Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Re-submission

olaparib, 50mg, hard capsules (Lynparza®) SMC No. (1047/15)

AstraZeneca UK

07 October 2016

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission assessed under the ultra-orphan and end of life process

olaparib (Lynparza®) is accepted for use within NHS Scotland.

Indication under review: monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed *BRCA*-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

Olaparib was assessed in a phase II randomised, placebo-controlled study of patients with high grade serous, recurrent, platinum-sensitive ovarian, fallopian-tube or primary peritoneal cancer in which there had been an objective response to the most recent platinum-based chemotherapy regimen. In a pre-planned analysis of the sub-group of patients with *BRCA* mutation, olaparib was associated with a significantly improved progression-free survival compared with placebo. An interim analysis of overall survival in the *BRCA* mutation sub-group (70% maturity) demonstrated a benefit of more than four months for olaparib over placebo.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of olaparib. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

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

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed *BRCA*-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

Dosing Information

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

The recommended dose is 400mg (eight capsules) taken orally twice daily, equivalent to a total daily dose of 800mg. Patients should start treatment no later than eight weeks after completion of their final dose of the platinum-containing regimen.

It is recommended that treatment be continued until progression of the underlying disease. There are no data on retreatment with olaparib following subsequent relapse.

Due to the effect of food on olaparib absorption, patients should take it at least one hour after food, and refrain from eating preferably for up to two hours afterwards.

Product availability date

22nd May 2015
Olaparib has been designated an orphan medicine for the treatment of ovarian cancer by the European Medicines Agency in 2007. Olaparib meets SMC ultra-orphan and end-of-life criteria.

Background

Olaparib is a poly ADP-ribose polymerase (PARP) inhibitor. PARP enzymes are involved in the efficient repair of deoxyribonucleic acid (DNA).[1] In the absence of functional *BRCA* genes, inhibition of PARP enzymes lead to cancer cell death due to the activation of alternative error-prone pathways of DNA repair.[2]

Olaparib is the first PARP inhibitor to receive a marketing authorisation in the UK and the first agent to be licensed to specifically target patients whose ovarian cancer has the *BRCA* mutation.

Olaparib is eligible for consideration by SMC under its decision-making framework for the assessment of ultra-orphan medicines.

Nature of condition

In Scotland, women with no family history have a lifetime risk of developing ovarian cancer of 1 in 55. The aetiology is unknown and because the early stages tend to be asymptomatic or associated with non-specific symptoms, it is often detected at an advanced stage. Mutation of the breast cancer

susceptibility genes (*BRCA1/2*) increases an individual's risk of developing cancers, especially ovarian or breast cancer, and approximately 17% of patients with serous ovarian cancer have a *BRCA* mutation.[1,9]

Currently in NHS Scotland, patients who respond to platinum-based chemotherapy are monitored for disease progression and then considered for a subsequent course of chemotherapy. Bevacizumab has not been recommended for use in NHS Scotland by SMC when used in combination with carboplatin and gemcitabine and then as a maintenance treatment. Olaparib was designated as an orphan medicine for the treatment of ovarian cancer on 06 December 2007. It also meets SMC ultra-orphan and end-of-life criteria. The results of the pivotal study supporting the use of olaparib suggest that patients who are managed with a watch and wait strategy have a median survival of approximately 30 months, although this is confounded by subsequent PARP inhibitor treatment. Retrospective analysis of an Australian ovarian cancer cohort estimated median overall survival to be 22 months.[10]

Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely that there is no maintenance therapy available in this specific setting. Bevacizumab, in combination with carboplatin and paclitaxel, is now available for the front-line treatment of advanced International Federation of Gynaecology and Obstetrics (FIGO) stage IV epithelial ovarian, fallopian tube, or primary peritoneal cancer.

A patient and clinician engagement (PACE) meeting was held to consider the added value of olaparib in the context of treatments currently available in NHS Scotland. At the PACE meeting, attention was drawn to age at diagnosis, with patients who carry *BRCA* mutations often being younger than most ovarian cancer patients and likely to be working or to have other family members to care for. In addition, emphasis was given to the psychological impact of disease recurrence on patients and their families.

