Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2338

niraparib 100mg hard capsules (Zejula®)

GlaxoSmithKline UK

9 April 2021

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 under the end of life and orphan medicine process

niraparib (Zejula®) is accepted for use within NHSScotland.

Indication under review: 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.

In a randomised, double-blind, phase III study, niraparib significantly improved progression-free survival compared with placebo.

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.

Chairman
Scottish Medicines Consortium

Indication

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.[1]

Dosing Information

The recommended starting dose of niraparib is 200mg orally once daily. However for those patients who weigh ≥77kg and have baseline platelet count ≥150,000/microlitre, the recommended starting dose is 300mg orally once daily. The capsules should not be chewed or crushed. Niraparib can be taken without regard to meals.

The summary of product characteristics (SPC) provides recommendations for dose modifications for adverse events.

Treatment with niraparib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.[1]

Product availability date

October 2020.
Niraparib meets SMC orphan and end of life criteria for this indication.

Summary of evidence on comparative efficacy

Niraparib is an orally administered, highly selective poly (adenosine diphosphate-ribose) polymerase (PARP) -1 and -2 inhibitor exhibiting potent anti-tumour activity through the direct inhibition of PARP. The cytotoxicity of niraparib was observed in tumour cells regardless of the presence of deficiencies in the breast cancer tumour suppressor genes BRCA1/2. Niraparib is already accepted for restricted use in NHSScotland as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy, restricted to patients who do not have a germline BRCA mutation (SMC1341/18). Niraparib has recently received marketing authorisation for earlier maintenance treatment for patients in response after first-line platinum-based chemotherapy.[1, 2]

The key evidence to support this new indication comes from the PRIMA study. PRIMA is an ongoing, multicentre, randomised, double-blind, phase III study evaluating the efficacy and safety of niraparib maintenance therapy compared with placebo in patients with newly diagnosed advanced ovarian cancer at high risk for relapse who had a response to platinum-based chemotherapy. Eligible patients were aged ≥18 years with newly diagnosed, histologically confirmed advanced (FIGO [International Federation of Gynaecology and Obstetrics] stages III or IV), high-grade, serous or endometrioid ovarian cancer (including cancer of ovary, fallopian tubes

or peritoneum). Patients with stage III disease were required to have visible residual tumour after primary cytoreductive surgery, interval cytoreductive surgery or inoperable disease. Tumour samples were available and were tested centrally for homologous recombination deficiency (HRD). Patients had received six to nine cycles of first-line platinum-based chemotherapy, had achieved an investigator assessed complete or partial response and were randomised within 12 weeks of day 1 of their last cycle of chemotherapy. They had normal Cancer antigen 125 (CA-125) or CA-125 that had decreased by >90% during chemotherapy. They also had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Eligible patients were randomised in a ratio of 2:1 to receive niraparib (n=487) or placebo (n=246) orally once daily. Initially, the niraparib dose was fixed at 300mg once daily but per protocol amendment (November 2017) it was changed for patients weighing <77kg or with a platelet count <150,000/microlitre or both to 200mg once daily. Randomisation was stratified according to clinical response after first-line platinum-based chemotherapy (complete versus partial response), use of neoadjuvant chemotherapy (yes versus no), tumour homologous recombination status (deficient versus proficient or not determined). Study treatment was continued for 36 months or until disease progression.[2, 3]

The primary outcome was progression-free survival (PFS), defined as the time between the date of randomisation, after completing platinum-based chemotherapy, to the date of first progression assessed by blinded central review or death due to any cause, whichever occurred first. Progressive disease was determined radiologically according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria and/or clinically including CA-125 progression. The primary outcome was assessed in the HRD population and the overall intention-to-treat (ITT) population and a hierarchical statistical testing strategy was applied for the primary outcome of PFS and the key secondary outcome of overall survival with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Therefore, the results reported for these outcomes are descriptive only and non-inferential (no p-values reported). The hierarchical order was: PFS in the HRD group, PFS in the ITT population, overall survival in the ITT population and overall survival in the HRD group.[2, 3] Other secondary outcomes included PFS on subsequent therapy (PFS2: defined as the time from randomisation to disease progression on the next anticancer treatment or death from any cause whichever occurred first) and time to first subsequent treatment (TFST: defined as the time from randomisation to first subsequent anticancer treatment or death whichever occurred first). At the time of the primary PFS analysis (data cut-off date 17 May 2019), the median duration of follow up in the ITT population was 13.8 months. PFS was significantly longer in niraparib-treated patients compared with placebo-treated patients in both the HRD and ITT populations. There was no significant difference between treatments on overall survival.[2,3] Details are presented in table 1.

