Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2224

rucaparib 200mg, 250mg, 300mg film-coated tablets (Rubraca®)

Clovis Oncology UK Ltd

7 February 2020

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan medicine process

rucaparib (Rubraca®) is accepted for restricted use within NHSScotland.

Indication under review: 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.

SMC restriction: to patients who do not have a BRCA mutation

Rucaparib significantly improved progression free survival compared with placebo in a phase III study in patients with platinum-sensitive serous or endometrioid ovarian, primary peritoneal or fallopian tube carcinoma who had received at least two previous platinum based chemotherapy regimens.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/list price that is equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Vice Chairman
Scottish Medicines Consortium

Indication

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. [1]

Dosing Information

The recommended dose is 600mg twice daily, equivalent to a total daily dose of 1200mg, until disease progression or unacceptable toxicity.

For the maintenance treatment, patients should start the maintenance treatment with rucaparib no later than eight weeks after completion of their final dose of platinum containing regimen.

There is no requirement for BRCA testing prior to using rucaparib for the maintenance treatment of adult patients with relapsed high-grade epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

If a patient vomits after taking rucaparib, the patient should not retake the dose and should take the next scheduled dose.

If a dose is missed, the patient should resume taking rucaparib with the next scheduled dose.

Treatment with rucaparib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

See the summary of product characteristics for dose adjustments to manage adverse reactions.[1]

Product availability date

20 March 2019

Rucaparib has conditional marketing authorisation from the European Medicines Agency (EMA).

Rucaparib meets SMC end of life and orphan equivalent criteria for this indication.

Summary of evidence on comparative efficacy

Rucaparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, PARP-1,2 and 3. Inhibition of PARP enzymes in tumour cells results in increased DNA damage, apoptosis and cell death.[1]

Rucaparib is the third PARP inhibitor to be licensed for the maintenance treatment of relapsed, platinum-sensitive advanced ovarian cancer. Olaparib capsules are licensed for use in patients with BRCA-mutated ovarian cancer. The licences for niraparib and olaparib tablets are not dependent on BRCA-mutation status. However, SMC has previously restricted niraparib to patients who do not have a germline BRCA mutation and is still to receive a submission for olaparib tablets in this indication. The company has requested that SMC consider rucaparib in the licensed population i.e. patients with or without a BRCA mutation.

The clinical evidence is from an ongoing phase III, randomised, double-blind, placebo-controlled study (ARIEL3) in patients aged ≥18 years with a histologically high grade (grade 2 or 3) serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer. Patients were platinum-sensitive (documented as radiological disease progression more than six months after the penultimate dose) and had received at least two prior platinum-based chemotherapy regimens. Response to chemotherapy could be either complete or partial as defined by Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1 or a serological response according to Gynaecologic Cancer InterGroup (GCIG) cancer antigen 125 (CA 125) criteria. There was no restriction on residual carcinoma size for those defined as having a partial response. Patients who had persistent lesions of >2cm were defined as having bulky residual disease. The response (partial or complete) had to be maintained throughout chemotherapy and up until entry into the study. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate organ function.[2, 3]

Patients were randomised in a 2:1 ratio to receive oral rucaparib 600mg twice daily or placebo in continuous 28 day cycles within eight weeks of their last dose of platinum-based chemotherapy, with stratification at randomisation into three subgroups: BRCA mutant cohort (included germline and somatic BRCA mutation); non-BRCA homologous recombination deficiency (HRD, included germline and somatic BRCA mutation or non-BRCA with high genomic loss of heterozygosity); and biomarker negative. Other stratification variables were progression-free interval following penultimate platinum based regimen (6 to 12 months or >12months) and best response to the most recent platinum based regimen (complete or partial).[2, 3] Treatment with rucaparib or placebo continued until disease progression or death. Dose reductions were permitted in 120mg decrements for those with ≥grade 3 or persistent grade 2 adverse events. Treatment was also discontinued for patients who had a toxicity related treatment break for more than 14 consecutive days. Tumour response/disease progression was assessed at screening and every 12 weeks during treatment, following clinical symptoms and at treatment discontinuation. The primary outcome was investigator-assessed progression-free survival (PFS), defined as the time from randomisation to disease progression according to RECIST version 1.1 or death; this was assessed in the BRCA mutant cohort, HRD cohort and intention to treat (ITT) population using a step-down multiple comparison approach.[2, 3] The primary outcome in the three nested cohorts is shown in Table 1.

