SMC2799

rucaparib film-coated tablets (Rubraca®)

pharmaand GmbH (pharma&)

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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

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

Indication under review: as monotherapy for the maintenance treatment of adult patients with advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

In a phase III study, maintenance treatment with rucaparib significantly improved investigator-assessed progression-free survival, compared with placebo, in patients with advanced ovarian cancer who were in response to first-line platinum-based chemotherapy.

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

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

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]

The recommended dose of rucaparib is 600 mg taken orally twice daily. Patients should start maintenance treatment with rucaparib no later than 8 weeks after completion of their final dose of the platinum containing regimen. Patients can continue treatment until disease progression, unacceptable toxicity or completion of 2 years treatment.[1]

1.2. Disease background

Ovarian cancer is the sixth most common cancer in females in Scotland. The incidence increases with age with the highest rates in people aged 75 to 79 years. It is classified according to the International Federation of Gynaecology and Obstetrics (FIGO) staging system ranging from I to IV. The early stages of ovarian cancer tend to be asymptomatic or associated with non-specific symptoms and consequently, patients are often diagnosed with disease at an advanced stage (FIGO stages III and IV) which is associated with poor outcomes. Ovarian cancer tumours either have epithelial or non-epithelial origin, with epithelial tumours accounting for more than 90% of all ovarian cancers. The 5-year survival rate in advanced disease is 42% in FIGO stage III and 26% in FIGO stage IV.[2-5]

1.3. Treatment pathway and relevant comparators

Treatment of advanced ovarian cancer includes cytoreductive surgery and chemotherapy; either primary debulking surgery followed by adjuvant chemotherapy, or neoadjuvant chemotherapy with subsequent interval debulking surgery followed by additional chemotherapy. The relapse rate is high and treatment that prolongs the benefit of first-line platinum chemotherapy (most commonly with carboplatin plus paclitaxel) may reduce the risk of recurrence and improve survival outcomes. In patients who respond to first-line chemotherapy with a BRCA1/2 mutation or with homologous recombination deficiency (HRD) positive tumours, maintenance therapy with a PARP inhibitor with or without bevacizumab is recommended. Olaparib has been accepted for use by SMC for patients in response (complete or partial) with BRCA1/2 mutations (as monotherapy), or with HRD positive status defined by either a BRCA1/2 mutation and/or genomic instability (in combination with bevacizumab) (SMC2209 and SMC2368). Niraparib has been accepted for use by SMC as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO stages III or IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy (SMC2338). Bevacizumab, in combination with carboplatin and paclitaxel, followed by continued bevacizumab monotherapy, is an alternative first-line treatment option and has been accepted for restricted use by SMC for patients with FIGO stage IV disease (SMC806/12). The choice of maintenance therapy with either niraparib or bevacizumab in HRD-negative tumours depends on disease and clinical characteristics of the patient.[4-7] Cancer Medicines Outcome Programme Public Health Scotland (CMOP-PHS) data indicate that most patients received niraparib as maintenance

PARP inhibitor treatment after platinum-based chemotherapy, a smaller proportion received olaparib monotherapy and few received olaparib plus bevacizumab.[8] The submitting company considered niraparib and routine surveillance were the most relevant comparators for this submission however olaparib monotherapy or in combination with bevacizumab may also be relevant for patients with specific genetic alterations.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of rucaparib for the indication under review is from the ATHENA-MONO study as detailed in Table 2.1.

Table 2.1. Overview of relevant studies[4, 9]