Impact of new technology

Summary of evidence on comparative efficacy

The evidence for olaparib comes from a multi-centre, randomised, double-blind, placebo-controlled phase II study (Study 19).[3,4] The study recruited adults with high grade serous, recurrent ovarian or fallopian-tube cancer or primary peritoneal cancer. Patients had completed at least two courses of platinum-based chemotherapy, the last course of which consisted of a minimum of four cycles. The cancer was required to be platinum-sensitive (an objective response to the penultimate platinum-based regimen of more than six months) and the most recent regimen had to have induced an objective response. Objective response was either: partial or complete response as per Response Evaluation Criteria in Solid Tumours (RECIST) 1.0, or a Cancer Antigen 125 (CA-125) response, as per the Gynecological Cancer InterGroup criteria. Patients' pre-treatment CA-125 value was within the upper limit of normal, or if greater, then a repeated level after seven days had increased by less than 15% of the first measurement. Patients' Eastern Co-operative Oncology Group (ECOG) performance status was 0 to 2 and their life expectancy at least 16 weeks. Patients were required to commence study treatment within eight weeks of their previous platinum-based regimen.[1,3]

Patients were randomly assigned 1:1 to olaparib (n=136) 400mg orally twice daily or placebo (n=129) and stratified by several factors: interval between disease progression and completion of penultimate platinum-based regimen (6 to 12 months versus >12 months), objective response to most recent regimen (complete versus partial), and ancestry (Jewish versus non-Jewish). *BRCA1/2* mutations are

more frequently present in Jewish populations. Blinded study treatment was continued until objective disease progression (defined by RECIST) or unacceptable toxicity; although patients could continue to receive study treatment following objective disease progression if the investigator considered that the patient was gaining benefit from treatment, and did not meet any other discontinuation criteria.[1] Treatment interruptions for treatment-related grade 3 or 4 adverse events and dose reductions to 200mg or 100mg twice daily were permitted. Treatment was discontinued if toxicity did not resolve within four weeks or if a third treatment interruption was necessary.[3]

The primary endpoint was progression-free survival (PFS) assessed by the local investigator and defined as the time from randomisation until objective disease progression according to RECIST, or death for any reason. In the overall study population after accrual of 153 events in 44% (60/136) of olaparib patients and 72% (93/129) of placebo patients, there was a statistically significant PFS advantage for olaparib, hazard ratio (HR)=0.35 (95% confidence interval [CI]: 0.25 to 0.49), p<0.001. Median PFS was 8.4 months in the olaparib group and 4.8 months in the placebo group.[3]

A pre-planned retrospective analysis of outcomes by *BRCA* status was conducted. *BRCA* status was known at study onset for 37% of patients and was established retrospectively for 60% of patients. The sub-group of patients with *BRCA* mutation (n=136) represents the population of patients who would be eligible for olaparib under its licensed indication. When compared with placebo, olaparib was associated with statistically significantly prolonged PFS, time to first subsequent therapy (TFST) and time to second subsequent therapy (TSST). No advantage with overall survival was observed at the November 2012 cut-off.[4] Updated analyses of overall survival were conducted in September 2015. At this cut off, 15% (11/74) of patients with *BRCA* mutation had received at least five years treatment with olaparib.[5]

At the November 2012 cut off, and also at the September 2015 cut off, 23% (14/62) of patients in the *BRCA* mutation placebo subgroup had subsequently received a PARP inhibitor.[4] Two post hoc exploratory analyses were employed in an attempt to explore the potential confounding effect of crossover on overall survival in patients who had received placebo in the study but received PARP inhibitors after study discontinuation. The first analysis excluded all study centres where any placebo patient had received a post-study PARP inhibitor as subsequent treatment: crossover site excluded (CSE) analysis which excluded 11 of the 82 study sites and 29% (39/136) of *BRCA* mutation patients. The second analysis used the rank preserving structural failure time (RPSFT) model which reconstructs data for the placebo arm to simulate a situation where switching had not occurred.[7]

Results are presented in the table below.