Table 1: Primary outcome results for the ARIEL3 study [2, 3]

Analysis Population	Randomised treatment	Median PFS (months)	HR (95% CI)*
BRCA mutant cohort (n=196)	rucaparib (n=130)	16.6	0.23 (0.16 to 0.34)
	placebo (n=66)	5.4	
HRD cohort (n=354)	rucaparib (n=236)	13.6	0.32 (0.24 to 0.42)
	placebo (n=118)	5.4	
ITT population (n=564)	rucaparib (n=375)	10.8	0.36 (0.3 to 0.45)
	placebo (n=189)	5.4	

PFS=progression-free survival, Cl= confidence interval, HR= hazard ratio, HRD= homologous recombination deficiency, ITT= intention to treat, *p<0.001

Progression free survival assessed by blinded, independent, central radiology review (BICR) was the key secondary outcome and the results are shown in Table 2.

Table 2: Secondary outcome of progression free survival assessed by BICR[2]

Analysis population	Randomised treatment	Median PFS (months)	HR (95%CI)*
BRCA mutant cohort (n=196)	rucaparib (n=130)	28.8	0.2 (0.13 to 0.32)
	placebo (n=66)	5.4	
HRD cohort (n=354)	rucaparib (n=236)	22.9	0.34 (0.24 to 0.47)
	placebo (n=118)	5.5	
ITT population (n=564)	rucaparib (n=375)	13.7	0.35 (0.28 to 0.45)
	placebo (n=189)	5.4	

BICR = blinded independent radiology review, CI = confidence interval, HR = hazard ratio, HRD= homologous recombination deficiency, ITT= intention to treat, * p<0.001

Other secondary outcomes included time to worsening of the disease-related symptoms - physical (DRS-P) subscale of the Functional Assessment of Cancer Therapy (FACT) Ovarian Symptom Index (FOSI-18) and the complete (total score), and overall survival. There was no significant difference in the time to worsening according to the FOSI-18 DRS-P scale in the BRCA mutant cohort, and therefore no formal testing of this outcome was performed in the other groups. [2, 3]

Overall survival data are immature. Overall survival could not be determined in the BRCA mutant cohort and the HRD population. In the ITT population, median overall survival was 29.6 months in the rucaparib group and not assessable in the placebo group. There were no differences in survival between rucaparib and placebo treatments in any of the three populations by stratified long-rank analysis or by stratified Cox proportional hazards model. [3]

In the absence of direct comparative evidence, the submitting company presented Bayesian network meta-analyses (NMAs) to compare rucaparib with olaparib and niraparib in patients who had platinum-sensitive, relapsed, ovarian, fallopian tube or primary peritoneal carcinoma who had received two or more prior lines of chemotherapy and had achieved a complete or partial response to the most recent platinum regimen. The NMAs included the ARIEL3 study and three other placebo-controlled studies for the comparator treatments (Study 19[4], NOVA[5] and SOLO2[6]). The key outcomes assessed were PFS, overall survival and safety outcomes (discontinuation due to adverse events (AEs), any grade ≥3 AEs and specific AEs of interest). Supplementary efficacy outcomes included progression-free survival to second disease progression, time to first subsequent therapy and time to second subsequent therapy. The populations considered in the NMAs for efficacy outcomes were patients with a BRCA mutation for the comparison of rucaparib with olaparib, and patients without a BRCA mutation for rucaparib compared with niraparib. For safety outcomes, the NMA was conducted in the ITT populations. No difference was observed between the treatments for any efficacy outcome in either the BRCA/non-BRCA mutation groups. In general, the credible intervals for safety outcomes were wide and crossed one due to the small number of events in each of the studies.

