SMC2518

olaparib film-coated tablets (Lynparza®)

AstraZeneca UK Ltd

08 September 2023

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

ADVICE: following a full submission assessed under the orphan medicine process

olaparib (Lynparza®) is accepted for use within NHSScotland.

Indication Under Review: as monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline *BRCA1/2*-mutations who have human epidermal growth factor receptor 2 (HER2)-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy.

In a phase III study, adjuvant olaparib after the completion of neoadjuvant or adjuvant chemotherapy, significantly improved invasive disease-free survival compared with placebo in patients with high-risk, HER2-negative early breast cancer with a germline *BRCA1/2*-mutation.

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

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

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Olaparib is an inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2 and PARP-3), and has been shown to inhibit tumour growth by exploiting deficiencies in DNA repair pathways to preferentially target and kill tumour cells. The recommended dose of olaparib as monotherapy or in combination with endocrine therapy is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg. It is recommended that patients are treated for up to 1 year, or until disease recurrence, or unacceptable toxicity, whichever occurs first.[1, 2] Olaparib is also licensed for HER2-negative locally advanced or metastatic breast cancer with a germline *BRCA1/2*-mutation but has not been accepted for use in NHS Scotland by SMC for this indication (SMC2436) in the absence of a submission from the holder of the marketing authorisation.[2]

1.2. Disease background

Early stage breast cancer is defined as a malignancy localised to the breast with or without regional lymph node involvement in the absence of metastatic disease. Germline *BRCA1* or *BRCA2* mutations are present in approximately 5% of breast cancer patients and are typically observed in younger patients with a strong family history of breast cancer. Patients with this type of breast cancer often have high-risk disease characteristics, which are associated with a poorer prognosis. Most patients with a *BRCA1* mutation develop triple-negative breast cancer (TNBC) which is HER2, oestrogen and progesterone receptor negative; early recurrence is more likely in this group of patients with a shorter time between recurrence and death. Hormone receptor-positive tumours are more common in patients with a *BRCA2* mutation; these are also associated with an increase in high-risk disease factors compared with other types of breast cancer.[1, 3]

1.3. Treatment pathway and relevant comparators

Treatment options for early breast cancer include surgery, radiotherapy and systemic anticancer treatment. Neoadjuvant or adjuvant chemotherapy is recommended for most patients with TNBC, and in patients with hormone receptor-positive, HER2-negative breast cancer, the decision is based on tumour characteristics, anticipated response to endocrine therapy and patient preferences. Standard chemotherapy regimens include sequential treatment with an anthracycline and taxane; selected patients with TNBC may be suitable for the addition of a platinum agent however, this is not routinely recommended. Adjuvant capecitabine (off-label) may be considered for patients with TNBC who do not achieve a pathological complete response following optimal neoadjuvant chemotherapy. Adjuvant endocrine therapy with tamoxifen, an aromatase inhibitor or ovarian suppression is indicated for patients with oestrogen receptor-positive disease and bisphosphonates are also recommended for post-menopausal patients with low oestrogen expression at high risk of relapse.[1, 4, 5] After completion of neoadjuvant or adjuvant chemotherapy patients receive regular follow-up, therefore 'watch and wait' is an appropriate comparator for this submission. Capecitabine may also represent an additional comparator for selected patients with TNBC. Clinical practice in this area may be changing as abemaciclib and pembrolizumab have recently been licensed for use in specified patients in the early breast cancer setting (SMC2494 and SMC2538).

1.4. Category for decision-making process

- Eligibility for a PACE meeting

Olaparib meets SMC orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of olaparib for the indication under review comes from the ongoing OlympiA study.[3] Details are summarised in Table 2.1.