Table: Key efficacy results in patients with *BRCA* mutation [4,5,6,8]

Outcome		Olaparib (n=74)	Placebo (n=62)	HR (95% CI), p-value
PFS (Primary outcome) June 2010 [4]	**Events, n (%)**	26/74 (35%)	46/62 (74%)	0.18 (0.10 to 0.31) p<0.0001
	Median	11.2 months	4.3 months	
Overall survival November 2012 [4]	**Events, n (%)**	37/74 (50%)	34/62 (55%)	0.73 (0.45 to 1.17) p=0.19
	Median	34.9 months	31.9 months	

Overall survival September 2015 [5]	**Events, n (%)**	47/74 (64%)	48/62 (77%)	0.62 (0.41 to 0.94) P=0.025
	Median	34.9 months	30.2 months	
Median TFST November 2012 [4]		15.6 months	6.2 months	0.33 (0.22 to 0.50) p<0.0001
Median TSST November 2012 [4]		23.8 months	15.2 months	0.44 (0.29 to 0.67) p=0.00013

PFS=progression free survival; HR=hazard ratio; CI=confidence interval; TFST=time to first subsequent treatment; TSST=time to second subsequent treatment.

Several measures were used to assess effects on health-related quality of life in exploratory analyses: trial outcome index (TOI), functional assessment of cancer therapy for ovarian cancer (FACT-O) and the FACT-O symptom index (FOSI). There was no significant difference between the treatment groups in the proportion of patients with improvements, nor in the time to worsening for any of the quality of life measures.[4]

Summary of evidence on comparative safety

In the *BRCA* mutation population, almost all patients reported an adverse event: 97% (72/74) of olaparib patients and 94% (58/62) of placebo patients. Common adverse events of any severity reported in more than 20% of olaparib patients were: nausea (73% of olaparib patients versus 32% of placebo patients), fatigue (54% versus 37%), vomiting (36% versus 8.1%), diarrhoea (30% versus 19%), anaemia (26% versus 4.8%), and abdominal pain (23% versus 29%). The majority of these adverse events were Grade 1 or 2 in severity. Adverse events of at least grade 3 in severity were reported in a greater proportion of olaparib patients than placebo, 38% versus 18%.[4]

Serious adverse events in the overall study population were reported by 18% of olaparib patients and by 8.6% of placebo patients. The most common serious adverse event was small intestinal obstruction: two patients in the olaparib group and three patients in the placebo group.[1]

The summary of product characteristics notes that a small number of cases of (often fatal) myelodysplastic syndrome/acute myeloid leukaemia have been reported in patients taking olaparib as monotherapy or in combination with other anti-cancer treatments. In all patients there was at least one contributory factor such as: previous platinum chemotherapy, radiotherapy, history of previous cancer or bone marrow dysplasia. A safety signal for pneumonitis is also noted, but the clinical pattern is inconsistent and confounded by predisposing factors.[2]

The European Medicines Agency concluded that further data from phase III and phase IV studies are required to provide longer-term safety data for this agent.[1]

Summary of clinical effectiveness issues

The primary outcome in the pivotal study was PFS. In the sub-group of patients with *BRCA* mutation there was a statistically significant advantage for those treated with olaparib compared with placebo, with a clinically significant increase in median PFS of 6.9 months. In the context of current practice in NHS Scotland, which is 'watch and wait' (active surveillance), placebo is considered to be a relevant comparator.

TSST was measured and considered as a surrogate for PFS on subsequent treatment (PFS2). Results for TSST suggested that response to subsequent treatment was not affected by the use of olaparib as maintenance therapy.

The study did not prospectively and exclusively recruit patients with *BRCA* mutation; however, baseline characteristics of the *BRCA* mutation sub-group were balanced between the treatment groups.[4] Analysis of outcomes in the sub-group was conducted retrospectively.

There are very limited efficacy data in patients with somatic *BRCA* mutations although similar efficacy with germline *BRCA* mutations (based on biological rationale) is expected. Phase III and IV studies, which are on-going, are expected to provide additional efficacy and safety data.

The study was not powered to compare overall survival. Overall survival data are still immature; however, an interim analysis (70% maturity in the *BRCA* mutation sub-group) demonstrated a benefit of 4.7 months for olaparib over placebo. Five year survival was 37% and 24% in the respective groups.[5] Although the study did not permit patient crossover, approximately one quarter of patients in the *BRCA* mutation sub-group who received placebo were subsequently treated with a PARP inhibitor, confounding the overall survival comparison. Results of two post-hoc exploratory analyses that aimed to account for post-study crossover suggest that the actual overall survival benefit of olaparib over placebo may be greater than observed in the study.[7] Statistical advice sought by SMC notes limitations with both analyses.