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

Safety data are available from a later data cut-off from the ARIEL3 study at 31 December 2017. The mean duration of treatment was 12 months for rucaparib and 6.7 months for placebo. Treatment related adverse effects (TRAE) of any grade were reported in 97% (362/372) and 74% (139/189) of the rucaparib and placebo groups respectively, and grade ≥3 TRAEs were reported in 46% (171/372) and 4.8% (9/189) of the groups. One or more serious TRAEs occurred in 9.4% (35/327) and 1.6% (3/189) of the rucaparib and placebo groups respectively. [2, 3]

Treatment discontinuation due to TRAEs occurred in 13% (49/372) and 0.5% (1/189) of the rucaparib and placebo groups respectively.[3] Treatment interruptions due to TRAEs occurred in 55% (205/372) of the rucaparib group and 4.8% (9/189) of the placebo group.[3] The ARIEL3 study permitted dose decrements of 120mg for adverse events. More patients in the rucaparib group than the placebo group required a dose reduction due to TRAEs: 54% (200/372) and 3.7% (7/189). [2, 3]

The most common ≥grade 3 adverse events in the rucaparib group versus placebo included anaemia and/or low or decreased haemoglobin (22% [80/ 372] versus 0.5% [1/189]), thrombocytopenia and/or low/decreased platelet count (5.4% [20 /372] versus 0%), neutropenia (5.1% [19 /372] versus 0.5% [1 /189]) asthenia or fatigue (26% [7 /372] versus 2.6% [5 /189]), and increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (10% [38 /372] versus 0%). [2, 3]

Two patients developed fatal treatment related adverse events while being treated or within 28 days of their last dose of rucaparib. One died from myelodysplastic syndrome (MDS) and the other from acute myeloid leukaemia (AML). The EMA will continue to monitor the incidence of AML/MDS. [3]

Summary of clinical effectiveness issues

Ovarian cancer is a relatively rare disease, but has a high mortality rate among gynaecological cancers. It is often at an advanced stage at the time of diagnosis and treatment is not usually curative.[7] In patients with advanced disease, first-line chemotherapy should include a platinum agent either in combination or as a single agent. Patients with relapsed platinum-sensitive ovarian cancer may be retreated with platinum-based chemotherapy and, following response to this, patients may receive maintenance treatment with olaparib capsules (in patients with BRCA mutated disease) or niraparib (in patients without a germline BRCA mutation). Despite these treatments, life expectancy in patients with relapsed ovarian cancer is estimated to be less than three years. Rucaparib meets SMC end of life and orphan equivalent criteria in this indication.

The key strengths and uncertainties of the clinical evidence are summarised below:

Key strengths

- The key ARIEL3 study showed significant improvements in investigator assessed PFS in the subgroups of patients with BRCA mutations, those with a mutation in a homologous recombination gene other than BRCA (HRD cohort) and in the ITT population. Median PFS was extended by 11.2 months, 8.2 months and 5.4 months in the respective groups, which was considered clinically meaningful by the EMA. [3]
- The primary analysis did not evaluate PFS in the subgroup of patients without BRCA mutations, however exploratory analyses in pre-specified BRCA wild-type subgroups showed that PFS was improved compared with placebo in these groups.[3]

Key uncertainties

- Overall survival was a secondary outcome in ARIEL3 and the data are immature.
- There is no direct evidence comparing rucaparib with the other PARP inhibitors currently available in Scotland. Limitations of the NMA provided by the company included differences in the patient population of included studies, differences in maturity of overall survival data, differences in the definition of PFS, difference in depth of response to the most recent platinum-regimen, and differences in post-progression PARP inhibitor treatment.
- More patients in the rucaparib group than the placebo group discontinued treatment due to an adverse event. The emergence of AEs could potentially have unblinded the investigator to treatment allocation. However, the results of the secondary outcome of PFS assessed by BICR were similar to the primary outcome results.
- Patients had ECOG performance status of 0 or 1 and patients with symptomatic or untreated CNS metastases were excluded, therefore effectiveness in patients with more severe disease is uncertain.
- Previous treatment with a PARP inhibitor was not permitted, so efficacy in patients who have received previous treatment with a PARP inhibitor is not known.

Rucaparib would provide an alternative PARP inhibitor to olaparib and niraparib. The rucaparib licence allows use in a wider range of epithelial ovarian cancer types (not just serous epithelial ovarian cancer). There are also differences in the safety profile between the three medicines.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of rucaparib, as an end of life and orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Recurrent ovarian cancer is incurable and is managed as a chronic condition. Patients with a BRCA mutation tend to be diagnosed at a younger age when they may have family and work commitments. Living with fear of a possible recurrence requiring further rounds of chemotherapy can have a significant psychological and emotional impact on both patients and their families.