Table 2.1. Overview of the OlympiA study.[1, 3]

Criteria	OlympiA
Study Design	Multicentre, randomised, double-blind, phase III study.
Eligible Patients	• Adults aged ≥18 years. • Histologically confirmed non-metastatic primary breast cancer with a high-risk phenotype, (TNBC or hormone HER2-negative breast cancer) •For patients who received **neoadjuvant chemotherapy** followed by surgery: ○ Both TNBC and hormone receptor-positive, HER2-negative patients must have had residual invasive breast cancer in the breast and/or resected lymph nodes (non-pathological complete response) ○ Hormone receptor-positive, HER2-negative patients were also required to have a clinical and pathological stage (CPS) and oestrogen-receptor status and histologic grade (EG) score ≥3 (scoring system which classifies patients as 'high risk' based on clinical stage, pathologic stage, oestrogen receptor status and nuclear grade; range 0 to 6) • For patients who underwent initial surgery and received **adjuvant chemotherapy**: ○ TNBC patients must have had axillary node-positive disease or axillary node-negative disease with invasive primary tumour >2cm ○ Hormone receptor-positive (oestrogen receptor [ER] and/or progesterone receptor [PR]), HER2-negative patients must have had ≥4 pathologically confirmed positive lymph nodes • Documented germline *BRCA1* or *BRCA2* mutation • Completed at least six cycles of neoadjuvant or adjuvant chemotherapy, which contained anthracyclines, taxanes or both. Platinum chemotherapy was permitted. • All local therapy completed within 12 weeks prior to randomisation. • Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
Treatments	Olaparib 300mg orally twice daily (n=921) or placebo (n=915) for up to 52 weeks, or until disease recurrence or unacceptable toxicity. Adjuvant bisphosphonates and adjuvant endocrine therapy in patients with hormone receptor-positive disease was permitted as per local guidelines.
Randomisation	Equal randomisation.
Primary outcome	Invasive disease-free survival which was defined as the time from randomisation until first invasive disease occurrence (including ipsilateral invasive breast cancer, locoregional invasive disease, distant recurrence, contralateral invasive breast cancer or second primary invasive cancer) or death from any cause. This was assessed in the intention-to-treat population.

Secondary outcomes	Distant disease-free survival: the time from randomisation until documented evidence of first distant recurrence of breast cancer (including metastatic breast cancer and new primary non-breast invasive cancer) or death from any cause. Overall survival: the time from randomisation until death from any cause.
Statistical analysis	A hierarchical multiple testing strategy was applied to the primary and key secondary outcomes in the study.

At an interim analysis conducted in March 2020, after a median follow-up of 2.5 years, olaparib demonstrated superiority to placebo for the primary outcome, invasive disease-free survival (IDFS) and key secondary outcome, distant disease-free survival (DDFS); a statistically significant improvement for overall survival was not observed at this data cut. The independent data monitoring committee considered that the predefined threshold for superiority of olaparib compared with placebo had been met in the intention-to-treat (ITT) population and therefore this was considered the primary analysis for IDFS. At a subsequent planned interim analysis for overall survival, conducted in July 2021 when 330 IDFS events had occurred, there was a statistically significant improvement in overall survival for olaparib compared with placebo.[1, 3, 6-8] The results for the primary and selected secondary outcomes have been presented in Table 2.2.

Table 2.2: Primary and selected secondary outcomes in the ITT from the OlympiA study.[1, 3, 6-8]

	Olaparib (n=921)	**Placebo (n=915)**	**Olaparib (n=921)**	**Placebo (n=915)**
Data cut-off	27 March 2020		12 July 2021	
Median follow-up	2.5 years		3.5 years	
Primary outcome: investigator-assessed IDFS				
IDFS events, n	106	178	134	207
Hazard ratio	0.58 (99.5% CI: 0.41 to 0.82) p<0.001		0.63 (95% CI: 0.50 to 0.78)	
KM estimated IDFS at 3 years	86%	77%	*	*
Secondary outcome: investigator-assessed DDFS				
DDFS events, n	89	152	*	*
Hazard ratio	0.57 (99.5% CI: 0.39 to 0.83) p<0.001		0.61 (95% CI: 0.48 to 0.77)	
KM estimated DDFS at 3 years	88%	80%	*	*
Secondary outcome: overall survival				
Deaths	59	86	75	109
Hazard ratio	0.68 (99% CI: 0.44 to 1.05) p=0.02		0.68 (98.5% CI: 0.47 to 0.97) [A]p=0.009	
KM estimated survival at 3 years	92%	88%	93%	89%

