NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer

1 Recommendations

1.1 Rucaparib is recommended for use within the Cancer Drugs Fund as an option for maintenance treatment of relapsed, platinum-sensitive high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to platinum-based chemotherapy in adults, only if the conditions in the managed access agreement for rucaparib are followed.

1.2 This recommendation is not intended to affect treatment with rucaparib 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.

Why the committee made these recommendations

The clinical evidence shows that rucaparib extends the time until cancer progresses compared with routine care. How much longer people live after taking rucaparib is uncertain because the data from the trial are not available yet. Because of the uncertainty in the clinical evidence, the estimates of cost effectiveness are very uncertain. Therefore, rucaparib cannot be recommended for routine use in the NHS.

Rucaparib has the potential to be cost effective if further data confirm the estimated overall-survival benefit. Rucaparib is therefore recommended for use within the Cancer Drugs Fund as an option for the maintenance treatment of relapsed, platinum-sensitive high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to platinum-based chemotherapy in adults, while further data are collected.

2 Information about rucaparib

Marketing authorisation indication	Rucaparib (Rubraca, Clovis Oncology) 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	Rucaparib is taken orally as tablets. The recommended dosage is 600 mg (two 300 mg tablets) twice daily, with or without food (1,200 mg total daily dose). Interruption of treatment or dose reduction can be considered for adverse event management (600 mg to 500 mg [two 250 mg tablets] to 400 mg [two 200 mg tablets] to 300 mg [one 300 mg tablet]). Patients should start maintenance treatment no later than 8 weeks after completion of their final dose of the platinum-containing regimen.
Price	The list price for rucaparib taken from the company submission is £3,562.00 per 60-tablet pack of 300 mg, 250 mg or 200 mg tablets. The company estimates that the average cost of a course of treatment until discontinuation is £110,897 (estimated from the deterministic base-case economic analysis using the list price). The company has a commercial arrangement (managed access agreement including a patient access scheme). This makes rucaparib 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

The appraisal committee (section 5) considered evidence submitted by Clovis Oncology, a review of this submission by the evidence review group (ERG), and the

technical report developed through engagement with stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that 1 issue was resolved during the technical engagement stage, and agreed that:

- For the long-term extrapolation of progression-free survival for the subgroup of people without a BRCA mutation it is most plausible to use the lognormal distribution, because this is more aligned with time to treatment discontinuation. For the subgroup of people with a BRCA mutation who have had 2 lines of platinum-based chemotherapy it is most plausible to use the lognormal distribution, because this is more aligned with what was seen in Study 19 at 6-year follow up.

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 2, page 34), and took these into account in its decision making. It discussed the following issues (issues 1,2,3,4,5,7 and 8), which were outstanding after the technical engagement stage.

Clinical need and treatment pathway

Relapsed ovarian, fallopian tube and peritoneal cancer has a high disease burden

3.1 The patient experts explained in their written submissions that ovarian cancer negatively affects many aspects of life including physical and mental wellbeing, self-esteem and body image. The disease is often diagnosed after the cancer has spread beyond the ovary, making curative treatment difficult, and the diagnosis is often associated with devastation, shock, disbelief and fear. People with advanced disease are likely to face a future of recurrent disease, needing multiple rounds of treatment to manage it. Living under the shadow of the disease and not knowing when it will recur can significantly affect their quality of life. The committee

understood these factors and concluded that there is a high disease burden for people with recurrent, platinum-sensitive disease.

Limited treatment options are available

3.2 The patient experts explained that the risk of developing resistance to platinum is high, and treatments for platinum-resistant disease are extremely limited. Recurrence and the development of resistance to platinum need to be delayed for as long as possible. Maintenance treatment with a poly-ADP-ribose polymerase (PARP) inhibitor such as rucaparib may extend time between recurrences, allowing people more freedom to lead a normal life. For some people, PARP inhibitors can have a long-lasting effect. There are currently no PARP inhibitors routinely commissioned for maintenance treatment after response to second-line platinum-based chemotherapy, although niraparib is currently available through the Cancer Drugs Fund. Olaparib capsules are recommended for routine commissioning after third line chemotherapy for people with a BRCA mutation. There is also an ongoing NICE appraisal of olaparib tablets for maintenance treatment in people with relapsed disease that has responded to platinum. The committee concluded that the availability of a PARP inhibitor after response to second-line platinum would be greatly valued by patients and their families.