- Recurrence is associated with significant symptoms that can be difficult to control and women may require intermittent chemotherapy courses over time. Chemotherapy has a significant impact on patients and their families, due to time spent in hospital for administration and side-effects, which can be severe.

- Maintenance treatment, for example with rucaparib, increases the time interval to recurrence, and some women may have a prolonged response to treatment. This would positively impact on patients and their families by allowing them to continue with normal life for longer, and would delay the time to chemotherapy and the associated burden on both the patient and their family. There would be a positive emotional impact of knowing that the patient is on a treatment to control their cancer.

- Rucaparib would provide a maintenance treatment for the small group of patients with endometrioid and poorly differentiated tumours, where there is no other licensed PARP inhibitor.

- Rucaparib would provide a treatment option for women who are not suitable for maintenance with the alternative PARP inhibitor (depending on BRCA mutation status). It would increase choice for patients and clinicians, with the option of different side-effect profiles.

Additional Patient and Carer Involvement

We received patient group submissions from Target Ovarian Cancer and Ovacome Ovarian Cancer Charity. Target Ovarian Cancer is a registered charity and Ovacome Ovarian Cancer Charity is a charitable incorporated organisation. Target Ovarian Cancer has received 2% pharmaceutical company funding in the past two years, with none from the submitting company. Ovacome Ovarian Cancer Charity has received 5.2% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis (CUA) to evaluate rucaparib versus olaparib or niraparib 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. Olaparib was the comparator treatment in patients with a BRCA mutation, and niraparib the comparator in patients without a BRCA mutation.

However, as the submitting company network meta-analysis found no statistically significant advantage between the treatments for any outcome, a cost-minimisation analysis (CMA) was provided upon request. Both the CUA and CMA results are presented, but given the findings of the NMA, the CMA was the main source of economic evidence considered by SMC.

A partitioned survival model was used featuring three main health states: 'progression-free' (where all patients enter the model), 'progressed' and 'dead'. The progression-free health state is divided into 'on maintenance' and 'off maintenance' to represent current treatment status. The time horizon was 30 years (tested in scenario analysis to 50 years) and cycle length was one month.

Clinical data informing the analyses were taken from the ARIEL3 study. For progression- free survival the network meta analysis studies (Study 19[4] for olaparib and NOVA[5] for niraparib) were used to derive hazard ratios comparing the intervention with the comparators, as all were placebo controlled trials. Data were modelled beyond the trial follow up period by applying extrapolation distributions to both the progression free survival (PFS), overall survival (OS) data and time to treatment discontinuation or death. For PFS the parametric distributions applied to the data are compared against the observed median and so it is possible to compare them with the observed clinical results. However, for overall survival the data were immature for the ARIEL3 and NOVA trials and so the olaparib Study 19 data (which was the study included in the network meta-analysis with the most mature OS data) was used to estimate OS values. As an alternative, a ratio of 2:1 overall survival to progression- free survival was estimated, and a 1:1 ratio tested in scenario analysis. Utility data were based on EQ-5D-3L data collected for the ARIEL3 trial.

Resource use included the relevant components, namely medicines costs, their administration costs and monitoring of disease and health state (i.e. progression- free status), although there does appear to be variation in the components included in clinical practice in Scotland compared with England the impact is expected to be minor.

A one-off cost of genetic testing for the BRCA mutation status was applied to both arms in the model cycle and a one- off cost was also applied upon entry to the death state. The cost associated with subsequent therapies was based on those received by patients in the ARIEL3 trial as long as these were treatments available in the NHS. Costs of adverse events (AEs) experienced by >5% of patients in any treatment arm in ARIEL3 were included. The list of AEs was expanded to include 3 additional AEs: nausea & vomiting was suggested for inclusion with a UK clinical expert, and hypertension and thrombocytopenia were added for consistency with the NICE appraisal on niraparib.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. PAS discounts are in place for olaparib and niraparib and these were included in the results used for decision-making by SMC by using estimates of the comparator PAS prices.