CI=confidence interval; DDFS=distant disease-free survival; IDFS=invasive disease-free survival; ITT=intention-to-treat; HR=hazard ratio; KM=Kaplan-Meier. [A]As the predefined threshold for superiority of olaparib versus placebo was met at the first interim analysis for IDFS and DDFS, only overall survival was formally tested at the second interim analysis (when 330 IDFS events had occurred). *Some results from the July 2021 data cut-off were considered confidential by the company.

Prespecified subgroup analyses based on prior chemotherapy, hormone receptor status, *BRCA* mutation, prior surgery, disease stage and baseline demographics were generally consistent with the primary analysis and favoured the olaparib group for IDFS, DDFS and overall survival. At the July 2021 data cut-off, in the subgroup of 1,509 patients with TNBC, there were fewer IDFS events in the olaparib group compared with placebo (14% [109/751] versus 23% [173/758]; hazard ratio (HR) 0.62 (95% confidence interval [CI]: 0.49 to 0.79). In the subgroup of 325 patients with hormone receptor-positive disease, subgroup results were similar and favoured the olaparib group compared with placebo (15% [25/168] versus 22% [34/157]; HR: 0.68 [95% CI: 0.40 to 1.13]). In the latter subgroup, 90% of patients had concomitant endocrine therapy.[1]

2.2. Health-related quality of life outcomes

Health-related quality of life was assessed using the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue symptom scale score and the European Organisation for Research and Treatment of Cancer quality of life (EORTC-QLQ-C30) questionnaire. There were no clinically meaningful differences between the olaparib and placebo groups at 6 or 12 months for the FACIT-fatigue score in patients who had received prior neoadjuvant or adjuvant therapy. The EORTC-QLQ-C30 global health status scores and functioning subscales were similar in both groups at 6 and 12 months with no clinically significant between group differences. The EORTC-QLQ-C30 gastrointestinal (GI) nausea and vomiting symptom score was higher in the olaparib group compared with placebo at 6 and 12 months indicating worse symptom severity; this returned to baseline at 18 and 24 months with comparable scores between groups.[1]

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

3. Summary of Safety Evidence

In the OlympiA study at data cut-off July 2021, 76% in the olaparib group and 82% in the placebo group completed at least 11 months of treatment with most discontinuing after 11.5 months. Any adverse event (AE) was reported by 92% (836/911) of patients in the olaparib group and 84% (756/904) in the placebo group. In each group respectively, patients reporting a grade 3 or higher AE were 24% versus 11%, patients with a reported serious AE (including deaths) were 8.7% versus 8.6%, patients with a dose reduction due to an AE were 23% versus 3.7%, the proportion of AEs that led to dose interruptions were 31% versus 11% and patients discontinuing therapy due to an AE was 11% versus 4.6%.[1]

At data cut-off July 2021, the most frequently reported AEs of any grade were: nausea (57% versus 24%), fatigue (40% versus 27%), anaemia (24% versus 3.9%), vomiting (23% versus 8.2%), headache (20% versus 17%), diarrhoea (18% versus 14%), neutrophil count decreased (16% versus 6.5%), white blood cell (WBC) count decreased (16% versus 5.8%), decreased appetite (13% versus 5.9%), dysgeusia (12% versus 4.2%) and dizziness (11% versus 7.3%). Grade ≥3 AEs with an incidence >1% in the olaparib group versus the placebo group were: anaemia (8.7% versus 0.3%), neutrophil count decreased (4.9% versus 0.8%), WBC decreased (3.0% versus 0.3%), fatigue (1.8% versus 0.7%) and lymphocyte count decreased (1.3% versus 0). The regulator concluded that safety data of olaparib in OlympiA were consistent with the known safety profile of olaparib in other indications and no new adverse drug reactions were identified. Please see the Summary of

