapsed ovarian cancer, irrespective of BRCA mutation status.

Adverse events

Olaparib has a manageable adverse-event profile

1.7 The most common adverse events with olaparib in study 19 and SOLO 2 were nausea, fatigue, vomiting, diarrhoea, anaemia and abdominal pain. The number of people withdrawing because of adverse events was low in both trials. Grade 3 or higher adverse events happened in 43.4% of people in the olaparib group (compared with 21.9% for placebo) in study 19. In SOLO 2 these events happened in 36.9% of people in the olaparib group (compared with 18.2% for placebo). The clinical and patient experts explained that olaparib was generally well tolerated and adverse effects could be readily managed. Therefore the committee concluded that olaparib had a manageable adverse-event profile.

Cost effectiveness

The main economic model presented by the company is methodologically sound, but is based on study 19 data

1.8 To estimate the cost effectiveness of olaparib compared with routine surveillance, the company presented a 3-state (progression-free, progressed disease and death) partitioned survival model. The proportion of people in each health state was estimated based on 1-knot

spline modelling of data exclusively from study 19. Results were presented for the overall population and for subgroups based on BRCA mutation status. The ERG considered that the model structure was appropriate but preferred a 50-year time horizon instead of the company's choice of 30 years. This was because a small proportion of people were alive and their disease had not progressed at the end of the company's time horizon. The committee noted that this had only a small effect on the results and concluded that the model structure was suitable for decision making.

For modelling progression-free survival, time to first subsequent therapy is not a reliable method

1.9 In its main model, the company used data on time to first subsequent therapy to model time spent in the progression-free health state. It considered this to be more clinically relevant for modelling clinical effectiveness than radiological disease progression. However, the ERG considered that time to treatment discontinuation would better reflect the timing of disease progression, and used that in its amended base-case analysis. The committee considered whether radiological disease progression, time to treatment discontinuation or time to first subsequent therapy most accurately reflected the timing of disease progression for the purposes of modelling. The clinical experts explained that in UK clinical practice people stop taking olaparib after disease progression, defined by symptoms and increased levels of CA125 protein. Progression-free survival based on radiological progression, although a more robust and objective measure of clinical efficacy, may not fully reflect what happens in clinical practice. The committee noted that the model's mean estimates were more similar for progression-free survival and time to treatment discontinuation than for progression-free survival and time to first subsequent therapy. It concluded that using time to first subsequent therapy for modelling progression meant that the health benefits of having progression-free disease would be accrued within the model, without associated treatment costs, favouring olaparib.

The company's alternative model for people with a BRCA mutation is not sufficiently robust to recommend olaparib for

routine commissioning

1.10 For people with a BRCA mutation, the company presented an alternative model based on data from SOLO 2. Mean radiological progression-free survival assessed by blinded independent central review was used to inform time spent in the progression-free health state. The committee noted that this was not the primary outcome measure in the trial, which was investigator-assessed progression. Overall survival was estimated by assuming a 1:2 ratio of mean progression-free survival gain to mean overall survival gain. This ratio was derived from data on progression-free and overall survival data from study 19 and then applied to the progression-free survival results from SOLO 2. The ERG considered that the model structure was inappropriate and preferred the partitioned survival approach used in the company's main model. The ERG highlighted that the means-based structure did not include the effect of weighting costs and utilities by the proportions of people accruing these costs over time. Therefore it produced simplified estimates of costs and quality-adjusted life years (QALYs). The ERG also raised serious concerns about assuming a 1:2 progression-free to overall survival ratio. It noted that the alternative model produced substantially higher survival gains for olaparib than the main model, which were not supported by the clinical trial results. Therefore, the ERG considered that the alternative model's assumptions were unreliable. The committee shared the ERG's concerns about the company's alternative modelling approach and using a 1:2 ratio for estimating the mean overall survival gain from the mean progression-free survival gain, which had not been accepted as robust in previous NICE guidance on niraparib for ovarian cancer. During consultation, the company presented a scenario analysis that assumed a 1:1.5 ratio for progression-free survival to overall survival gain. The committee welcomed the company's more conservative analysis but it noted that the scenario did not reduce the uncertainty around the overall survival estimates. The committee concluded that the overall survival estimates from the company's alternative model were not adequately supported by the current trial evidence. Therefore, it did not accept that the results from the alternative model were sufficiently certain to recommend olaparib for routine commissioning.

Olaparib is not cost effective compared with routine surveillance

for the overall population or for people without a BRCA mutation

1.11 At the first committee meeting, the company's base-case incremental cost-effectiveness ratios (ICERs) using its main model were all substantially above the range normally considered a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained). These were for the overall population and for the subgroups with and without a BRCA mutation. None of the company's sensitivity analyses substantially changed the results. The ERG's amended base case produced slightly higher ICERs than the company's base case, using the ERG's preferred assumptions:

- a longer time horizon of 50 years (see section 1.8) and
- using time to treatment discontinuation instead of time to first subsequent therapy to model progression-free survival (see section 1.9).