The results presented do not take account of the PAS for olaparib and niraparib or the PAS for rucaparib but these were considered in the results used for decision-making at NDC. SMC is unable to present the

results provided by the company which used an estimate of the PAS price for olaparib and niraparib due to commercial confidentiality and competition law issues. As such, the results presented below use the list price for all medicines.

Table 3: Cost- minimisation analysis base case results at list prices for all medicines – patients with a BRCA mutation

Technologies	Total costs (£)	Incremental costs (£)
Olaparib	£118,015	
Rucaparib	£195,341	£77,326

Table 4: Cost-minimisation analysis base case results list prices for all medicines – patients without a BRCA mutation

Technologies	Total costs (£)	Incremental costs (£)
Niraparib	£134,472	
Rucaparib	£120,242	-£14,231

Table 5: Cost- utility analysis results at list prices for all medicines – patients with a BRCA mutation

Technologies	Incremental cost-effectiveness ratio (cost per QALY)
Rucaparib versus olaparib	£353,816

Table 6: Cost- utility analysis results at list prices for all medicines – patients without a BRCA mutation

Technologies	Incremental cost-effectiveness ratio (cost per QALY)
Rucaparib versus niraparib	Rucaparib dominant (cheaper, more effective)

For the cost-utility analysis, deterministic, probabilistic and scenario analyses were undertaken. At list prices for all treatments, the deterministic sensitivity analysis found that the model is sensitive to the parameters used to derive PFS and time to treatment discontinuation or death, for both the BRCA and non-BRCA groups. Most scenarios had limited impact on the results, except the method used to estimate overall survival, which when changed to the OS/PFS ratio method changed the ICER to £399,574 when rucaparib was compared with olaparib. For rucaparib compared with niraparib, results were only sensitive to a constant probability being applied to discontinuation of treatment which changes the ICER from rucaparib being dominant to £47,165 at list prices for both treatments.

Assuming equivalence of treatments in terms of clinical effectiveness, for the chosen scenarios results were only sensitive to the choice of distribution fitted to progression-free survival data (namely the use of generalised gamma compared with the log-normal distribution in the base case) for rucaparib

compared with olaparib. This changed incremental costs at list prices for both treatments from £77,326 to £107,824. For rucaparib compared with niraparib, results were only sensitive to the application of a constant probability being applied to discontinuation of treatment for all interventions in the model, which alters the comparative costs of rucaparib at list prices for both treatments from -£14,231 in the base case to £771**.**

The key issues with the analysis were as follows:

- In the CUA, there was some lack of clarity regarding how PFS and OS had been extrapolated into the longer term although the submitting company did provide further information on this. Nevertheless, while the sensitivity analyses indicate these parameters do have an impact on the cost utility results, this is not the key issue because the main factor affecting the economic analysis was the absence of benefit found within the network meta-analysis. As such, the modelled QALY gains with rucaparib were subject to uncertainty and the CMA results were used as the main source of evidence informing the SMC decision.
- In terms of the CMA, the results indicated differing levels of cost-effectiveness against the relevant comparator depending on the BRCA status of the patient.

The Committee considered the benefits of rucaparib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as rucaparib is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process and after application of the appropriate SMC modifiers the Committee accepted rucaparib for restricted use in NHSScotland.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) revised 'SIGN 135: Management of epithelial ovarian cancer' issued in 2018 recommends that patients with relapsed, platinum-sensitive, epithelial ovarian cancer are treated with carboplatin combined with either paclitaxel or pegylated liposomal doxorubicin hydrochloride. It is advised that women with platinum-resistant relapsed ovarian cancer should be offered bevacizumab in combination with paclitaxel. Additionally, olaparib monotherapy should be considered for maintenance treatment after response to platinum for patients with relapsed platinum-sensitive BRCA-mutated ovarian cancer and niraparib monotherapy should be considered for maintenance treatment after response to platinum for patients with relapsed platinum-sensitive non-germline BRCA-mutated ovarian cancer. Lastly, hormonal therapy with tamoxifen or an aromatase inhibitor can be used for women with recurrent, platinum-resistant, ovarian cancer or in those wishing to avoid or delay further chemotherapy, particularly where their original tumour is expressing the oestrogen receptor.[7]