Product Characteristics (SPC) for further safety information.[1-3]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Phase III randomised, placebo-controlled study. Placebo is an appropriate proxy for the "watch and wait" approach that is commonly taken in this setting.
- In the OlympiA study, at the March 2020 data cut-off (primary analysis for IDFS and DDFS), with a median follow-up of 2.5 years, adjuvant olaparib was associated with a significant improvement in the primary outcome, IDFS and secondary outcome, DDFS, in patients with high-risk, HER2-negative early breast cancer with a germline *BRCA1* or *BRCA2* mutation. For IDFS, there was a reduction in the risk of recurrence of disease at any given time point of 42% with 8.8% of patients disease free at 3 years, for DDFS the risk reduction at any given time point was 43% with 7.1% of patients free of distant disease at 3 years. At the July 2021 data cut-off (primary analysis for overall survival), olaparib was associated with a significant improvement in overall survival with a median follow-up of 3.5 years; the reduction in risk of death at any given time point was 32%. These results were considered clinically relevant and the regulator concluded that benefit had been demonstrated as monotherapy and in combination with endocrine therapy.[1, 3]
- Subgroup analysis results showed consistent benefit of olaparib across all pre-defined subgroups.

4.2. Key uncertainties

- At the July 2021 data cut-off, median follow-up for overall survival was 3.5 years in the olaparib group and 3.6 years in the placebo group; data maturity was 10%.[1] Therefore the longer-term effect of adjuvant olaparib on overall survival is uncertain. Lower event rates are expected in the adjuvant setting and further data are likely to be confounded by the efficacy of subsequent anticancer treatments.
- OlympiA included patients with high-risk early breast cancer as defined by criteria based on prior neoadjuvant or adjuvant chemotherapy and response at the time of surgery, CPS and EG score (hormone receptor-positive only), and lymph node involvement as detailed in Table 2.1.[3] SMC clinical experts indicated that similar criteria are likely to be used in Scottish clinical practice to select patients for adjuvant treatment with olaparib, however there could be variation across Scotland regarding use of the CPS + EG scoring system.
- There is no direct or indirect evidence comparing olaparib with capecitabine in the adjuvant setting, which may be used off-label in patients with TNBC who do not achieve a pathological complete response following neoadjuvant treatment. Although the number of patients with a germline BRCA1/2 mutation that receive adjuvant capecitabine are expected to be low.
- The proportion of patients with hormone receptor-positive disease may be lower than is typically observed in Scottish clinical practice because they were initially excluded from the OlympiA study until a protocol amendment in October 2015 (16 months after

randomisation had begun). As a result, only 325 patients (18%) in the study population had HER2-negative, hormone positive disease. Pre-planned subgroup analysis in patients with hormone receptor-positive disease were consistent with the primary analysis however OlympiA was not powered to detect differences between subgroups and therefore results should be interpreted with caution.[1, 3]

4.3. Clinical expert input

Clinical experts consulted by SMC considered that olaparib fills an unmet need for this indication and that it is a therapeutic advancement because of clinically favourable results demonstrated in the OlympiA study, the tolerable safety profile and advantages associated with the oral route of administration. They indicated that it would be used as per the licensed indication following neoadjuvant or adjuvant chemotherapy.

4.4. Service implications

Laboratory services may be impacted as germline *BRCA* testing is required to select patients eligible for treatment. Although some patients that meet certain criteria are currently tested, the availability of olaparib is likely to increase testing volume. Additional oncology clinical and pharmacy resource may be required to manage supply, monitor treatment effect and adverse events.

Diagnostic test required to identify patients eligible for treatment: contact local laboratory for information.