Table 1: Results of primary and secondary outcomes in the HRD and ITT populations of the PRIMA study[2, 3]

	HRD population		ITT population	
	Niraparib (n=247)	**Placebo (n=126)**	**Niraparib (n=487)**	**Placebo (n=246)**
Median duration of follow up, months	NR		13.8	
Primary outcome: PFS by BICR				
PFS events	81	73	232	155
Median PFS, months	21.9	10.4	13.8	8.2
Difference: hazard ratio (95% CI), p-value	0.43 (0.31 to 0.59), p<0.001		0.62 (0.50 to 0.76), p<0.001	
Kaplan Meier 12-month estimated PFS	72%	42%	53%	35%
Overall survival				
Number of deaths	16	10	48	31
Median overall survival, months	30.3	NE	30.3	NE
Difference: hazard ratio (95% CI), p-value	0.61 (0.27 to 1.39), p=0.232		0.70 (0.44 to 1.11), p=0.124	
Kaplan Meier 24-month estimated overall survival	91%	85%	84%	77%
PFS2				
Events	37	20	92	53
Median PFS-2, months	NE	NE	27.2	NE
Difference: hazard ratio (95% CI), p-value	0.84 (0.48 to 1.45)		0.81 (0.58 to 1.14)	
Time to first subsequent treatment				
Events	76	66	210	138
Median TFST, months	NE	13.7	18.6	12.0
Difference: hazard ratio (95% CI), p-value	0.46 (0.33 to 0.64)		0.65 (0.52 to 0.80)	

HRD=homologous recombination deficiency; ITT=intention to treat; NE=not estimable; NR=not reported; PFS=progression-free survival; BICR=blinded independent committee review; CI=confidence interval; PFS2= progression-free survival on subsequent therapy; TFST= time to first subsequent treatment.

Patients reported outcomes included the Functional Assessment of Cancer Therapy – Ovarian Symptoms Index (FOSI) total score, European Organisation for Research and Treatment of Cancer Quality of Life of Cancer patients questionnaire (EORTC-QLQ-C30), EORTC-QLQ-ovarian cancer 28 (OV28) and the European Quality of Life scale 5 dimensions (EQ-5D-5L). During the study, there were no significant changes from baseline in each treatment group for the FOSI total score, EORTC-QLQ-OV28 and EQ-5D-5L. Most assessments of EORTC-QLQ-C30 were similar with the exception of gastrointestinal related assessments which found that constipation, nausea/vomiting and appetite loss were worse in niraparib treated patients and diarrhoea was worse in placebo treated patients. [2, 3]

Summary of evidence on comparative safety

In the PRIMA study at data cut-off May 2019, the median duration of treatment in the niraparib group was 11.1 months and in the placebo group was 8.3 months. Any treatment-emergent adverse event (AE) was reported by 99% (478/484) of patients in the niraparib group and 92% (224/244) in the placebo group and these were considered treatment-related in 96% and 69% respectively. In the niraparib and placebo groups respectively, patients reporting a grade 3 or higher AE were 70% versus 19%, patients with a reported serious AE were 32% versus 13%, patients with a dose reduction due to treatment emergent AEs were 71% versus 8.2%, the proportion of AEs that led to dose interruptions were 80% versus 18% and patients discontinuing therapy due to an AE was 12% versus 2.5%.[2, 3]

The most frequently reported treatment-emergent AEs of any grade in the niraparib group versus the placebo group were: anaemia (63% versus 18%), nausea (57% versus 27%), thrombocytopenia (46% versus 3.7%), constipation (39% versus 19%), fatigue (35% versus 30%), decreased platelet count (27% versus 1.2%), neutropenia (26% versus 6.6%), headache (26% versus 15%), insomnia (25% versus 14%), vomiting (22% versus 12%) and abdominal pain (22% versus 31%).[2, 3]

During the study, a protocol amendment led to the introduction of an individualised dosing regimen with patients weighing <77kg and/or having a platelet count <150,000/microlitre starting study treatment on a lower dose of 200mg daily. The incidence of haematological AEs was lower in patients who started treatment on the lower individualised dose of niraparib (n=169) compared with the fixed dose (n=315) including anaemia (50% and 71% respectively), thrombocytopenia (34% and 52% respectively) and neutropenia (24% and 28% respectively). The incidence of haematological AEs of grade 3 or higher was also lower: anaemia (22% and 36% respectively), thrombocytopenia (15% and 36% respectively) and neutropenia (9.5% and 15% respectively).[2]