The assessment of quality of life was not powered to detect significant differences between treatments. Study patients had good ECOG performance status, and quality-of-life scores were obtained up to progression when patients were still in good health. Olaparib was not associated with any deterioration of health-related quality of life.[4]

Clinical experts consulted by SMC considered that olaparib is a therapeutic advancement due to the delays in disease progression and time to subsequent chemotherapy courses demonstrated in the pivotal study. The experts also considered the place in therapy of olaparib to fit with its licensed indication.

Feedback from the Molecular Pathology Evaluation Panel noted that there would be service implications from introducing somatic *BRCA* mutation testing for patients who are designated *BRCA* mutation-negative with germline testing, however somatic *BRCA* mutation testing is confirmed as now being available through the genetics consortium.

With the availability of a new treatment pathway, patients may require more frequent monitoring whilst on olaparib e.g. full blood counts should be monitored on a monthly basis for the first year of treatment, and periodically thereafter.[2]

At the PACE meeting, it was noted that any extension to the time before further chemotherapy is a very valuable benefit to patients and their families as this is often a time period associated with good quality of life and functioning because symptoms are well controlled. It may also help fortify patients so that they are able to cope with further chemotherapy upon relapse. Treatment may allow patients to maintain their independence for longer and fulfil any caring roles that they themselves perform. In addition, the possibility of long-term disease free survival offers patients optimism for the future.

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

Patient and clinician engagement (PACE)

A patent and clinician engagement (PACE) meeting with patent group representatives and clinical specialists was held to consider the added value of olaparib, as an end-of-life and ultra-orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Relapsed ovarian cancer is incurable and has a devastating impact on patients and their families. Median survival at this stage in the disease is around two years. Patients who carry *BRCA* mutations are often younger than most ovarian cancer patients and are likely to be working or to have other family members to care for.

- Recurrence is associated with significant morbidity and symptoms which can be very difficult to alleviate e.g. bowel obstruction. Aside from the physical impact of chemotherapy, the knowledge that the cancer has recurred has a devastating psychological and emotional impact on patients and their families.

- There is no other licensed maintenance treatment for this group of patients. Olaparib is oral and is self administered at home. This is the first molecular targeted therapy for ovarian cancer and will allow individualisation of care.

- Olaparib has been shown to prolong progression free survival and delay time to both first and second subsequent therapies in patients with platinum sensitive *BRCA* ovarian cancer. It also offers the possibility of long-term disease free survival (more than 5 years) in a proportion of patients. Any extension of time before further chemotherapy is very meaningful for patients and their families.

- Olaparib is a new targeted therapy where the group most likely to benefit has been clearly identified. These patients are still relatively well when starting olaparib so the additional time it provides would be of high quality. Olaparib keeps women well for longer and provides quality of life and clinically meaningful survival benefits, with a small proportion remaining disease-free for an extended period.

Additional Patient and Carer Involvement
We received patient group submissions from Ovarian Cancer Action, Ovacome and Target Ovarian Cancer. Ovarian Cancer Action has not received any pharmaceutical company funding in the past two years. Ovacome has received 4% pharmaceutical company funding in the past two years, but none from the submitting company. Target Ovarian Cancer has received <1% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from Ovacome and Target Ovarian Cancer also participated in the PACE meeting. The keys points of their submissions have been included in the full PACE statement. Ovarian Cancer Action did not participate in the PACE meeting, however the key points of their submission were covered in the PACE Statement.

Value for money

The submitting company presented a cost-utility analysis comparing olaparib maintenance therapy with a 'watch and wait' approach in women with platinum-sensitive relapsed *BRCA*-mutated high grade serous ovarian cancer who are in response to platinum-based chemotherapy. The comparator was appropriate. A fifteen year time horizon was used.

A 4 state semi-Markov structure was used and included health states for progression-free (PF), first subsequent treatment (FST), second subsequent treatment (SST) and death. FST and SST outcomes in the model were estimated using the exploratory endpoints of TFST and TSST from Study 19. Extrapolation of these data were necessary to estimate the longer term outcomes in the model and the extrapolations carried out by fitting various parametric curves to the data. For example, for the key transition from PF to FST, a single parametric curve with a log-normal distribution was fitted, with an adjustment factor depending on whether treated with olaparib or placebo (watch and wait). In addition, as the data in Study 19 for watch and wait patients were confounded by subsequent use of PARP inhibitors, the company performed an adjustment to the data. To achieve this, the company assumed that the transitions from PF to FST for these patients were equal to the transitions for olaparib-treated patients. This had the impact of assuming that the effect of the treatment lasts only until the first disease progression and that after this point, there is no difference in the risk of death or progression between treatment arms.