5. Patient and clinician engagement (PACE)

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

The key points expressed by the group were:

- Breast cancer with a BRCA1/2 germline mutation is a rare type of cancer and is typically diagnosed in younger patients, many of whom will be working and could have families with dependent children. Early breast cancer with a BRCA1/2 mutation has a high risk of recurrence compared with other early breast cancers. The fear of cancer returning or spreading to other parts of the body is extremely distressing for patients and their family.

- There are currently no licensed medicines for early breast cancer that specifically target BRCA positive tumours. Therefore, there is a high unmet need for effective treatments that reduce the risk of relapse or recurrent disease which can be incurable.

- Olaparib is a targeted therapy that when given in the adjuvant setting, has been shown to reduce the risk of disease recurrence compared with current standard of care alone in patients with high-risk, HER2-negative early breast cancer with a germline BRCA1/2 mutation. This is likely to improve the psychological wellbeing of patients and their family who live with the fear of cancer returning and having to undergo subsequent complex treatments. Most patients can

return to work, continue family responsibilities and function well during treatment therefore disruption to daily life is minimal.

- PACE participants agreed that patients and clinicians would welcome the introduction of adjuvant olaparib as an effective treatment, with a convenient oral route of administration that is likely to have minimal service impact.

- Most patients tolerate treatment well and are able to complete the course; the side effect profile is not expected to significantly limit daily activities. Oncology teams are experienced in the monitoring and management of common side effects of olaparib because of its use in other cancer settings.

- PACE participants agreed that the place in treatment should be as per the licensed indication.

Additional Patient and Carer Involvement

We received a patient group submission from Breast Cancer Now, which is a registered charity. Breast Cancer Now has received 0.7% pharmaceutical company funding in the past two years, including from the submitting company. Breast Cancer Now funded researchers are involved in PARP inhibitor research. Breast Cancer Now receives from The Institute of Cancer Research (ICR) a share of royalties/payments from sales of olaparib by the submitting company. A representative from Breast Cancer Now participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost utility analysis
Time horizon	57 years (tested in scenario analysis)
Population	The analysis covers the full licensed indication ie the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer (eBC) who have previously been treated with neoadjuvant or adjuvant chemotherapy.
Comparators	Olaparib is compared with a “watch and wait” strategy
Model description	Markov state transition model was presented with 5 main health states: invasive disease free survival, loco-regional recurrence, early onset metastatic disease, late onset metastatic disease and death. Subsequent therapies are include at first and second line therapy for recurrent disease, as are surgical and radiological options.
Clinical data	Clinical effectiveness data came from the OlympiA phase III study.[3] The data were split by early breast cancer type whereby triple negative disease subgroup data were used for this study sub-population and the ITT analysis data were used to inform estimates for the HR positive/HER2 negative subgroup, as the specified subgroup data for these patients were not available.
Extrapolation	Survival upon recurrence is taken from external studies from the literature, depending on whether or not patients had triple negative disease or HR positive/HER2 negative disease. Distributions were fitted to estimates but these were tested in scenario analysis. Invasive

	disease free survival estimates required general population mortality data. This was adjusted to account for the BRCA mutation status of patients, with an assumed 5% risk of recurrence over 10 years.
Quality of life	EORTC-QLQ-C30 data collected in the OlympiA study were mapped to the EQ-5D using published algorithms. Base case values were 0.869 for disease free, 0.777 for non-metastatic recurrence, and 0.685 for early and late onset metastatic recurrence. Testing the choice of mapping algorithm used to convert the EORTC data to the EQ-5D reduced the disease-free and non-metastatic utilities to 0.802. Using literature-derived estimates instead of utilising the OlympiA data further reduced disease free and non-metastatic values to 0.779. Testing the literature source of metastatic disease utility reduced it from 0.685 in the base case to 0.521 in scenario analysis.
Costs and resource use	Medicines costs included acquisition and administration costs of olaparib, endocrine therapies for HR positive/HER2 negative patients, and various subsequent therapies for patients who experience a recurrence. All patients discontinue treatment after a maximum of 1 year, but adjustments to the duration of therapy associated with early discontinuation were accounted for. Nevertheless, the impact of dose reductions was not accounted for and the adverse event profile of olaparib does not seem to have been fully considered in the model. Resource use included routine outpatient, primary care, imaging (mammogram and CT) tests and blood tests. Costs of managing specific adverse events (neutropenia and anaemia) were included. The costs of BRCA testing for all patients in the HR+/HER2- cohort of the economic model were also included.
PAS	A 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.

