Technology Guidance

PARP inhibitors and bevacizumab

for treating advanced ovarian cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Olaparib 100 mg and 150 mg tablets for treating advanced ovarian cancer in line with specific clinical criteria.

Subsidy status

Olaparib 100 mg and 150 mg tablets are recommended for inclusion on the Medication Assistance Fund (MAF) with effect from 1 September 2022 for the following indications:

- As maintenance monotherapy for patients with advanced BRCA-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Treatment should be continued until disease progression or unacceptable toxicity or for a maximum of 24 months;
- In combination with bevacizumab biosimilar (subsidised brand) as maintenance treatment of patients with advanced homologous recombination deficiency (HRD) positive high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy in combination with bevacizumab biosimilar. Treatment with olaparib should be continued until disease progression or unacceptable toxicity or for a maximum of 24 months; and
- As maintenance monotherapy for patients with platinum-sensitive relapsed BRCA-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy. Patients must not have received prior treatment with a PARP inhibitor for ovarian cancer. Treatment should be continued until disease progression or unacceptable toxicity.

MAF assistance **does not** apply to olaparib 50 mg capsules, or to any formulations or strengths of bevacizumab reference biologic (Avastin) or niraparib.

Clinical indications, subsidy status and MediShield Life claim limits for all drugs included in the evaluation are provided in the Annex.

Updated: 12 July 2022

Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1 The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of bevacizumab and poly adenosine diphosphate-ribose polymerase (PARP) inhibitors (olaparib and niraparib) for treating ovarian, fallopian tube or primary peritoneal cancer (henceforth referred to as "ovarian cancer"). The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for all drugs was considered in line with their registered indications. Additional expert opinion was obtained from the MOH Oncology Drug Subcommittee (ODS) who assisted ACE ascertain the clinical value of the drugs under evaluation and provided clinical advice on their appropriate and effective use based on the available clinical evidence.

1.2 Olaparib 50 mg capsule was excluded from evaluation as the manufacturer confirmed that it was being discontinued and replaced by 100 mg and 150 mg tablets. Niraparib 200 mg and 300 mg tablets were excluded from evaluation as these strengths are not commercially available in Singapore. Rucaparib 200 mg, 250 mg and 300 mg tablets were also excluded from evaluation as the manufacturer confirmed that they did not intend to seek HSA regulatory approval for them.

1.3 The technology evaluation of bevacizumab biosimilar (Mvasi) for treating different types of cancer in line with its registered indications is discussed in a separate guidance.

1.4 The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.5 Additional factors, including social and value judgments, may also inform the Committee's subsidy considerations.

Clinical need

2.1 The Committee noted that approximately 200 patients are diagnosed with advanced ovarian cancer each year in Singapore and there was a high clinical need to consider effective treatments for subsidy to improve treatment affordability and ensure

appropriate patient care.

2.2 Newly diagnosed ovarian cancer
The Committee acknowledged that bevacizumab in combination with carboplatin and paclitaxel is the standard of care for patients with newly diagnosed ovarian cancer who are at high risk of progression (inoperable Stage III, sub-optimally debulked Stage III, or Stage IV). Patients with less severe disease are treated with platinum-based chemotherapy such as carboplatin plus paclitaxel (CP).

2.3 Patients who have a complete or partial response to platinum-based chemotherapy may undergo routine surveillance or receive maintenance therapy with bevacizumab or a PARP inhibitor depending on the chemotherapy regimen used and the patient's BRCA mutation or homologous recombination deficiency (HRD) status.

2.4 Recurrent ovarian cancer
The Committee acknowledged that local clinical practice for recurrent ovarian cancer is in line with international clinical guidelines. Chemotherapy regimens containing bevacizumab are standard of care for treating recurrent disease. Patients with platinum-sensitive BRCA-mutated disease who are in complete or partial response to platinum-based chemotherapy may receive maintenance therapy with a PARP inhibitor if they have not received one previously for ovarian cancer.

Clinical effectiveness and safety

3.1 Treatment of newly diagnosed ovarian cancer
The Committee reviewed the available clinical evidence (ICON7 and GOG-0218) comparing CP alone or in combination with bevacizumab followed by bevacizumab maintenance therapy in patients with newly diagnosed ovarian cancer. The Committee considered that the treatment regimens in ICON7 were representative of local clinical practice.