Criteria	ATHENA-MONO
Study design	Multicentre, randomised, double-blind, phase III study.
Eligible patients	• Adults aged ≥18 years (≥20 years for patients enrolled in South Korea, Taiwan and Japan). • Newly diagnosed, histologically confirmed, advanced (FIGO stages III and IV), high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer. • Completed cytoreductive surgery, either prior to chemotherapy (primary surgery) or after neoadjuvant chemotherapy (interval debulking). • Completed four to eight cycles of first-line platinum-doublet treatment, including at least four cycles of a platinum/taxane combination (bevacizumab was allowed during the chemotherapy phase but not during maintenance), and achieved an investigator-assessed response. Patients with a partial response must have received at least six cycles. • A pretreatment CA-125 within ULN or if >ULN, a second sample >7 days after that was not ≥15% the first value. • Had sufficient FFPE tumour tissue available for planned analyses and a known BRCA mutation result (either positive or negative) via central testing. • Randomised within 8 weeks of the first day of the last cycle of chemotherapy. • ECOG performance status of 0 to 1.
Treatments	Rucaparib 600 mg orally twice daily starting on cycle 1 day 1 plus IV placebo every 4 weeks starting on cycle 2 day 1 in 28-day cycles or matching oral placebo plus IV placebo. Both groups received IV placebo as additional study groups (not reported here) received IV nivolumab as part of the ATHENA-COMBO study. Patients could continue treatment for up to 2 years, or until disease progression, unacceptable toxicity or death, whichever occurred first. Patients who experienced radiologic disease progression per RECIST v1.1 criteria but still derived clinical benefit (as per the investigator) were allowed to continue treatment.
Randomisation	Randomisation was in a 4:1 ratio. Patients were stratified according to HRD classification (BRCA mutation, BRCA wild-type and LOH high [≥16%], BRCA wild-type and LOH low [<16%], and BRCA wild-type and LOH indeterminate), disease status after chemotherapy (no residual disease versus residual disease) and timing of surgery (primary surgery versus interval debulking).
Primary outcome	PFS, defined as time from randomisation to disease progression assessed by the investigator per RECIST v1.1 criteria, or death from any cause, whichever occurred first.
Secondary outcomes	OS, defined as the time from randomisation to death from any cause.

	ORR, defined as the proportion of patients with a confirmed CR or PR per RECIST v1.1 assessed by the investigator, in patients with measurable disease at baseline.
Statistical analysis	A hierarchical statistical testing strategy was applied in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Each outcome in the hierarchy was tested in the HRD population (BRCA mutation or BRCA wild-type and LOH high) and then in the ITT population. Outcomes were tested in the following order: investigator-assessed PFS, OS and ORR.

CA-125 = cancer antigen 125; CR = complete response; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed paraffin-embedded; FIGO = International Federation of Gynaecology and Obstetrics; HRD = homologous recombination deficiency; ITT = intention-to-treat; IV = intravenous; LOH = loss of heterozygosity; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours version 1.1; ULN = upper limit of normal

At the March 2022 data cut-off, median follow-up was approximately 26 months for the intention-to-treat (ITT) population. Compared with placebo, rucaparib was associated with a statistically significant improvement in investigator-assessed progression-free survival (PFS) in the HRD and ITT populations; overall survival (OS) data were immature and median OS was not reached. The submitting company has provided results from subsequent data cut-offs in March 2023 (performed for regulatory purposes, approximately 3 years follow-up) and May 2024 (approximately 4 years follow-up), which were not prespecified, and these have been used in the economic analysis. At the 2022 data cut-off and subsequent interim analysis, a stopping rule in the hierarchical statistical testing was applied as OS data were highly immature, therefore results are descriptive only. The final OS analysis is planned when 70% of deaths have occurred. Detailed results are presented in Table 2.2.[4, 9, 10]

Table 2.2: Primary and selected secondary outcomes from ATHENA-MONO in the HRD and ITT population[4, 9-11]

	HRD population		ITT population	
	Rucaparib (n=185)	**Placebo (n=49)**	**Rucaparib (n=427)**	**Placebo (n=111)**
Primary outcome: investigator-assessed PFS per RECIST v1.1				
Data cut-off: March 2022				
Events	80	31	230	78
Median PFS	28.7 months	11.3 months	20.2 months	9.2 months
HR (95% CI)	0.47 (0.31 to 0.72), p<0.001		0.52 (0.40 to 0.68), p<0.001	
KM estimated PFS at 24 months	56%	35%	45%	25%
Data cut-off: May 2024				
Events	-	-	Not available	Not available
Median PFS	-	-	20.2 months	9.2 months
HR (95% CI)	-	-	0.54 (0.42 to 0.69)	
KM estimated PFS at 48 months			33%	18%