The European Society of Medical Oncology (ESMO), updated its clinical practice guidelines for newly diagnosed and relapsed epithelial ovarian carcinoma in 2013.[8] These guidelines note that despite optimal upfront surgery and the administration of front-line paclitaxel plus carboplatin and chemotherapy, approximately 70% of patients will relapse in the first 3 years. In patients who relapse after at least six months, and especially after 12 months, carboplatin-doublet is the treatment of choice. The selection of which combination to use should be based upon the toxicity profile and convenience of administration. Additionally, this guideline recommends bevacizumab in combination with carboplatin and gemcitabine in "platinum-sensitive" relapsed ovarian cancer patients who have not previously received bevacizumab.[8] In a eUpdate to this publication, published in 2016, ESMO recommends that patients with recurrent high grade serous ovarian cancer and a germline or tumour BRCA mutation should be offered maintenance olaparib after a response to platinum based chemotherapy. The guidelines also recommend that patients with high grade tumours should be tested for a germline BRCA mutation and that consideration should be given to testing tumours for a somatic BRCA mutation.[9]

The British Gynaecological Cancer Society (BGCS) published 'Epithelial Ovarian / Fallopian Tube / Primary Peritoneal Cancer Guidelines: Recommendations for Practice' in 2017.[10] They note that treatment with a PARP inhibitor may offer longer-term remission and response for some BRCA-mutation carriers and that olaparib is an option for treating women with relapsed, platinum-sensitive ovarian cancer who have BRCA1 or BRCA2 mutations and whose disease has responded to platinum-based chemotherapy, if they have had at least three courses of platinum-based chemotherapy.[10]

Additional information: comparators

Olaparib capsules, niraparib.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
rucaparib	**600mg orally twice daily**	**86,438**
olaparib capsules	400mg orally twice daily	46,150
niraparib	300mg orally once daily	87,750

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS online/BNF online on 08 October 2019. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The number of patients assumed to be eligible for treatment is estimated to be 194 rising to 232 patients in year five. However, based on displacing 25% of the market share each for olaparib and niraparib, rucaparib is expected to result in an uptake rate of 15 patients per year rising to 32 in year five, although with a high rate of discontinuations the number of patients is expected to be 3 in year 1 and 2 in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

1. Clovis Oncology I. Rucaparib (Rubraca). Summary of Product Characteristics2019.
2. Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A*, et al.* Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390(10106):1949-61. Epub 2017/09/17.
3. European Medicines A. European Public Assessment Report: Rubraca. 2019 19 February 2019 [cited; Available from: https://www.ema.europa.eu/en/documents/variation-report/rubraca-h-c-4272-ii-0001-epar-assessment-report-variation_en.pdf.
4. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G*, et al.* Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012;366(15):1382-92. Epub 2012/03/29.
5. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A*, et al.* Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016;375(22):2154-64.
6. Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM*, et al.* Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet Oncology. 2017;18(9):1274-84. Epub 2017/07/30.
7. Scottish Intercollegiate Guidelines N. SIGN 135 Management of epithelial ovarian cancer. 2018 2018 [cited; Available from: https://www.sign.ac.uk/assets/sign135_oct2018.pdf.
8. Ledermann JA, Raja FA, Fotopoulou C, Gonzalez-Martin A, Colombo N, Sessa C*, et al.* Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2013;24 Suppl 6:vi24-32. Epub 2013/10/23.
9. Ledermann JA, Sessa C, Colombo N. eUpdate - Ovarian Cancer Treatment Recommendations. 2016 21 September 2016 [cited; Available from: https://www.esmo.org/Guidelines/Gynaecological-Cancers/Newly-Diagnosed-and-Relapsed-Epithelial-Ovarian-Carcinoma/eUpdate-Treatment-Recommendations.
10. Fotopoulou C, Hall M, Cruickshank D, Gabra H, Ganesan R, Hughes C*, et al.* British Gynaecological Cancer Society (BGCS) epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines: recommendations for practice. EURO European Journal of Obstetrics and Gynecology. 2017;213:123-39.

This assessment is based on data submitted by the applicant company up to and including 18 November 2019.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.