6.2. Results

The base case results are presented in Table 6.2.

Table 6.2 – Base case results inclusive of PAS discount

	Treatment	ICER (£/QALY gained)
Triple negative patients (subgroup data)	"Watch & wait"	-
	Olaparib	£18,532
HR+/HER2- patients (ITT)	"Watch & wait"	-
	Olaparib	£20,179

ITT = intention to treat; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life-year; HER2: human epidermal growth factor 2; HR: hormone receptor

6.3. Sensitivity analyses

A number of sensitivity analyses were provided and the key scenarios are summarised in Table 6.3. Aside from the choice of discount rate, the comparison with the watch and wait strategy was most sensitive to the utility estimates, the probability of recurrences (transition probabilities 1 and 2 in the model) and the time point at which patients are no longer at a risk of recurrence.

Table 6.3 – Scenario analyses inclusive of PAS discount

Scenario Number	Scenario	Base case value	Scenario analysis value	ICER (£/QALY) (TNBC)	ICER (£/QALY) (HR+/HER2-)
1	Base case	–	–	£18,532	£20,179
2	Age-adjusted utilities	Yes	No	£17,156	£18,758
3	TP1/TP2: conditional prob. recurrence	Combined treatment arms	By individual treatment arms	£18,351	£19,808
4	TP1/TP2 distribution	Lognormal	Loglogistic	£18,236	£22,263
5			Generalised gamma	£19,239	£22,578
6	TP6 distribution	Exponential	Loglogistic	£19,303	£21,129
7			Gompertz	£19,028	£20,789
8			Lognormal	£19,235	£21,045
9	TP6: assume the same risk of death across arms	No	Yes	£18,098	£19,647
10	TP1/2 & TP6 combined	TP1/2: lognormal TP6: exponential	TP1/2: generalised gamma TP6: Gompertz	£19,787	£23,371
11			TP1/2: loglogistic TP6: Gompertz	£18,703	£23,000
12	Utility values	DF: 0.869 Non-mBC: 0.777 mBC: 0.685	DF: 0.802 Non-mBC: 0.802 mBC: 0.685	£20,435	£22,252
13			DF: 0.869 Non-mBC: 0.869 mBC: 0.521	£17,908	£19,489
14			DF: 0.779 Non-mBC: 0.779 mBC: 0.685	£21,121	£23,002
15			DF: 0.842 Non-mBC: 0.764 mBC: 0.685	£19,218	£20,927
16			DF: 0.815 Non-mBC: 0.750 mBC: 0.685	£19,956	£21,732

Abbreviations: : DF: disease-free; HER2: human epidermal growth factor 2; HR: hormone receptor; ICER: incremental cost-effectiveness ratio; mBC: metastatic breast cancer; QALY: quality adjusted life year; TNBC: triple negative breast cancer; TP: transition probability

6.4. Key strengths

The economic analysis had a number of strengths, including the extent to which clinical input was sought to validate the parameters, and attempts to keep the analysis consistent with previous submissions in this disease area.

6.5. Key uncertainties

- Some SMC clinical experts noted that capecitabine may be a treatment option at this point

in the treatment pathway for some patients with triple negative disease. An analysis versus capecitabine was not provided but it was included in the economic model as a subsequent therapy for loco-regional recurrence and as a first line treatment for metastatic disease recurrence. The Committee considered the lack of comparison with capecitabine was not critical, as it would only be a relevant comparator for a small proportion of patients.