Secondary outcome: overall survival				
Data cut-off: March 2022				
Deaths	30	7	106	27
Median OS	NR	NR	38.8 months	NR
HR (95% CI)	0.97 (0.43 to 2.19)		0.96 (0.63 to 1.47)	
KM estimated OS at 24 months	85%	85%	77%	77%
Data cut-off: March 2023				
Deaths	46	12	144	42
Median OS	NR	NR	NR	46.2 months
HR (95% CI)	0.84 (0.44 to 1.58)		0.83 (0.58 to 1.17)	
KM estimated OS at 24 months	86%	88%	77%	78%
Secondary outcome: investigator-assessed ORR per RECIST v1.1 in patients with measurable disease at baseline				
Data cut-off: March 2022				
ORR, n/N (%)	10/17 (59%)	1/5 (20%)	20/41 (49%)	1/11 (9.1%)
CR, n/N (%)	0	0	1/41 (2.4%)	0
PR, n/N (%)	10/17 (59%)	1/5 (20%)	19/41 (46%)	1/11 (9.1%)
Exploratory outcome: investigator-assessed PFS2				
Data cut-off: March 2023				
Events	71	20	207	59
Median PFS2	NR	39.9 months	36.0 months	26.8 months
HR (95% CI)	0.75 (0.46 to 1.24)		0.84 (0.63 to 1.13)	
Data cut-off: May 2024				
Events	Not reported	Not reported	Not reported	Not reported
Median PFS2, months	57.3 months	39.9 months	35.0 months	26.9 months
HR (95% CI)	0.74 (0.47 to 1.17)		0.72 (0.55 to 0.93)	

CI = confidence interval; CR = complete response; HR = hazard ratio; HRD = homologous recombination deficiency; ITT = intention-to-treat; KM = Kaplan-Meier; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFS2 = progression-free survival on subsequent line of treatment; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours version 1.1.

PFS was also assessed by blinded independent central review at the March 2022 data cut-off. The results in the ITT population were similar to the investigator assessment and indicated an improved PFS with rucaparib compared with placebo: 25.9 months versus 9.1 months; hazard ratio (HR) 0.47 (95% confidence interval [CI] 0.36 to 0.63).[4]

Exploratory subgroup analyses of the primary outcome based on HRD classification were consistent with the primary analysis in the ITT population and favoured rucaparib. However, the treatment effect was more pronounced in those with a BRCA mutation: BRCA mutation positive (n=115) HR 0.40 (95% CI 0.21 to 0.75); BRCA wild-type with high loss of heterozygosity (≥16%) (n=119) HR 0.58 (95% CI 0.33 to 1.01); and BRCA wild-type with low loss of heterozygosity (<16%) (n=238) HR 0.65 (95% CI 0.45 to 0.95). Additional exploratory subgroup analyses of the primary

outcome in the ITT population based on demographics, ovarian cancer history and disease burden were also broadly consistent with the primary analysis and favoured rucaparib.[1, 4, 9]

At the March 2023 data cut-off, time to discontinuation of oral dose was assessed as an exploratory post-progression outcome; the results showed improvements in the rucaparib group compared with placebo in the ITT population: 14.7 months versus 9.9 months, HR 0.74 (95% CI 0.60 to 0.92).[4]

2.2. Health-related quality of life outcomes

Health-related quality of life (HRQoL) was assessed as exploratory outcomes using the Functional Assessment of Cancer Therapy–Ovarian (FACT-O) questionnaire (assesses physical, social/family, emotional and functional wellbeing, and an ovarian cancer specific subscale) and the EQ-5D-5L. Completion rates were approximately 90% for each instrument during the first 12 months of treatment and baseline scores for both treatment groups were similar. The FACT-O and EQ-5D-5L scores were largely maintained during treatment with no notable differences between groups at most time points. Overall, these results suggest that rucaparib did not have a detrimental effect on HRQoL.[4, 9, 12]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing rucaparib with niraparib, the submitting company presented an anchored matching-adjusted indirect comparison (MAIC). This has been used to inform the economic analyses. The results have been detailed in Table 2.3.

Table 2.3: Summary of indirect treatment comparison[4, 9-11, 13, 14]

Criteria	Overview
Design	Naive comparison and anchored MAIC.
Population	Adults with newly diagnosed, advanced, high-grade ovarian, fallopian tube or peritoneal cancer who responded to first-line platinum-based chemotherapy.
Comparators	Niraparib.
Studies included	ATHENA-MONO (for rucaparib) and PRIMA (for niraparib).
Outcomes	Investigator-assessed PFS, PFS2 and OS.
Results	A naive (unadjusted) comparison suggested similar outcomes for rucaparib and niraparib. The results of the MAIC suggest that rucaparib is superior to niraparib for investigator-assessed PFS and PFS2 but there was no significant difference between treatments for OS. The company considers the results to be academic in confidence.