3.2 Results from ICON7 showed that CP plus bevacizumab led to statistically longer progression-free survival (PFS) and overall survival (OS) compared to CP alone in a subgroup of patients with high risk of progression only. CP plus bevacizumab was associated with higher rates of grade ≥3 adverse events, the most common being hypertension, venous thromboembolic events and arterial thromboembolic events, compared to CP alone.

3.3 Maintenance treatment with PARP inhibitors for newly diagnosed ovarian cancer
The Committee reviewed the available clinical evidence (SOLO1, PAOLA-1 and PRIMA) which investigated olaparib monotherapy, olaparib in combination with bevacizumab and niraparib monotherapy respectively compared with placebo in patients with newly diagnosed ovarian cancer who had at least partial response to platinum-based chemotherapy. The Committee noted that the patient populations

differed between the three trials in terms of comparators, disease severity and biomarker status, and the significant heterogeneity made it difficult to compare outcomes across trials.

3.4 Results showed that PARP inhibitors led to statistically longer PFS compared to placebo, however, OS results were immature. The Committee noted SOLO1 had a longer follow-up and a higher percentage of OS maturity than PRIMA. Findings for PRIMA (niraparib) remained consistent following subgroup analysis by HRD status, but findings for PAOLA-1 (olaparib plus bevacizumab) remained consistent for patients with HRD-positive disease only and there was no PFS gain for patients with HRD-negative or HRD-unknown disease. PARP inhibitors were associated with higher rates of grade ≥3 adverse events compared to placebo.

3.5 In the absence of head-to-head trials and indirect evidence between olaparib and niraparib, the Committee considered that there was insufficient evidence to determine the comparative effectiveness of olaparib and niraparib.

3.6 Maintenance treatment with PARP inhibitors for platinum-sensitive relapsed ovarian cancer

The Committee reviewed the available clinical evidence for the PARP inhibitors olaparib (Study 19 and SOLO2) and niraparib (NOVA) compared with placebo in patients with relapsed ovarian cancer who had at least a partial response to platinum-based chemotherapy. Results showed that PARP inhibitors led to statistically longer PFS compared to placebo. Median OS was 51.7 months for olaparib tablets and 38.8 months with placebo but the difference was not statistically significant. OS results for niraparib were immature. Both PARP inhibitors were associated with higher rates of grade ≥3 adverse events compared to placebo.

3.7 The Committee reviewed an indirect comparison of the PARP inhibitors (Staropoli et al. 2018) and noted that there was no statistically significant difference in PFS between olaparib and niraparib in patients with relapsed ovarian cancer. The PARP inhibitors as a drug class showed significant improvement in PFS compared with placebo for all patient subgroups, and patients with BRCA-mutated disease had a greater reduction in risk of disease progression or death compared to patients with BRCA wild-type disease.

Cost-effectiveness

4.1 The manufacturers of all drugs under evaluation were invited to submit value-based pricing (VBP) proposals for their products for subsidy consideration.

4.2 Bevacizumab

Treatment of newly diagnosed ovarian cancer

In the absence of a local economic analysis for bevacizumab, the Committee reviewed

evaluations from overseas HTA agencies. They noted that NICE (UK) did not consider Avastin plus CP to be cost-effective (£77,884/QALY) compared to CP alone for newly diagnosed advanced ovarian cancer. The Committee agreed that the results were likely to be generalisable to the Singapore setting, as the price of bevacizumab used in the evaluation was lower than the local cost of Avastin.

4.3 The Committee acknowledged that they had already established therapeutic equivalence between bevacizumab reference biologic (Avastin) and bevacizumab biosimilar (Mvasi) in a separate technology evaluation, and that a cost-minimisation approach was appropriate to assess the cost effectiveness of Avastin. At the price proposed by the manufacturer, Avastin did not represent a cost-effective treatment option compared to Mvasi.

4.4 Olaparib

Maintenance treatment for newly diagnosed ovarian cancer

The Committee reviewed evaluations from overseas HTA agencies and noted that Australian PBAC only considered olaparib to be a cost-effective option (less than AU$55,000/QALY) for maintenance treatment when a price reduction and confidential risk-sharing arrangement was taken into consideration to provide budgetary certainty. The Committee agreed that the results were likely to be generalisable to the Singapore setting, after taking the manufacturer's proposed price and confidential price volume agreement (PVA) into consideration.