Most relevant population

The intention-to-treat population is the most relevant population for decision making

3.3 ARIEL3 is a double-blind randomised clinical trial of rucaparib compared with placebo in people with platinum-sensitive, high-grade serous or endometroid ovarian, fallopian tube or primary peritoneal carcinoma who have had 2 or more platinum-based chemotherapy regimens with a complete or partial response to the last regimen. The company submitted results for the overall intention-to-treat (ITT) population and also a

subgroup of people who have a BRCA mutation and have had 3 or more courses of platinum-based chemotherapy (the BRCA 3L+ population) for the comparison of rucaparib with olaparib. At clarification stage, the ERG requested additional subgroup analyses of people without a BRCA mutation, and people with a BRCA mutation who have had 2 courses of platinum-based chemotherapy (the BRCA 2L population). However, the company commented that these analyses are not robust because they are post hoc and based on small sample sizes. The clinical experts explained that PARP inhibitors have been shown to have greater benefit in the subgroup of people with a BRCA mutation, but there are some people without a BRCA mutation whose disease responds in a similar way. Some people without a BRCA mutation may gain long-term benefit from PARP inhibitors, as seen in a trial of olaparib (Study 19). The clinical experts therefore considered that the ITT population is the most relevant population for the decision problem. The committee concluded that the results for the subgroups were not robust, and the ITT population is the most relevant for decision making.

Clinical trial results from ARIEL3

ARIEL3 is generalisable to UK clinical practice

3.4 The clinical experts explained that ARIEL3 is representative of patients treated in the UK. Importantly, inclusion in ARIEL3 was not restricted based on the extent of residual disease unlike some previous studies of PARP inhibitors. The clinical experts also explained that the proportions of people whose disease had a partial or complete response to platinum were similar to what would be seen in clinical practice. The committee noted that the proportion of people with a BRCA mutation is higher in ARIEL3 than in clinical practice (35% compared with 20%). The clinical experts explained that although this is higher than would be expected in the UK population, it is closer to the UK percentage than some other studies of PARP inhibitors. For example, 50% of people in Study 19 had a

BRCA mutation. The committee concluded that ARIEL3 is broadly generalisable to clinical practice in England.

Rucaparib improves progression-free survival

3.5 The primary endpoint of ARIEL3 is progression-free survival (PFS). A statistically significant improvement in PFS was seen at data cut-off for the overall ITT population. Median PFS was 10.8 months in the rucaparib arm and 5.4 months in the placebo arm (hazard ratio [HR] 0.36, 95% confidence interval [CI] 0.30 to 0.45). The committee concluded that rucaparib improves PFS compared with placebo.

Overall-survival data are immature but rucaparib is expected to be similar to other PARP inhibitors

3.6 Overall survival (OS) is a secondary endpoint in ARIEL3. At data cut-off, 88% of patients were still alive. Median OS was not reached and no statistically significant difference between the treatment arms had been seen. The clinical experts explained that there is a high possibility of a class effect for PARP inhibitors, and they expect rucaparib to show a broadly similar improvement in OS to that shown by olaparib in Study 19. The committee concluded that rucaparib is expected to provide a similar survival benefit to other PARP inhibitors.

Study 19 provides the most mature OS data for PARP inhibitors

3.7 Because of its immaturity, the company did not use ARIEL3 OS data in the cost-effectiveness analysis. It used OS data from Study 19 to model the long-term outcomes of rucaparib compared with routine surveillance. The committee noted that there were several differences between ARIEL3 and Study 19 in terms of trial design and patient characteristics, which may influence the results. For example, BRCA mutation status, a known prognostic factor, was a stratification factor at randomisation in ARIEL3 but it was confirmed retrospectively in Study 19. Also, a lower proportion of people had a BRCA mutation in ARIEL3 (35% compared with 50% in

Study 19). The clinical experts highlighted that a higher proportion of people in ARIEL3 had rucaparib after 2 lines of platinum rather than after 3 or more lines (63% compared with 43% in Study 19), and that earlier use of PARP inhibitors is associated with better outcomes. Conversely, the use of a PARP inhibitor in subsequent treatment lines in the placebo arm is substantially higher in ARIEL3 than in Study 19, which will probably reduce the magnitude of the difference in OS between rucaparib and placebo in ARIEL3. The committee appreciated that the populations in the trials were not strictly comparable. However, it noted that Study 19 provides the most mature data available for a PARP inhibitor, with over 6 years of follow up. The committee concluded that Study 19 provides the best OS data currently available for a PARP inhibitor and that it is reasonable to use this data for modelling in the absence of mature OS data from ARIEL3.

Cost effectiveness

The company's economic model is suitable for decision making

3.8 The company submitted a partitioned survival model with 3-states (progression-free, progressed disease and death) to estimate the cost effectiveness of rucaparib compared with routine surveillance. The committee considered that the model is suitable for decision making.

The post-progression survival is uncertain, but the ERG's modelling of post-progression survival is the most plausible

3.9 The way post-progression survival is modelled is one of the key drivers of the model results. Time spent in the progression-free health state is informed by ARIEL3 data. However, to model post-progression survival (PPS) for rucaparib, the company used the difference between Study 19 PFS and OS outcomes, assuming that PPS outcomes for rucaparib are equivalent to those for olaparib in Study 19. The ERG considered that this method is unconventional because the calculation of PPS is disconnected

from the PFS used elsewhere in the model, and results in OS benefits that are implausible. The ERG's preferred approach is to calculate PPS as the difference between OS in Study 19 and PFS in ARIEL3. However, the company considered the ERG's approach to be inappropriate because it leads to a higher rate of death after progression for rucaparib than for olaparib. This results in shorter PPS outcomes for rucaparib, because PFS in ARIEL3 is longer than in Study 19. The committee considered that the company's approach is optimistic because it combines a greater PFS benefit for rucaparib from ARIEL3 and all the PPS benefit of olaparib from Study 19, resulting in a higher OS with rucaparib than for olaparib. The committee questioned the plausibility of this and recalled its earlier conclusion that rucaparib is expected to provide a similar survival benefit to other PARP inhibitors (see section 3.6). Therefore, the committee concluded that the ERG's approach is preferable, although it acknowledged that there is uncertainty associated with the modelling that will not be fully resolved until more mature OS data from ARIEL3 are available.