CI = confidence interval; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; PFS2 = progression-free survival on subsequent line of treatment.

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

3. Summary of Safety Evidence

Evidence from ATHENA-MONO supports the relative safety of rucaparib compared with placebo for the treatment of patients with advanced ovarian cancer, placebo was considered a proxy for routine surveillance within this submission which may be a relevant comparator if current maintenance options are declined or not tolerated. The European regulator concluded that the safety profile of rucaparib for the indication under review was consistent with the known safety profile apart from a slightly higher incidence of some adverse events observed in the key study.[4]

In the ATHENA-MONO study at the March 2022 data cut-off, the median duration of treatment was 14.7 months in the rucaparib group and 9.9 months in the placebo group; the median dose intensity was 0.88 and 1.00 in each group respectively. Any treatment emergent adverse event (TEAE) was reported by 97% (411/425) of patients in the rucaparib group and 93% (102/110) of patients in the placebo group, and these were considered treatment-related in 92% and 68%. In the rucaparib and placebo groups, patients with a reported serious TEAE were 21% versus 6.4%, patients with a grade 3 or higher TEAE were 60% versus 23%, patients with a treatment interruption or dose reduction due to an TEAE were 64% versus 22% and patients discontinuing treatment due to an TEAE were 12% versus 5.5%.[4, 9]

The most frequently reported ≥grade 3 TEAEs in the rucaparib group were anaemia/decreased haemoglobin (29%), neutropenia/decreased neutrophil count (15%) and increased alanine aminotransaminase (ALT)/aspartate aminotransaminase (AST) (11%). The Summary of Product Characteristics notes that myelosuppression associated with anaemia, neutropenia and thrombocytopenia is typically observed after the first 8 to 10 weeks of treatment and is usually manageable with routine treatment or dose adjustment. Elevated ALT or AST events mostly occurred within the first few weeks of treatment and were reversible; raised AST/ALT may require treatment interruption or dose reductions. Myelodysplastic syndrome/acute myeloid leukoma (MDS/AML) has been reported in patients that receive rucaparib; at the final safety analysis (data cut-off March 2023), three cases had occurred in the rucaparib group. The SPC advises if MDS/AML is suspected, the patient should be referred to a haematologist for further investigation and if confirmed, rucaparib treatment should be discontinued. See the SPC for further safety information.[1, 4, 9, 15]

The final safety analysis (data cut-off March 2023) was generally consistent with the primary analysis.[15]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the phase III ATHENA-MONO study, maintenance treatment with rucaparib following first-line platinum-based chemotherapy demonstrated a statistically significant improvement in investigator-assessed PFS compared with placebo in patients with advanced ovarian cancer. The delay in disease progression with rucaparib compared with placebo was 17.4 months and 11.0 months in the HRD and ITT populations respectively.[4, 9]
- The results from a later data cut-off in May 2024 were consistent with the primary analysis in the ITT population.[10]
- Exploratory subgroup analyses based on HRD classification were consistent with the primary analysis and favoured rucaparib.[4]