During PRIMA, the incidence of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) was 0.2% in the niraparib group compared with 0% in the placebo group. However the duration of follow-up in the PRIMA study is currently too short to assess the potential risk of this and follow-up will be continued. Exposure to chemotherapy is a confounding factor, and all the patients have received at least one previous chemotherapy regimen.[2]

Summary of clinical effectiveness issues

The early stages of ovarian cancer tend to be asymptomatic or associated with non-specific symptoms and as a result, patients are often diagnosed with disease at an advanced stage. Treatment of advanced disease 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 may reduce the chance of recurrence and improve survival outcomes.[2, 4] Bevacizumab, in combination with carboplatin and

paclitaxel, followed by continued bevacizumab monotherapy, is a first-line treatment option and has been accepted for restricted use by SMC for patients with FIGO stage IV disease (SMC806/12). Olaparib has been licensed and accepted by SMC as monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) 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 (SMC2209). Olaparib in combination with bevacizumab has recently received marketing authorisation for 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 combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability. [5, 6] Clinical experts consulted by SMC considered that there is an unmet need for maintenance treatment following response to first-line platinum-based chemotherapy. Niraparib meets SMC orphan and end of life criteria.

Results from the PRIMA study have shown that maintenance treatment with niraparib following first-line platinum-based chemotherapy significantly improved PFS in advanced ovarian cancer patients with and without HRD. The improvement in PFS with niraparib over placebo was 11.5 months in the HRD population and 5.6 months in ITT population. The results were considered clinically relevant by the European Medicines Agency (EMA) in a patient population with limited treatment options. Results for the key secondary outcome of overall survival did not show a significant survival benefit with niraparib compared with placebo, but are currently considered immature. Further overall survival data are awaited with final results expected in 2024. Results for the other secondary outcomes, PFS2 and TFST did not show significant improvement over placebo, and are also immature. Maintenance treatment with niraparib did not appear to have a detrimental effect on the quality of life of treated patients as illustrated in the patients reported outcomes assessed in PRIMA.[2, 3, 7]

To reduce haematological adverse events, the PRIMA study was amended to introduce individualised dosing according to patient's body weight and/or platelet count; this is the licensed dose for this indication. However, only approximately a third of study patients received individualised dosing and the study was not powered to compare individualised with fixed dosing. Post hoc exploratory analyses indicated that there may be a modest reduction in treatment effect at the 200mg starting dose compared with the 300mg starting dose for the HRD and ITT populations but the benefit observed was still considered clinically relevant by the EMA. The SPC recommends a fixed dose of 300mg daily for the maintenance treatment patients with relapsed disease.[1, 2]

The safety data from the PRIMA study are consistent with the known safety profile for niraparib and included haematological and gastrointestinal adverse events. It is unclear if the incidence of adverse events will be lower in practice than in the study when patients receive the licensed individualised dose.

The PRIMA study excluded patients with stage III disease and no visible residual disease after primary debulking surgery. These patients are included within the marketing authorisation for niraparib, although the treatment effect has not been specifically studied. These patients are likely to have a better prognosis than other stage III and IV patients. However, the EMA considered that the benefit: risk of niraparib in these patients would be positive.[2]

The PRIMA study compared niraparib with placebo only, reflective of routine surveillance in clinical practice. There are no direct comparative data for niraparib with bevacizumab in patients with stage IV disease or with olaparib in the subgroup of patients with a BRCA mutation. Differences between studies made any indirect comparison with olaparib in patients with a BRCA mutation uncertain and the company assumed that niraparib and olaparib were clinically equivalent. The company did not consider bevacizumab a relevant comparator and the recently licensed combination of olaparib with bevacizumab was not included as a comparator.

The introduction of niraparib for the maintenance treatment of patients with advanced ovarian cancer in response following first-line platinum-based chemotherapy would offer an oral treatment for all patients regardless of BRCA mutation status. This would be the first oral PARP inhibitor licensed for use in these patients who do not have a BRCA mutation. This would offer convenience to patients and the service. Clinical experts consulted by SMC considered that niraparib was a therapeutic advancement offering an active maintenance treatment option with its place in therapy being for maintenance treatment following response to first-line platinum-based chemotherapy in patients with stage III disease without a BRCA mutation.