- It is difficult to validate the model inputs from the clinical evidence from the OlympiA study as the subgroup data have been used for patients with triple negative disease, and the ITT data were used for the HR positive/HER2 negative group. The submitting company stated that the subgroup data were sufficiently mature, whereas the low number of events in the HR positive/HER2 negative subgroup meant that it was not yet possible to provide a robust analysis specifically using data for these patients. Instead, the ITT data were used as a proxy. Survival rates for the comparator groups of the OlympiA study were found to be similar for the TNBC and HR positive/HER2 negative subgroups.
- The immaturity of the survival data necessitated the use of external data sources to validate the longer-term effects. The estimates that have the largest impact on results were those related to the probability of recurrence from the invasive disease free state (transition probabilities one and two), and the survival of patients who have early onset distant recurrence (transition probability six). The submitting company had explored the combined effect of changes to the distributions in scenario analyses 10 and 11, which provided reassurance.

7. Conclusion

The Committee 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 as olaparib is an orphan medicine, SMC can accept greater uncertainty in the economic case.

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

8. Guidelines and Protocols

The European Society for Medical Oncology (ESMO) published Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up in 2003 and these were updated in 2019. See here

The National Institute for Health and Care Excellence (NICE) updated its national guideline (NG) 101: Early and locally advanced breast cancer: diagnosis and management in 2018. See here

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline 134 Treatment of primary breast cancer: a national clinical guideline in 2013. See here

9. Additional Information

9.1. Product availability date

7 September 2022

9.2. Summary of product characteristics

See the SPC for further information including dosing and safety.

Olaparib 100mg film-coated tablets (Lynparza®) SPC

Olaparib 150mg film-coated tablets (Lynparza®) SPC

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Olaparib	**300mg twice daily orally**	**60,255**

Costs from BNF online on 25/11/22. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 15 patients eligible for treatment with olaparib in year 1, rising to 25 patients in year 5, to which confidential uptake rates were applied. SMC clinical expert responses indicate the uptake rate is likely to be higher than estimated by the submitting company.

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.**

References

1. The European Medicines Agency (EMA) European Public Assessment Report. Olaparib (Lynparza®). 03.10/2022 EMEA/H/C/003726/II/0051/G. Available at: https://www.ema.europa.eu/en/documents/variation-report/lynparza-h-c-3726-ii-0051-g-epar-assessment-report-variation_en.pdf.
2. AstraZeneca UK Ltd. Olaparib film-coated tablets (Lynparza®). Summary of product characteristics. Electronic Medicines Compendium. Available at: https://www.medicines.org.uk/emc/product/9488/smpc Last upated: 17 November 2022. [cited.
3. Tutt A, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, *et al.* Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. New England Journal of Medicine. 2021;384(25):2394-405.
4. F. Cardoso, S. Kyriakides, S. Ohno, et. al. Early Breast Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30(8):1194-1220.
5. National Institute for Health and Care Excellence (NICE). NICE Guideline [NG101]: Early and locally advanced breast cancer: diagnosis and management. 18 July 2018 Available at: https://www.nice.org.uk/guidance/ng101
6. AstraZeneca data on file. A Randomised, Double-Blind, Parallel Group, Placebo-Controlled Multi-Centre Phase III Study to Assess the Efficacy and Safety of Olaparib Versus Placebo as Adjuvant Treatment in Patients With Germline BRCA1/2 Mutations and High Risk HER2 Negative Primary Breast Cancer Who Have Completed Definitive Local Treatment and Neoadjuvant or Adjuvant Chemotherapy. Primary Clinical Study report. 03 September 2021.
7. Tutt ANJ, Garber G, Gelber RD, Phillips KA, Eisen A, al. e. VP1-2022: Pre-specified event driven analysis of Overall Survival (OS) in the OlympiA phase III trial of adjuvant olaparib (OL) in germline BRCA1/2 mutation (gBRCAm) associated breast cancer. ESMO Virtual Plenary. 2022.
8. AstraZeneca Data on file. Data cut-off 2 (12 July 2021) efficacy. .

This assessment is based on data submitted by the applicant company up to and including 30 May 2023.

**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.