NICE National Institute for Health and Care Excellence

NICE guidance

Olaparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube or peritoneal cancer after 2 or more courses of platinum-based chemotherapy

Technology appraisal guidance
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www.nice.org.uk/guidance/ta908

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations 4

2 Information about olaparib 6

Marketing authorisation indication 6

Dosage in the marketing authorisation 6

Price 6

3 Committee discussion 7

Clinical need and current management 7

Clinical evidence 9

Economic model 11

Costs in the economic model 13

Cost-effectiveness estimate 14

End of life 15

Conclusion 15

4 Implementation 16

5 Appraisal committee members and NICE project team 17

Appraisal committee members 17

NICE project team 17

This guidance replaces TA620 and TA381.

1 Recommendations

1.1 Olaparib is recommended as an option for the maintenance treatment of relapsed, platinum-sensitive, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer in adults whose cancer has responded to platinum-based chemotherapy, only if:

- they have a BRCA1 or BRCA2 mutation
- they have had 2 or more courses of platinum-based chemotherapy
- the company provides olaparib according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with olaparib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

This appraisal is a partial review of NICE's technology appraisal guidance on olaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (TA620, now withdrawn). TA620 recommended olaparib for routine use in the NHS as an option for people who have had 3 or more courses of platinum-based chemotherapy. It also recommended it for use in the Cancer Drugs Fund as an option for people who have had 2 courses of platinum-based chemotherapy. This partial review specifically reviews the Cancer Drugs Fund recommendation for people who have had 2 courses of platinum-based chemotherapy. This updated guidance means that olaparib is now recommended for routine use in the NHS as an option for people who have had 2 or more courses of platinum-based chemotherapy. This guidance updates and replaces TA620. The committee discussion for TA620 is still available in the evidence section for this appraisal on the NICE website. This appraisal refers only to evidence covered by the

partial review.

Why the committee made these recommendations

The original appraisal (TA620) concluded that olaparib extends the time until the cancer progresses compared with routine surveillance, regardless of whether the person has a BRCA mutation. But the company offered a commercial arrangement that applied to olaparib tablets when used for people with a BRCA mutation who have had 2 or more courses of platinum-based chemotherapy. This meant that olaparib is cost effective only when used for the subgroup of people with a BRCA mutation.

The new evidence includes data collected while olaparib was available in the Cancer Drugs Fund in England. The new clinical trial evidence confirms that people taking olaparib have more time before their cancer comes back than those having routine surveillance, and they also live longer.

The cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources. So, olaparib is recommended for routine use in the NHS.

2 Information about olaparib

Marketing authorisation indication

2.1 Olaparib (Lynparza, AstraZeneca) as tablets is indicated 'as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for olaparib.

Price

2.3 The list price for olaparib tablets is £2,317.50 per 14-day pack (56 × 150 mg tablets); £4,635.00 per 28-day cycle (excluding VAT; BNF online, accessed March 2023).

2.4 The company has a commercial arrangement. This makes olaparib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

This committee discussion focuses only on olaparib for people who have had 2 courses of platinum-based chemotherapy. The committee discussed the evidence for people who have had 3 or more courses of platinum-based chemotherapy in NICE's technology appraisal guidance on olaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (TA620, now withdrawn). The committee papers and committee discussion for TA620 are still available in the evidence section for this appraisal on the NICE website.

The appraisal committee considered evidence submitted by AstraZeneca, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for this appraisal (TA908) for full details of the evidence for people who have had 2 courses of platinum-based chemotherapy.

Clinical need and current management

Ovarian, fallopian tube and peritoneal cancer has a high disease burden

3.1 The patient and clinical experts explained that relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (from here ovarian cancer refers to ovarian, fallopian and peritoneal cancer) are devastating conditions. After relapse, the goal of treatment is to manage rather than cure the condition. Maintenance treatment helps to extend the time before progression. This extends the time between courses of chemotherapy, which 1 patient expert described as gruelling. The patient experts said that the diagnosis of the first relapse can be more devastating than the initial diagnosis of ovarian cancer. They said that it is a huge emotional burden knowing that the cancer is likely to keep coming back and that the treatment outcomes are worse for each successive relapse. The clinical experts explained that survival rates and outcomes for ovarian cancer are worse in the UK than in other developed countries. The committee understood these factors and concluded that there is a high disease burden for people with relapsed, platinum-

sensitive ovarian cancer.