For clarity, the key changes made since the first submission included:

- Updated time to event data (leading to selection of different parametric functions for some of the model estimates)
- A revised complex patient access scheme
- Sensitivity analysis was also provided whereby crossover was accounted for by using the crossover site excluded (CSE) analysis.

There were also minor changes to the adverse event rate and unit costs.

Utilities were estimated by mapping findings from the FACT-O data collected in Study 19 into the EQ-5D instrument. This used a published algorithm and utilities were predicted based on a number of relevant factors from a mixed effects regression. In the base case, patients receiving olaparib maintenance therapy had the same utility score (0.769) as patients who did not receive maintenance therapy during the progression-free phase. As such, no allowance was made for adverse events on treatment on the basis that this was not a significant factor in the regression modelling.

In terms of resource use, the cost of olaparib was estimated from extrapolated time to discontinuation data from Study 19 at a mean daily dose of 675mg. The costs of chemotherapy at FST and SST were estimated based on the most commonly used regimens in Study 19 and the analysis also included costs associated with monitoring and background health care resource uses. The base case did not include any costs associated with genetic testing on the assumption that germline testing was already standard practice in NHS Scotland. Additional costs of somatic testing were included as a sensitivity analysis.

A complex patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland.

The incremental cost per quality adjusted life year (QALY) for olaparib maintenance therapy compared to a strategy of watch and wait was £41,505 with the PAS.

A range of sensitivity analyses were carried out and the one-way analyses showed that the incremental cost-effectiveness ratio (ICER) was most sensitive to the costs of olaparib, the on-treatment utility on olaparib and the utility values associated with FST and SST. If the utility for olaparib patients in the on-treatment phase reduced to 0.61 then the ICER rose to £55,602 with PAS. While such a low value may not be appropriate, it does suggest that if there were on-treatment disutilities associated with being on olaparib that have not been accounted for in the method used, the ICER may be higher than estimated. The two scenario analyses which did use a slightly worse utility value for while on olaparib treatment (very small differences of 0.004 and 0.009) increased the ICERs to £41,663 with PAS and £42,115 with PAS, respectively. The company also provided analysis using a value taken from expert opinion of 0.72 which resulted in an ICER of £44,008 with PAS.

Scenario-based sensitivity analysis also tested some key factors of the model and showed that the choice of functions used for extrapolation and adjusting for crossover had the potential to increase the ICER. For example in analysis that was adjusted for crossover (as per base case) but which used the generalised gamma form to predict time to FST, the ICER rose to £48,006 with PAS. This is of interest given that the generalised gamma was the best fit on AIC criteria (log-normal was better on BIC criteria and used in base case) but the submitting company argued that this approach produced implausible estimates of long term survival for watch and wait patients, as validated by an expert. An additional analysis using estimates of long term survival for watch and wait patients from an expert consulted by the company gave an ICER of £ £43,508 with PAS. If the trial results were adjusted for the use of subsequent PARP inhibitors by using the CSE analysis, the ICER rose to £45,525 with PAS. While adjusting for subsequent treatment is a reasonable approach, this sensitivity analysis does highlight that the results are sensitive to the methods used to adjust the data. Shortening the time horizon gave an ICER of £45,410 with PAS at 10 years.

In addition to a high base case ICER, the analysis had a number of uncertainties or weaknesses:

- The results showed sensitivity to the method of adjusting for crossover as noted above. Additional information was also provided by the company to show the HR when the OS data were adjusted using the RPSFT method. Compared to the CSE method of adjustment, this gave a higher HR and wider confidence intervals. However, the company was unable to use these results directly within the analysis because the model structure does not utilise OS data directly, but rather estimates it via FST/ SST/ time to death. The company did however provide an informal analysis to show the possible impact of using RPSFT and this resulted in an ICER of £47,256 with PAS.
- The final analysis of overall survival data from Study 19 is not yet available. While the updated data cut used in the current resubmission demonstrated an improved OS hazard ratio and narrower confidence interval, there will still be some uncertainty associated with the predicted survival gain in the model given the need for extrapolation. The scenario-based analyses which tested different extrapolation methods for time to FST showed smaller predicted life year gains and resulting higher ICERs.
- Utility values were estimated from regression equations and the resulting figures used in the base case meant that there was no on-treatment decrement associated with being on olaparib maintenance treatment. Sensitivity analysis using alternative regressions that did result in a very small decrement while taking olaparib did change the ICER but only by less than £1000 and using a decrement of 0.049 gave an ICER of £44,008.
- The economic model is driven by data extrapolated from the exploratory variables in Study 19 i.e. time to FST and SST and treatment discontinuation rather than the primary outcome of the

study (PFS).