While niraparib meets SMC orphan and end of life criteria in this indication, the company did not request a Patient and Clinician Engagement (PACE) meeting to consider the added value of niraparib in the context of treatments currently available in NHS Scotland.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis of niraparib against routine surveillance as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and 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. The base case analysis was based on the ITT population from the PRIMA study, with additional analysis performed to capture the broader population captured by the marketing authorisation. The company also provided an exploratory cost-minimisation analysis versus olaparib in the BRCA mutation subgroup.

A partitioned survival cohort simulation model was used. The model consisted of three mutually exclusive health states; progression free disease (PFD), progressed disease (PD) and death. The cycle length was one month with patients either remaining in state, or transitioning to PD or death at the end of each cycle. The model projected two primary outcomes –overall survival and PFS. An

NHS perspective and a 39-year lifetime horizon were selected in the base case of the economic model.

The cost-utility analysis was based on clinical effectiveness data from the following sources:

- For the ITT population, overall survival, PFS and time on treatment parameters were informed by the PRIMA study. In the case of overall survival, the extrapolations were validated using long-term data from the University of Edinburgh ovarian cancer database for the routine surveillance arm, and using long-term data for olaparib to estimate a PFS:overall survival relationship for the niraparib arm.
- For the full market authorisation population, the PAOLA-1 trial for olaparib plus bevacizumab was used to estimate a HR between the bevacizumab monotherapy arms of the visible residual disease (VRD) and no visible residual disease (NVRD) subgroups.
- For the BRCA mutation subgroup, clinical equivalence between niraparib and olaparib was assumed on the basis of a naïve comparison between the PRIMA and SOLO-1 trials.

Outcomes data were limited to the duration of the PRIMA trial and extrapolation of overall survival and PFS was required. Fully fitted parametric curves were fitted to the PRIMA Kaplan-Meier data. The generalised gamma curve was chosen as the base case distribution for PFS on niraparib and routine surveillance, on the basis of best statistical fit and clinical expert feedback.

The log-logistic curve was chosen as base case distribution for overall survival on routine surveillance as it aligned most closely with the real-world data from the ovarian cancer database. In order to estimate overall survival (OS) for niraparib, a mean change in PFS: change in OS relationship of 1:2 was selected for the base case. This was based on mature overall survival data from a trial which compared olaparib with routine surveillance as second line maintenance treatment.[8]

Utility values were based on EQ5D-5L data from the PRIMA study. These values were cross-walked to generate EQ5D-3L. In the base case, health states were defined by progression status and were determined as a mean across the niraparib and control arm of PRIMA. Age related utility decrements not applied in the base case but adverse event disutilities were.

Acquisition costs for niraparib were based on the actual dose received by patients in the PRIMA study. This meant that costs were based on individualised dosing for about one-third of the patients rather than the recommended fixed dose for all patients. Costs associated with any subsequent treatments were also included in the analysis and were based on expert opinion reflective of clinical practice. Subsequent treatments based on PRIMA were not used in the base case due to the immaturity of data and the expected poorer prognosis of the PRIMA population, as they excluded better performing Stage 3 with NVRD patients covered by the market authorisation. Unit costs for disease management, managing adverse events, end of life care were also accounted for. Acquisition costs for olaparib were included in the cost-minimisation analysis for the BRCA mutation subgroup.

A stopping rule of three years was applied in the base case, but the model assumed that proportion of individuals would continue to have niraparib beyond three years. A two year stopping rule was applied to olaparib in the cost-minimisation analysis.

A Patient Access Scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a discount was offered on the list price for niraparib. A PAS is also in place for olaparib.

The base case analysis produced an ICER of 7,800 £/QALY (inclusive of PAS) against RS for the ITT population. The analysis for the full market authorisation population produced an ICER of 7,199 £/QALY (inclusive of PAS) against routine surveillance.

The company provided a range of sensitivity and scenario analysis, with selected results shown in table 2.