PARP inhibitors are a well-established and valued treatment option

3.2 The clinical experts explained that using poly-ADP-ribose polymerase (PARP) inhibitors, such as olaparib, as maintenance treatment after platinum-based chemotherapy has become standard care in the NHS. But not all PARP inhibitors, in all lines of treatment, are available for routine commissioning. Some are only available through the Cancer Drugs Fund. The specific PARP inhibitor available depends on how many courses of chemotherapy the person has had before. Also, they are only available for people who have not had treatment with a PARP inhibitor before. The clinical and patient experts explained that olaparib has manageable side effects, can be taken orally at home and is effective at delaying disease progression. They noted that people may have a psychological benefit from taking a maintenance treatment. One of the patient experts said that olaparib "massively improves quality of life" and that they can "live an amazing life" as a result of the treatment. The clinical experts said that the life expectancy for people with relapsed ovarian cancer has dramatically improved since PARP inhibitors became widely available. The committee concluded that the continued availability of olaparib, to extend periods of remission and improve quality of life, would be greatly valued by people with the condition and their families.

The number of people eligible for a PARP inhibitor after a second course of platinum-based chemotherapy is reducing, but there is still a need

3.3 The committee noted that the clinical pathway for relapsed ovarian cancer has changed significantly since olaparib entered the Cancer Drugs Fund. After their first course of chemotherapy, people will usually have a PARP inhibitor through the Cancer Drugs Fund (see NICE's technology appraisal guidance on niraparib, olaparib and olaparib plus bevacizumab). In the NHS, people are only offered a PARP inhibitor if they have not had one previously. But there is a need for PARP inhibitors to be available after later courses of chemotherapy. For example, the

clinical expert explained that people with stage 1 or stage 2 ovarian cancer cannot have a PARP inhibitor after the first course of chemotherapy. If their cancer relapses, they can have a PARP inhibitor after the second course of chemotherapy. Also, for some people, PARP inhibitors may not have been available on the NHS after their previous course of chemotherapy. But over time, this population is expected to reduce as more people have PARP inhibitors after the first course of chemotherapy. One of the patient experts explained that they started treatment with olaparib after fourth-line chemotherapy and that it had significantly extended their life. So, they felt that PARP inhibitor maintenance treatment should be available whenever it is needed, regardless of the number of previous courses of chemotherapy. The committee concluded that despite the small number of people who are currently eligible for olaparib after their second course of chemotherapy, it remains a much-valued treatment option for those who need it.

Clinical evidence

The clinical-effectiveness evidence is relevant to NHS clinical practice

3.4 The committee recalled that when olaparib entered the Cancer Drugs Fund, its preferred source of overall survival data for olaparib (from the SOLO2 clinical trial, a randomised, double-blind study comparing olaparib with placebo after platinum-based chemotherapy in people with a BRCA mutation) was not yet mature. So, olaparib's entry into the Cancer Drugs Fund was based on data from Study 19, but the committee felt that this data should be considered with caution. This was because most people in Study 19 with a BRCA mutation had had 3 or more courses of platinum-based chemotherapy before olaparib. This is more than would be expected in clinical practice. Also, some people in the study had a BRCA mutation and some did not, and their mutation status was determined retrospectively. The committee noted that the overall survival data from SOLO2 is now mature, and it is more relevant to the population being considered in this appraisal. The committee reviewed the baseline characteristics of the SOLO2 trial population. It noted that the baseline performance status was potentially slightly better than

might be expected in the NHS. The committee also noted that more people's cancer had a complete response to their previous treatment than might be expected (that is, there were no signs of cancer on their scans or tests). But it concluded that the population was broadly generalisable to the NHS population in England.