Rucaparib has not been shown to be cost effective compared with routine surveillance

3.10 At the appraisal committee meeting, the company's base-case incremental cost-effectiveness ratio (ICER) for rucaparib compared with routine surveillance in the ITT population was above the range that is normally considered a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained). None of the company's scenario analyses substantially changed the results. The committee concluded that it could not recommend rucaparib as a cost-effective use of NHS resources for people with relapsed platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer. After consultation, the company agreed to provide rucaparib to the NHS with a higher discount. The company and the ERG presented revised base-case ICERs including the agreed discount for rucaparib. The estimated ICERs for the ITT

population incorporating the updated patient access scheme range from £29,138 (company) to £32,455 (ERG) per QALY. Most of the difference is because of the alternative approaches used for modelling PPS (see section 3.9). The committee considered that the results are uncertain because of the immaturity of the overall-survival data and concluded that this uncertainty could only be resolved with the availability of more mature data from ARIEL3. Therefore, the committee was not confident that rucaparib represents a cost-effective use of NHS resources and could not recommend it for routine use in the NHS. However, if the company projections for PFS and OS prove to be correct when further evidence becomes available, then rucaparib would have the potential to be cost effective.

Rucaparib has not been shown to be cost effective compared with olaparib in people with a BRCA mutation who have had 3 lines of platinum-based chemotherapy

3.11 Olaparib capsules are a treatment option for people with a BRCA mutation who have had 3 lines of platinum-based chemotherapy. The company presented a cost-effectiveness analysis for this subgroup in which it was assumed that rucaparib and olaparib have equivalent efficacy. The results of the analysis showed that rucaparib was dominated by olaparib (that is, rucaparib costs more and worked equally as well). The committee noted that there is currently no robust efficacy data to inform this comparison. Therefore, the cost effectiveness of rucaparib compared with olaparib in this subgroup of patients is uncertain. The committee concluded that rucaparib cannot be recommended for routine use in people with a BRCA mutation who have had 3 lines of platinum-based chemotherapy.

Cancer Drugs Fund

Rucaparib meets the criteria for inclusion in the Cancer Drugs Fund for the maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer

3.12 Having concluded that rucaparib cannot be recommended for routine use, the committee considered if it could be recommended for use 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 recognised that PARP inhibitors are innovative treatments for recurrent disease. The key uncertainty associated with rucaparib is the immature OS data, and this could be addressed through the collection of additional data from ARIEL3. The committee took the view that if mature overall-survival data from ARIEL3 supports the survival estimate in the company's model, the ICERs for rucaparib 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 are met because:

- Rucaparib cannot be recommended for routine commissioning based on current clinical data but there is plausible potential for cost effectiveness.
- There is outstanding clinical uncertainty about the overall survival with rucaparib.
- The uncertainty is likely to be resolved by further data from ARIEL3.

Conclusion

Rucaparib is recommended for use within the Cancer Drugs Fund as an option for the maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer

3.13 Rucaparib increases PFS compared with routine surveillance but the benefit in OS is uncertain because mature data are not available yet from the trial. Because of the uncertainty about the OS benefit, the estimates of cost effectiveness are very uncertain and rucaparib cannot be recommended for routine use in the NHS. If mature OS data from ARIEL3 support the survival estimates in the company's model, rucaparib has the potential to be cost effective. Therefore, rucaparib is recommended for use within the Cancer Drugs Fund as an option for the maintenance treatment of relapsed platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer after response to platinum-based chemotherapy.

4 Implementation

4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has relapsed platinum-sensitive epithelial ovarian fallopian tube or peritoneal cancer that has responded to platinum-based chemotherapy and the doctor responsible for their care thinks that rucaparib is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or

treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

5 Recommendations for data collection

5.1 As a condition to the positive recommendation, the company is required to collect overall-survival data from the ARIEL3 trial.

6 Review of guidance

6.1 The data collection period is expected to end when the final analysis of the overall-survival data from the ARIEL3 trial is available. The process for exiting the Cancer Drugs Fund will begin at this point and the review of the NICE guidance will start.

6.2 As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund after the data collection period has ended and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the standard timelines described in NICE's Cancer Drugs Fund methods guide (addendum).

Jane Adam
Chair, appraisal committee
September 2019

7 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.

Caroline Bregman
Technical lead

Zoe Charles
Technical adviser

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