Table 2: **Selected scenario analysis for the ITT and market authorisation populations**

	Scenario	**ICER for PRIMA ITT population (£/QALY)**	**ICER for full market authorisation population (£/QALY)**
	Base Case	***7,800***	***7,199***
1	Time Horizon – 25 years	8,883	8,383
2	Alternate PFS distribution – Log-logistic	15,487	15,508
3	Mean ΔPFS:ΔOS relationship 1:1	16,572	17,704
4	Alternative ΔPFS:ΔOS relationship based on PRIMA OS HR	14,008	14,256
5	Alternate PFS distribution- merged generalised gamma and log-logistic distribution	10,819	9,696
6	Subsequent treatments based on PRIMA	16,201	13,663
7	Age related utility decrements	8,348	7,730
8	Combined scenario 2+6+7	29,998	30,691
9	Combined scenario- 3+7	17,744	18,810
10	Combined scenario 4+5+7	19,482	19,487

Abbreviations: ICER, incremental cost-effectiveness ratio; Δ, change; PFS, progression-free survival; OS, overall survival; RS, routine surveillance

The cost-minimisation analysis showed that the use of niraparib in place of olaparib in the BRCA mutation subgroup was associated with a cost reduction of £5,506 at list prices. These result do not take account of the PAS for olaparib but estimates of the PAS were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for comparator medicines due to commercial confidentiality and competition law issues.

There were a number of limitations with the analysis which include the following:

- There is uncertainty regarding the overall survival treatment benefit conferred by niraparib. While the company estimated overall survival for the routine surveillance arm by fitting a log-logistic model to the observed overall survival data from PRIMA, a similar approach could not be applied to the niraparib arm due to the immaturity of data. Instead, the company estimated overall survival on niraparib using a HR based on an assumption that a 1-month gain in PFS leads to a 2-month gain in overall survival. This assumption was based on long-term data from Study 19, which compared olaparib with routine surveillance as second line maintenance treatment. However, in the absence of mature data from PRIMA, there remains substantial uncertainty whether overall survival benefits of niraparib would match those observed for olaparib in Study 19.
- The HR derived from the 1:2 ratio used in the model does not reflect the HR observed for overall survival in PRIMA. Applying a HR to a model which does not assume proportional hazards is not methodologically correct. Furthermore, applying a HR assumes a constant treatment effect over time which may not be true in the case of niraparib. Overall, there was no way to validate the PFS: OS ratio. Scenario analysis showed that applying a more conservative 1:1 ratio increased the ICER (table 2, scenario 3). Following New Drugs Committee, the company provided further analysis based on observed OS HR from PRIMA (table 2, scenario 4). The company asserted this should be considered a lower bound estimate for the effect given data on olaparib from Study 19 demonstrating that OS treatment effects are improved over time relative to RS.
- The choice of distribution used to extrapolate PFS and the choice of subsequent treatments were key drivers of cost-effectiveness. The generalized gamma curve was the preferred choice for PFS extrapolation based on statistical fit and expert opinion, but the company did not provide a convincing rationale as to why the log-logistic distribution might be implausible. Further justification of this was provided following the New Drugs Committee meeting indicating that the log-logistic curve gave PFS at 5 and 10 years that would be lower than that observed in the University of Edinburgh ovarian cancer database. The company also provided a revised analysis using an average gamma/ log-logistic approach (table 2, scenario 5) as an alternative, which gave a reasonable fit to the quoted real world data for RS. However, the exclusion of subsequent treatments based on PRIMA was adequately justified and the use of expert opinion to inform this parameter was appropriate.
- The base case analysis did not include age-related utility decrements and potentially overestimates the modelled utility gains achieved by patients. Sufficient justification for its exclusion was not provided. Applying age related decrements led to a small increase in the ICERs (table 2, scenario 7).

- Because of a protocol change during the study, about two-thirds of people in PRIMA took a fixed dose of 300 mg of niraparib and around one-third took an individualised dose of niraparib based on weight and platelet count. The PRIMA study was not powered to show a difference in efficacy between dosing groups and hence there is some residual uncertainty about the PFS benefits achieved by niraparib in the individualised dosing group.
- There is some uncertainty about the assumed clinical equivalence between niraparib and olaparib for the BRCA mutation patient subgroup on the basis of a naïve comparison, as used in the cost-minimisation analysis. However, clinical expert opinion (both SMC and company experts) seem to support this assumption.

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

After considering all the available evidence, the Committee accepted to accept niraparib for use in NHSScotland.