To reflect the pathway at Cancer Drugs Fund entry, unadjusted overall survival data for the placebo arm is preferred

3.5 People in the SOLO2 trial could not switch treatment from placebo to olaparib. But, people in both groups could have a PARP inhibitor after disease progression as part of clinical practice. A substantial proportion of people in the placebo arm had a subsequent PARP inhibitor. The exact percentage is considered confidential by the company and cannot be reported here. In the company's original base case, it adjusted the placebo arm data to remove the benefit of subsequent PARP inhibitor use. This was to better reflect current NHS practice, in which very small numbers of people are now eligible for a PARP inhibitor after their third or later course of platinum-based chemotherapy. The NHS England Cancer Drugs Fund clinical lead (from here, Cancer Drugs Fund lead) noted that under the terms of reference for this Cancer Drugs Fund review, the cost-effectiveness analysis should be based on the clinical pathway at the point of Cancer Drugs Fund entry, not current NHS practice. So, it was not appropriate to assume zero use of subsequent PARP inhibitors in the placebo arm. The clinical experts said that if someone had not had a PARP inhibitor previously and their cancer responded to the third course of chemotherapy, they would be offered one. The committee concluded at the first committee meeting that the high levels of subsequent PARP inhibitor use in SOLO2 may be more reflective of NHS practice at the point of Cancer Drugs Fund entry than the adjusted data. So, it asked the company and ERG to use the unadjusted SOLO2 data for the placebo arm in their updated base cases. The ERG noted that there were some limitations with this approach, because it was necessary to make additional assumptions about the data. People in SOLO2 had access to PARP inhibitors, some of which are not routinely available on the NHS at that line of treatment. They may also have had retreatment with a PARP inhibitor after multiple courses of chemotherapy (which does not reflect NHS practice). So, it was necessary to assume that all subsequent PARP

inhibitor use in SOLO2 was olaparib and that it was taken after the third course of chemotherapy. The Cancer Drugs Fund lead said that the PARP inhibitor treatments have the same mode of action, so they could be expected to have similar efficacy and tolerability to olaparib. Noting the limitations of the unadjusted data outlined by the company and the ERG, the committee confirmed that it preferred the unadjusted overall survival data from SOLO2 for the placebo arm.

It is not necessary to adjust for treatment switching in the olaparib arm

3.6 Some people in the olaparib arm had a subsequent PARP inhibitor. The exact percentages are considered confidential by the company and cannot be reported here. The company did a scenario analysis showing that retreatment in the olaparib arm had a limited effect on overall survival. The ERG confirmed that this analysis was appropriate. The committee agreed that the olaparib arm did not need to be adjusted to remove any benefit of future treatment with a PARP inhibitor.

Olaparib improves progression-free survival and overall survival compared with placebo

3.7 The unadjusted data from SOLO2 shows that olaparib significantly delays disease progression after the second course of chemotherapy. It also improves median overall survival. The clinical expert noted that about 20% of people have a very good response to treatment. So, in addition to the median overall survival, it is also important to consider the tail of the curve and the hazard ratios, which better reflect this large benefit in a proportion of people. The exact data for progression-free survival and overall survival are considered confidential by the company and cannot be reported here. The committee concluded that olaparib extends progression-free survival and overall survival compared with placebo.

Economic model

The model structure is appropriate and consistent with the terms

of engagement for Cancer Drugs Fund entry

3.8 The company model used the same structure as in TA620 (see the committee discussion for TA620 in the evidence section for this appraisal on the NICE website), which was a 3-state (progression-free, progressed disease and death) partitioned survival model. The inputs were updated in line with the terms of engagement of Cancer Drugs Fund entry. So, the Study 19 data on overall survival, progression-free survival, time to stopping treatment, subsequent treatments and baseline characteristics were replaced with data from SOLO2. Also, the time horizon changed from 30 years to 50 years, in line with the committee's preference. The ERG agreed that the changes to the model inputs were appropriate and aligned with the terms of engagement for Cancer Drugs Fund entry.