4.2. Key uncertainties

- In the absence of direct evidence, the submitting company presented a MAIC comparing rucaparib with niraparib which was associated with a number of limitations. Not all key baseline characteristics were matched (including age and number of platinum chemotherapy cycles) and there were some differences between the populations after matching which could introduce potential bias (including the proportion of Asian patients). There were differences between studies in terms of the sample size of the placebo groups, length of follow-up and data maturity. It is uncertain if differences in niraparib dosing in the study are reflective of Scottish clinical practice and how this may impact estimates of the treatment effect within the MAIC. Although the MAIC suggested improved PFS associated with rucaparib compared with niraparib, the difference in OS was not statistically significant. There was also no comparison for safety or HRQoL outcomes. Due to these limitations, the results are uncertain.
- The submitting company provided no direct or indirect evidence comparing rucaparib with olaparib monotherapy in BRCA1/2 mutation positive patients or in combination with bevacizumab in HRD positive patients, and relative efficacy is unknown. Clinical experts consulted by SMC indicated these maintenance treatments are used in the relevant subpopulations of patients in NHSScotland and this was also reflected in CMOP-PHS data, particularly the use of olaparib monotherapy. There is also no direct or indirect evidence versus bevacizumab in patients with stage IV disease.
- Overall survival results were immature at the March 2022 data cut-off as approximately 75% of patients in the ITT population remained alive; the proportion of deaths was similar in both groups. In additional analysis requested by regulators (data cut-off March 2023), survival data were still immature (approximately 65% of the ITT population remained alive). The long-term survival benefit remains uncertain and results from later data cuts may be confounded by subsequent treatments. The European regulator noted that based on currently available data, a detrimental effect seemed unlikely. The final OS analysis is planned when 70% of deaths have occurred and results will be submitted to regulatory authorities as a post-authorisation efficacy study by June 2027.[4, 9]
- In the ATHENA-MONO study, most patients were aged <65 years and very few were aged ≥75 years (6.9% of the ITT population), therefore evidence in older patients is limited. This is particularly relevant as the incidence of ovarian cancer increases with age with the highest rates in the 75 to 79 age group. CMOP-PHS data indicated the median age of patients receiving PARP inhibitor maintenance treatment in NHSScotland was higher than in the ATHENA-MONO study (67 years compared with 61 years), which may affect the generalisability of results. Exploratory subgroup analysis based on age indicated less certainty in the benefit of rucaparib in patients aged >65 years, however the study was not powered to detect differences within subgroups and results should be interpreted with caution.[3, 4, 8, 9]

4.3. Clinical expert input

Clinical experts consulted by SMC indicated that rucaparib does not fill an unmet need as maintenance treatments are already available for this patient population. They noted that it is most likely to be used in BRCA wild-type patients who are in response following platinum-based chemotherapy and that it may provide an alternative treatment option in those unable to tolerate niraparib or bevacizumab because of hypertension.

4.4. Service implications

Service implications are likely to be minimal as maintenance treatments are already used in this setting. Rucaparib is an oral treatment which might be advantageous for some patients and may be associated with less intense monitoring than is required for other PARP inhibitors.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from Ovacome Ovarian Cancer Charity, Ovarian Cancer Action and Target Ovarian Cancer. All three organisations are registered charities.
- Ovacome Ovarian Cancer Charity has received 15% pharmaceutical company funding in the past two years, including from the submitting company. Ovarian Cancer Action has received 1.3% pharmaceutical company funding in the past two years, with none from the submitting company. Target Ovarian Cancer has received 5% pharmaceutical company funding in the past two years, with none from the submitting company.
- A diagnosis of ovarian cancer can be devastating. The disease symptoms, diagnosis and treatment all impact quality of life, mental health and cause upheaval in all aspects of the life of the entire family.
- For patients with advanced ovarian cancer knowing their cancer is likely to recur, having a maintenance therapy which extends PFS and continued input from oncology teams offers psychological as well as health benefits. There are limited options for maintenance treatment after first-line treatment, especially for those who do not have a BRCA mutation. Rucaparib provides an additional option for women and their families to feel they are actively stopping the disease from progressing.
- A choice of maintenance therapies should be available so that treatment can be tailored to the patient. Many women welcome the opportunity to be involved in making decisions about their care and treatments they receive. Clinicians should be able to choose and adapt the maintenance therapy based on the specific needs and toxicity risks of each patient. Rucaparib being available to this group would help with this.
- As an oral medication, rucaparib offers patients and carers greater flexibility regarding location of treatment than chemotherapy or IV treatments. It may reduce the need for women to live their life around their hospital appointments and treatment.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company presented an economic case, summarised in Table 6.1.