- The base case does not include an allowance for genetic testing on the assumption that this is already taking place. Sensitivity analysis showed that the ICERs rose to £ 42,209 and £43,020 with PAS if the costs of germline or somatic testing respectively had been included.

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

Impact beyond direct health benefits and on specialist services

At the PACE meeting, attention was drawn to psychological and emotional impact that patients and carers experience when there is recurrence of disease and hence the potential importance of olaparib in improving time to progression. It was also noted that progression of disease and the need for chemotherapy can cause a significant burden on family members who may have to give up work to care for the patient. This can lead to financial implications for patients and their families. By delaying progression and time to the next chemotherapy, the potential extra time that olaparib can offer patients is of high quality and will give the family a longer period of normal family life and allow them to share key life events together. Further to this, maintenance treatment with olaparib is not expected to involve frequent hospital attendance.

Olaparib is an oral treatment and is self-administered at home and thus would not be associated with service implications in terms of provision of intravenous chemotherapy.

Costs to NHS and Personal Social Services

The submitting company estimated the population eligible for treatment to be 65 patients in year 1 and then 36 patients per year thereafter to which confidential estimates of treatment uptake were applied.

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.

The submitting company did not estimate any costs outside of the NHS.

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

Conclusion

The Committee also considered the benefits of olaparib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that a number of the criteria were satisfied: a substantial improvement in life expectancy in the patient population targeted in the submission; and the absence of other treatments of proven benefit. In addition, as olaparib is an orphan 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 was able to accept olaparib for use in NHS Scotland.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network published SIGN 135: Management of epithelial ovarian cancer in November 2013.[9] In patients with advanced epithelial ovarian cancer, first-line chemotherapy should include a platinum agent either in combination or as a single agent, unless specifically contra-indicated. Carboplatin is the platinum agent of choice due to a more favourable toxicity profile compared with cisplatin. Paclitaxel is the preferred second cytotoxic agent to be given in combination with platinum, and pegylated liposomal doxorubicin or gemcitabine considered as alternatives in those unable to tolerate paclitaxel. Maintenance cytotoxic chemotherapy should not be given to patients with advanced ovarian cancer following standard first line chemotherapy. In patients with relapsed, platinum-sensitive disease, recommended treatment options are platinum-based combinations with paclitaxel, pegylated liposomal doxorubicin or gemcitabine. Bevacizumab in combination with carboplatin and gemcitabine is not recommended as a result of the advice of SMC.

The European Society of Medical Oncology updated its clinical practice guidelines for newly diagnosed and relapsed epithelial carcinoma in 2013.[11] Approximately 70% of patients will relapse within three years following the employment of optimal upfront surgery and administration of paclitaxel and carboplatin chemotherapy. Success of second and subsequent lines of therapy depends upon the duration of the progression-free interval. 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. The guideline also recommends bevacizumab in combination with carboplatin and gemcitabine in “platinum-sensitive” relapsed ovarian cancer patients who have not previously received bevacizumab. This is based on a significant improvement in progression free survival and objective response rates observed in the OCEANS study.

Neither guideline made any recommendations in relation to maintenance treatment following second-line chemotherapy or in patients with specific *BRCA* mutations. The guidelines above were published prior to the availability of olaparib.

The National Institute for Health and Care Excellence (NICE) published multiple technology appraisal (TA389) in April 2016: Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer.

NICE technology appraisal guidance [TA389] Published date: 27 April 2016 Healthcare Improvement Scotland advised that the recommendations are as valid for Scotland as for England and Wales. It does not include advice on olaparib.[12]

Additional information: comparators

There are no available comparators for platinum-sensitive ovarian cancer.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
olaparib	**400mg orally twice daily**	**46,150**

Cost is from company submission. Costs do not take any patient access schemes into consideration.

References

The undernoted references were supplied with the submission.

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This assessment is based on data submitted by the applicant company up to and including 15 July 2016.

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_statements/Policy_Statements

Drug 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 drug 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 NHS Scotland 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 NHS Scotland 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.