It is appropriate to use unadjusted SOLO2 data to model overall survival as it reflects the pathway at Cancer Drugs Fund entry

3.9 The updated company base case used the unadjusted overall survival data for the routine surveillance arm (see section 3.5), with a lognormal curve extrapolation curve fitted. The lognormal curve was selected based on statistical goodness-of-fit, visual inspection and external clinical validation. The company considered other parametric models but ruled these out because the survival estimates were not consistent with clinical opinion. For example, the percentage of people still alive at 20 years was considered too pessimistic. The company noted that estimates based on the lognormal curve are conservative because they overestimate survival in the routine surveillance arm between years 2 and 3 compared with the observed data from SOLO2. The ERG confirmed that the lognormal curve was appropriate and aligned with clinical expert opinion. The company also presented a scenario that used survival data from Study 19 for the routine surveillance arm. In Study 19 there were lower levels of subsequent PARP inhibitor treatment than in SOLO2. The company said this made the cost-effectiveness estimate more generalisable to current NHS practice, in which very few people would have olaparib after their third course of chemotherapy. It also noted that unadjusted data from Study 19 was used in NICE's technology appraisal guidance on niraparib. But the ERG said that using the Study 19 data would introduce more uncertainty because the population is less

relevant than the SOLO2 population. The committee recalled its conclusion from TA620 that because the Study 19 subgroup analysis of people with a BRCA mutation was retrospective, the results should be considered with caution (see section 3.4). It also noted the terms of reference for Cancer Drugs Fund entry, which specified that the company should update the overall survival estimate using SOLO2 trial data. The committee concluded that its preferred cost-effectiveness analysis was based on the extrapolated unadjusted data from SOLO2.

The ERG's corrections to the company model are appropriate

3.10 In the updated company base case, the committee requested that all subsequent PARP inhibitor use in SOLO2 was assumed to be olaparib (see section 3.5). The ERG identified that a small number of people who had taken PARP inhibitors had not been included in the company's updated analysis. To be consistent with the committee preferences, the ERG made a correction to the company base case to include these people. This made a modest improvement to the incremental cost-effectiveness ratio (ICER) in favour of olaparib. The committee agreed with the ERG that all subsequent PARP inhibitor use from SOLO2 should be included in the cost-effectiveness analysis and concluded that the ERG's correction to the company's base case was appropriate.

Costs in the economic model

If the benefits of subsequent PARP inhibitors are reflected in the model, the costs should also be included

3.11 The updated company model used the unadjusted overall survival data from SOLO2 for the routine surveillance arm. This data included people who had a PARP inhibitor as subsequent maintenance treatment. So, the company model also included costs for subsequent maintenance treatment with a PARP inhibitor. The ERG confirmed that the company's approach was appropriate. The committee concluded that the costs of subsequent maintenance treatment with PARP inhibitors should be considered alongside the benefits.

Cost-effectiveness estimate

The most likely cost-effectiveness estimate is within what NICE considers an acceptable use of NHS resources

3.12 NICE's guide to the methods of technology appraisal 2013 (section 6) notes that above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted that the updated company and ERG base cases were broadly consistent with the committee's preferences. It preferred the ERG-corrected company base case (also referred to as the ERG base case) because it included all subsequent PARP inhibitor use (see section 3.10). The committee noted that the data used in the cost-effectiveness model was high quality and generalisable to the NHS at the time of Cancer Drugs Fund entry. It also considered the company's view that estimates based on the lognormal distribution likely represent the upper bound of the cost-effectiveness estimate (see section 3.9). For these reasons, the committee considered that the maximum acceptable ICER would be towards the higher end of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). Because of confidential commercial arrangements for subsequent treatments in the pathway, the ICERs are confidential and cannot be reported here. But, when all confidential discounts were taken into account, the ERG's corrected company base-case ICER was within the range considered cost-effective. So, the committee recommended olaparib after 2 courses of platinum-based chemotherapy for routine use in the NHS.

End of life

The end of life criteria are not met for olaparib after 2 courses of platinum-based chemotherapy

3.13 In TA620 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 2013 (section 6). It agreed that the end of life criteria were not met for people who have olaparib after 2 courses of platinum-based chemotherapy.

Conclusion

Olaparib is recommended for routine use

3.14 The committee concluded that the ICER is within what NICE considers a cost-effective use of NHS resources for olaparib as a maintenance treatment for relapsed, platinum-sensitive, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer in adults whose cancer has responded to 2 courses of platinum-based chemotherapy and who have a BRCA1 or BRCA2 mutation. So, olaparib is recommended for routine use in the NHS.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has ovarian, fallopian tube or peritoneal cancer and the doctor responsible for their care thinks that olaparib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Alex Sampson
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Jo Richardson
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