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

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. Ovarian Cancer Action and Target Ovarian Cancer are registered charities and Ovacome Ovarian Cancer Charity is a charitable incorporated organisation.
- Ovacome Ovarian Cancer Charity has received 7.2% pharmaceutical company funding in the past two years, including from the submitting company. Ovarian Cancer Action has received 4.3% pharmaceutical company funding in the past two years, including from the submitting company. Target Ovarian Cancer has received 4% pharmaceutical company funding in the past two years, including from the submitting company.
- A diagnosis of ovarian cancer is devastating, impacting on every aspect of an individual's life - their relationships, work, family life and social life. Women not only suffer from the physical consequences of the disease (ascites, bloating, abdominal pain) but also have to live with the short- and long-term impact of its treatment. Women are often diagnosed at an advanced stage, so have a poor prognosis. One of the biggest challenges of living with ovarian cancer post-treatment is the fear of recurrence. This anxiety is also felt by family members in addition to the practical impact of the diagnosis, such as the travel to hospital for treatment.
- Standard treatment involves surgery and chemotherapy, which is gruelling and requires regular hospital visits. The time after treatment whereby women are under routine surveillance can be psychologically very hard to cope with. In advanced ovarian cancer

treatment is aimed at minimising the burden of the disease and maximising periods of wellness between treatments. As treatment lines are exhausted, women fear being told there is no more treatment available.

- Women in Scotland who do not have a BRCA mutation do not currently have the option of a PARP inhibitor maintenance treatment following first-line chemotherapy. Niraparib would offer a new treatment option regardless of BRCA mutation status. It is given in capsule form offering women greater convenience and reducing hospital visits. Women on maintenance treatments report that they allow better quality of life, added hope and more quality time with family members.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) first published guidance entitled Management of epithelial ovarian cancer: A national clinical guideline (SIGN 135)[4] in 2013; the guidance was subsequently updated in 2018. The SIGN guidance makes the following relevant recommendations for chemotherapy in advanced disease:

- First-line chemotherapy treatment of epithelial ovarian cancer should include a platinum agent either in combination or as a single agent.
- Paclitaxel is recommended in combination therapy with platinum in the first line post-surgery treatment of epithelial ovarian cancer where the potential benefits justify the toxicity of the therapy. In those unable to tolerate paclitaxel, pegylated liposomal doxorubicin or gemcitabine in combination with carboplatin can be used as an alternative.
- Patients who are unfit for combination therapy should be offered single agent carboplatin.
- A third cytotoxic agent should not be added to carboplatin and paclitaxel.
- Women with stage IV ovarian cancer should be offered bevacizumab in combination with carboplatin and paclitaxel.
- For advanced ovarian cancer, maintenance cytotoxic chemotherapy should not be given following standard first line chemotherapy.
- Olaparib monotherapy should be considered for maintenance treatment after response to platinum for patients with relapsed platinum-sensitive *BRCA*-mutated ovarian cancer.
- Niraparib monotherapy should be considered for maintenance treatment after response to platinum for patients with relapsed platinum-sensitive non-germline *BRCA*-mutated ovarian cancer.

This guideline predates the availability of olaparib and niraparib as maintenance treatment in newly diagnosed patients responding following completion of first-line platinum-based chemotherapy.

The European Society for Medical Oncology (ESMO) published Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical practice guidelines in 2013[9] and the guidance was subsequently updated in April 2020.[10] The guideline makes the following relevant recommendations for advanced disease:

- Chemotherapy is recommended for all patients with FIGO stage II–IV disease post surgery; paclitaxel plus carboplatin is standard first-line therapy; docetaxel plus carboplatin or pegylated liposomal doxorubicin plus carboplatin can be considered an alternatives.
- The addition of bevacizumab is recommended for patients with advanced ovarian cancer with poor prognostic features such as stage IV or suboptimal debulking. Bevacizumab should be given with paclitaxel or carboplatin with a treatment duration of one year.

Maintenance therapy with a PARP inhibitor (olaparib, niraparib or rucaparib) following a response to platinum-based therapy in patients with recurrent platinum-sensitive high-grade ovarian cancer is a new standard of care option, irrespective of BRCA status.[9, 10]

Additional information: comparators

Routine surveillance or other maintenance treatments following first-line platinum-based chemotherapy which include olaparib for patients with a BRCA mutation or bevacizumab for patients with stage IV disease.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
niraparib	200mg to 300mg orally once daily	58,500 to 87,750

Costs from BNF online on 2 February 2021. Costs do not take patient access schemes into consideration.

Additional information: 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.

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

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This assessment is based on data submitted by the applicant company up to and including 12 March 2021.

**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.