Table 6.1: Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility
Time horizon	Lifetime – maximum 40 years (base case starting age of 60).
Population	Adult patients who are in response (complete or partial) following completion of first-line platinum-based chemotherapy for advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer.
Comparators	The comparators in the model were routine surveillance and niraparib.
Model description	A four-state partitioned survival model including second progression was employed.
Clinical data	The principal source of evidence was the ATHENA-MONO study. This informed time to event functions for investigator-assessed progression-free survival (PFS, the primary endpoint in ATHENA-MONO), second progression, overall survival (OS), and time to treatment discontinuation (TTD), health-related quality of life, and treatment emergent adverse events. Analysis of progression was based on data cut-off (DCO) May 2024 and OS and TTD March 2023 (OS was not available for May 2024 DCO). Niraparib was not included as a comparator in the ATHENA-MONO study, and so a matched adjusted indirect comparison, based on the PRIMA study, was used (see Section 2.3 for details).
Extrapolation	Survival analyses were based mainly on flexible parametric spline models (a log-normal distribution was applied for routine surveillance OS), modelled independently for each arm of ATHENA-MONO. The model constrained PFS not to exceed OS, and hazards for mortality not to fall below those for the general population. The latest available hazard ratio for OS indicated rucaparib had yet to demonstrate a clear benefit for OS over placebo in ATHENA-MONO. A matched adjusted indirect comparison (based on ATHENA-MONO and PRIMA), adjusting for effect modifiers including risk categories provided hazard ratios for rucaparib relative to niraparib for both PFS endpoints and OS.
Quality of life	Quality adjusted life years were modelled based on utility estimates for progression free and progressed disease resulting from a mixed-effects linear regression. EQ-5D-5L data was mapped to EQ-5D-3L. The analysis resulted in utilities of 0.807 (95% confidence interval 0.798 to 0.816) for progression-free and 0.752 (0.740 to 0.764) for progressed disease. A value of 0.658 was assigned to second progression based on a previous technology appraisal.[16] QALY loses due to adverse events were estimated to be minimal and excluded from the base case analyses.
Costs and resource use	The model included medicine costs for first line maintenance treatment with rucaparib (two tablets twice daily) and niraparib (three capsules per day) until progression or two and three years respectively, subsequent therapies, and associated administration costs. Subsequent therapy costs were assumed identical following rucaparib and niraparib and based on a previous NICE technology appraisal. Additional subsequent therapy costs (PARP inhibitors, PARPi) were assumed for routine surveillance. Monitoring costs were assumed similar across health states, but with lower resource use when patients were progression free but no longer receiving treatment. Adverse event (AE) costs were included, based on annual rates of AEs derived from ATHENA-MONO, with a rate for niraparib estimated from the PRIMA study.
PAS	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. A PAS discount is in place for niraparib and bevacizumab. SMC considered results for decision-making that took into account all relevant PAS.

6.2. Results

The base case analyses compared rucaparib with niraparib and routine surveillance. SMC considered results for decision-making that took into account all relevant PAS. SMC is unable to present these results due to competition law issues.

6.3. Sensitivity analyses

Deterministic sensitivity analyses (DSA) indicated the greatest impact of individual parameters was seen for individual parameters of the base case selected time to event distributions for PFS and OS. For the comparison with niraparib the MAIC estimate of the HR for OS, and to a lesser extent PFS, were also notable.

A range of sensitivity and scenario analyses were considered and descriptions of these key scenarios are provided in Table 6.2.

Table 6.2: Scenario analysis

	Parameter	Base	Scenario
1	Extrapolation of OS	Odds-based spline model with 2 knots for rucaparib Log-normal for placebo	Log-normal for rucaparib
2			Log-logistic distribution for rucaparib and placebo
3			Generalised gamma for rucaparib and placebo
4	Extrapolation of PFS	Odds-based spline model with 1 knot for rucaparib and placebo	Log-normal distribution for rucaparib and placebo
5			Generalised gamma distribution for rucaparib and placebo
6	Extrapolation of PFS2	Normal-based spline model with 2 knots for rucaparib, Log-normal distribution for placebo	Log-normal distribution for rucaparib
7			Generalised gamma distribution for rucaparib and placebo
8	Extrapolation of OS, PFS and PFS2	As scenarios 1 - 7	OS. Weibull PFS. Weibull PFS 2. Weibull
9	Extrapolation of TTD for rucaparib	Exponential distribution for rucaparib	Log-logistic distribution
10	Niraparib 1L maximum length of treatment	36 months	24 months
11	AE disutility impact	Not Included	Included
12	PFS2 utility	Value from TA4066 (0.658)	Value from TA946 (0.689)
13	RDI for rucaparib 1L maintenance	100%	88%
14	RDI for niraparib 1L maintenance	63% (based on PRIMA)	70% (based on RWE)
15	Unit cost for medicine administration	Based on NHS Payment Scheme	Based on NHS Reference Costs