The committee therefore concluded that it could not recommend olaparib as a cost-effective use of NHS resources for people with relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer. After consultation the company agreed a commercial arrangement that applied to the use of olaparib tablets for people with a BRCA mutation who have had 2 or more courses of platinum chemotherapy. The arrangement does not apply for the subgroup of people without a BRCA mutation and no new evidence was provided that would alter the committee's previous conclusions about cost effectiveness in this group. So further discussion was limited to the cost effectiveness of olaparib in people with a BRCA mutation.

The cost-effectiveness estimates for olaparib for people with a BRCA mutation are above the range normally considered a cost-effective use of NHS resources

1.12 The company and the ERG presented revised base-case ICERs for the subgroup of people with a BRCA mutation by line of therapy, including the agreed commercial arrangement for olaparib. The company's base-case ICERs were informed by the alternative means-based model. The ERG's base-case ICERs were informed by the main partitioned survival model. The committee recognised that the ERG's ICERs were supported

by subgroup data on progression-free survival from study 19, which had been noted as less relevant for people with a BRCA mutation than the SOLO 2 data. It agreed with the company and the ERG that there were methodological reasons for using data from the same study to inform the proportions of people in the progression-free and death health states. The committee recalled its conclusions that only the main model was suitable for decision making for routine commissioning. On this basis, it decided that only the ERG's ICERs should be considered further. It concluded that the ERG's ICERs for people who have had 2 courses of platinum-based chemotherapy, and those who have had 3 or more, were above the range that can be considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained):

- People with a BRCA mutation who have had 2 courses of platinum-based chemotherapy: £47,935 per QALY gained.
- People with a BRCA mutation who have had 3 or more courses of platinum-based chemotherapy: £34,064 per QALY gained.

End of life

Olaparib is recommended for routine commissioning for people who have had 3 or more courses of platinum-based chemotherapy

1.13 The committee noted that the ERG's ICERs would not be within the range normally considered to be a cost-effective use of NHS resources unless the end-of-life criteria applied. The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. It noted that the company had made a case for applying the end-of-life criteria for people with relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that had responded to 2 or more courses of platinum-based chemotherapy. The committee noted that median overall survival in the placebo group of study 19 was 27.8 months, and the company's main model estimated a mean life expectancy on routine surveillance of 38.4 months. Although estimates from other sources were evaluated by the committee, it accepted that the company's main model was suitable

for decision making (see section 1.8). Therefore the committee took the view that it should take into account the life expectancy estimates from that model to inform its decision about the end-of-life criteria. Because the trial results and the modelled estimates of life expectancy exceeded 24 months, the committee was not persuaded that the end-of-life criteria were met for the overall population. It also noted that the end-of-life criteria had not been accepted for the appraisal of niraparib for people without a BRCA mutation, or for people with a BRCA mutation after 2 courses of platinum chemotherapy. For NICE's previous olaparib appraisal (TA381), the committee accepted that the end-of-life criteria applied for a subgroup of people who had responded to 3 or more courses of platinum-based chemotherapy. This was because of the poorer prognosis for this group, who would be at least 6 months further on in the course of their disease than people who have had 2 courses of platinum-based chemotherapy. The committee concluded that the end-of-life criteria only applied for people who have had 3 or more courses of platinum-based chemotherapy. Therefore olaparib was considered a cost-effective use of NHS resources for people with a BRCA mutation who have had 3 or more courses of platinum-based chemotherapy. But it was not cost effective for any of the other populations covered by the marketing authorisation.

Cancer Drugs Fund

Olaparib meets the criteria for inclusion in the Cancer Drugs Fund for people with a BRCA mutation after 2 courses of platinum-based chemotherapy

1.14 Having concluded that olaparib could only be recommended for routine use for people with a BRCA mutation who have had 3 or more courses of platinum-based chemotherapy, the committee considered whether it could be recommended for other groups within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). The committee recalled that none of the ICERs presented for the overall population or for people without a BRCA mutation showed that olaparib had plausible potential to be cost

effective in these groups. So it concluded that the criteria for inclusion in the Cancer Drugs Fund were not met for these populations. However, for people with a BRCA mutation, the committee took the view that if mature overall survival data from SOLO 2 supported the survival estimates in the company's alternative model, then the ICERs for olaparib after 2 courses of platinum-based chemotherapy could be within the range normally considered to be a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). The committee therefore concluded that the criteria for inclusion in the Cancer Drugs Fund were met for people with a BRCA mutation who have had 2 courses of platinum-based chemotherapy because:

- olaparib cannot be recommended for routine commissioning for this population based on current clinical data but there is plausible potential for cost effectiveness
- there is outstanding clinical uncertainty about the overall survival benefit for this group
- the uncertainty is likely to be resolved by further data from SOLO 2.

  The committee concluded that the ERG's and the company's ICERs for this subgroup (£47,935 and £16,877 per QALY gained respectively) provided a good estimate of the plausible ICER range.