16	Subsequent line PARPi use in RS arm	75%	0%
17			65%
18			85%
19	Subsequent line bevacizumab use in RS arm	22%	35%
20	Relative efficacy versus niraparib	HR for OS = point estimates from MAIC	HR for OS = 1.00; TTD for niraparib as ratio of TTD:PFS rucaparib

Abbreviations: 1L = first-line, AE = adverse event, HR = hazard ratio; MAIC = matching-adjusted indirect comparison OS = overall survival, PARPi = PARP inhibitor, PFS = progression-free survival, PFS2 = progression-free survival on subsequent line of treatment, RDI = relative dose intensity, RS = routine surveillance, RWE = real-world evidence, TA = technology appraisal, TTD = time to treatment discontinuation

6.4. Key strengths

- Though subject to certain limitations, the partitioned survival model adopted by the submitting company is an accepted approach. Where relevant the analysis has highlighted the necessity to cap certain functions.
- Where routine surveillance was a relevant competitor, the ATHENA-MONO study provided direct evidence to inform the comparison. While OS data were immature, rucaparib demonstrated as statistically significant effect in terms of PFS.
- Utility data and resource use were appropriately handled.

6.5. Key uncertainties

- While niraparib was the key comparator, the submitting company did not provide analyses against other comparators that could be relevant in certain populations. Specifically, olaparib monotherapy in BRCA1/2 mutation positive patients and olaparib in combination with bevacizumab in HRD positive patients.
- The economic model generates substantial OS gains however OS data from ATHENA-MONO were immature. A clear advantage for rucaparib versus placebo has yet to emerge in terms of OS, and the indirect comparison with niraparib showed no significant OS advantage for rucaparib. A scenario where the OS hazard ratio for rucaparib versus niraparib was set at 1 (no difference) was explored in scenario 20. OS gains were sensitive to alternative assumptions regarding longer term hazards which did not produce pronounced plateauing in projected survival. This was explored in scenario 8.
- Approximately 40% of total costs modelled for routine surveillance were due to assumed PARPi as subsequent therapy. This may be inappropriate if routine surveillance is reserved for people for whom first-line PARPi would not be appropriate.
- The model adopted an estimate of treatment discontinuation for niraparib that meant time on treatment needed to be capped at the modelled PFS. Niraparib treatment continued for all patients remaining progression free up to the maximum administration schedule but only a proportion of patients in the rucaparib arm who were progression free remained on treatment. It was uncertain whether this difference in treatment discontinuation between treatment arms of the model would reflect clinical practice. This assumption inflated medicine acquisition and administration costs plus disease management and AE costs in

the niraparib arm. However, the overall effect on the cost-effectiveness results was limited.

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

7. Conclusion

After considering all the available evidence, the Committee accepted rucaparib for use in NHSScotland.

8. Guidelines and Protocols

The European Society of Gynaecological Oncology (ESGO), the European Society for Medical Oncology (ESMO) and the European Society of Pathology (ESP) published ESGO-ESMO-ESP consensus conference recommendations on ovarian cancer: pathology and molecular biology and early, advanced and recurrent disease in 2024.[6]

The British Gynaecological Cancer Society (BGCS) published BGCS ovarian, tubal and peritoneal cancer guidelines: Recommendations for practice in 2017 and the guidance was subsequently updated in 2024.[17]

ESMO published: Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up, in 2013 with subsequent updates in 2020 and 2023.[7]

The Scottish Intercollegiate Guidelines Network (SIGN) published: SIGN 135 Management of epithelial ovarian cancer: A national clinical guideline, in 2013 and this was revised in 2018.[5]

9. Additional Information

9.1. Product availability date

15 January 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 28-day cycle (£)
rucaparib	**600 mg orally twice daily**	**6,648**

Costs from BNF online on 29/04/25. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

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. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

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

References

1. Pharmaand GmbH. Rucaparib film-coated tablets (Rubraca®) Summary of product characteristics. Medicines & Healthcare products Regulatory Agency www.products.mhra.gov.uk Last updated: 02/05/24
2. Public Health Scotland. Cancer Incidence in Scotland to December 2022. Publication date: 26 November 2024. Available at: www.publichealthscotland.scot.
3. Cancer Research UK. Ovarian cancer incidence statistics. Last reviewed July 2024. Available at: www.cancerreasearchuk.org
4. The European Medicines Agency (EMA) European Public Assessment Report. Rucaparib (Rubraca®). 12/10/23 EMA/CHMP/503870/2023. Available at: www.ema.europa.eu.
5. Scottish Intercollegiate Guidelines Network (SIGN). Management of epithelial ovarian cancer [SIGN 135]. 2018 [cited 2025 Feb 24]; Available from: https://www.sign.ac.uk/our-guidelines/management-of-epithelial-ovarian-cancer/.
6. Ledermann JA, Matias-Guiu X, Amant F, Concin N, Davidson B, Fotopoulou C*, et al.* ESGO–ESMO–ESP consensus conference recommendations on ovarian cancer: pathology and molecular biology and early, advanced and recurrent disease. Annals of Oncology. 2024;35(3):248-66. 10.1016/j.annonc.2023.11.015
7. González-Martín A, Harter P, Leary A, Lorusso D, Miller RE, Pothuri B*, et al.* Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34(10):833-48. Epub 20230817. 10.1016/j.annonc.2023.07.011
8. Public Health Scotland. Cancer Medicines Outcome Programme Public Health Scotland (CMOP-PHS) report for the Scottish Medicines Consortium (SMC) . First-line platinum-based chemotherapy followed by maintenance treatment for advanced high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer: SMC2799. Published 24th June 2025.
9. Monk BJ, Parkinson C, Lim MC, O'Malley D M, Oaknin A, Wilson MK*, et al.* A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). Journal of Clinical Oncology. 2022;381:JCO.22.01003. https://dx.doi.org/10.1200/JCO.22.01003
10. Fehm TN, Kristeleit RS, Schneeweiss A, Zettl F, Oaknin A, O'Malley DM et al. Exploratory PFS Results for the ATHENA Study as Maintenance Treatment Following Frontline Platinum-based Chemotherapy in Ovarian Cancer in the Context of ATHENA-MONO and ATHENA-COMBO Results. Poster #29. Charite Mayo Conference 2025. .
11. Ghamande, S., Miller, R.E., Solovyeva, E., et al. ATHENA-MONO Post-Progression Survival Data Update In Patients With Newly Diagnosed Advanced Ovarian Cancer. European Society of Gynaecological Oncology (ESGO) 26th European Congress of Gynaecological Oncology 20th to 23rd February 2025 Rome
12. FACIT.org Functional Assessment of Cancer Therapy – Ovarian (FACT-O). Available at: www.facit.org
13. Monk BJ, Barretina-Ginesta MP, Pothuri B, Vergote I, Graybill W, Mirza MR*, et al.* Niraparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer: final overall survival results from the PRIMA/ENGOT-OV26/GOG-3012 trial. Ann Oncol. 2024;35(11):981-92. Epub 20240914. 10.1016/j.annonc.2024.08.2241
14. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR*, et al.* Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. New England Journal of Medicine. 2019;381(25):2391-402. 10.1056/NEJMoa1910962
15. O'Malley DM, Monk BJ, Lim MC, Pradera JF, Buscema J, Wilson MK*, et al.* Final safety results from ATHENA–MONO (GOG-3020/ENGOT-ov45), a randomized, placebo-controlled, double-blind, phase 3 trial evaluating rucaparib monotherapy as maintenance treatment in

patients with newly diagnosed ovarian cancer. Journal of Clinical Oncology. 2024;42(16_suppl):5554-. 10.1200/JCO.2024.42.16_suppl.5554
16. National institute of H, Care E. TA946 - Olaparib with bevacizumab for maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer. 2024.
17. Moss E, Taylor A, Andreou A, Ang C, Arora R, Attygalle A*, et al.* British Gynaecological Cancer Society (BGCS) ovarian, tubal and primary peritoneal cancer guidelines: Recommendations for practice update 2024. Eur J Obstet Gynecol Reprod Biol. 2024;300:69-123. Epub 20240621. 10.1016/j.ejogrb.2024.06.025

This assessment is based on data submitted by the applicant company up to and including 11 July 2025.

**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:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

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.