4.5 **Maintenance treatment for platinum-sensitive relapsed ovarian cancer**

The Committee noted that a cost effectiveness analysis was conducted by ACE for maintenance treatment with olaparib in patients with relapsed disease. Results showed that olaparib was associated with a base-case incremental cost-effectiveness ratio (ICER) of more than SG$105,000 per QALY gained compared to routine surveillance. However, following VBP discussions, the Committee concluded that an MAF listing for olaparib was appropriate in view of acceptable cost-effectiveness at the proposed price and PVA agreed with the manufacturer.

4.6 Niraparib

Maintenance treatment for newly diagnosed ovarian cancer

The Committee noted that a cost effectiveness analysis was conducted by ACE for niraparib versus routine surveillance in patients with newly diagnosed ovarian cancer. Results showed that niraparib was associated with a base-case ICER of more than SG$105,000 per QALY gained compared to routine surveillance and did not represent a cost-effective treatment option. Furthermore, the base-case ICER was most sensitive to the selection of the parametric function used to extrapolate the immature OS data, resulting in high and uncertain ICER results. In addition, the Committee noted the Australian PBAC did not recommend the reimbursement of niraparib in this indication and considered the ICER to be uncertain and likely underestimated.

4.7 Maintenance treatment for platinum-sensitive relapsed ovarian cancer

At the proposed prices, the monthly cost of niraparib varied widely with an overlap with that of olaparib when relative dose intensities were taken into account. The Committee considered that the cost comparison was uncertain as the dose intensity observed in the PRIMA trial may not be generalisable to local patients who have lower disease severity. The Committee also noted that the Australian PBAC did not recommend niraparib for reimbursement in the relapsed setting.

Estimated annual technology cost

5.1 Based on local epidemiological rates and estimated drug utilisation in the public healthcare institutions, the annual cost impact in the first year of listing olaparib tablets on the MAF for ovarian cancer was estimated to be between SG$1 million and SG$3 million.

Additional considerations

6.1 The Committee acknowledged that, contingent on subsidy listing, the manufacturer had also agreed to continue the existing patient assistance programme for eligible patients who require olaparib, which would provide further savings to patients in addition to MAF financial assistance.

Recommendations

7.1 Treatment of newly diagnosed ovarian cancer

Based on available evidence, the Committee did not recommend bevacizumab reference biologic (Avastin) for subsidy for treating newly diagnosed ovarian cancer, due to unfavourable cost effectiveness compared to bevacizumab biosimilar (Mvasi) at the price proposed by the manufacturer.

7.2 The Committee noted that Mvasi had been recommended for listing on the SDL for use in line with its registered indications, including ovarian, fallopian tube or primary peritoneal cancer, as part of a separate review, with subsidy implementation effective from 1 April 2022.

7.3 Maintenance treatment of ovarian cancer

The Committee recommended olaparib 100 mg and 150 mg tablets be listed on the MAF in line with their registered indications as maintenance therapy in combination with bevacizumab biosimilar for newly diagnosed HRD-positive ovarian cancer and as maintenance monotherapy for newly diagnosed or relapsed BRCA-mutated disease, in view of the high clinical need and acceptable clinical effectiveness and cost-effectiveness at proposed prices and the PVA agreed with the manufacturer.

7.4 Based on available evidence, the Committee recommended not listing niraparib 100 mg tablet on the MAF for maintenance monotherapy of newly diagnosed or relapsed ovarian cancer, because of uncertain survival benefits and cost-effectiveness compared with both routine surveillance and olaparib at the price proposed by the manufacturer.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indications	Subsidy class (implementation date)	MediShield Life claim limit per month (implementation date)
Treatment of ovarian cancer			
Bevacizumab biosimilar (Mvasi) 100 mg/4 mL and 400 mg/16 mL concentrate for solution for infusion	1. For previously untreated patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who have suboptimally debulked Stage III disease with more than 1cm of residual disease OR Stage III unresectable OR Stage IV disease. 2. In combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel for the treatment of patients with recurrent, platinum-sensitive, epithelial ovarian, fallopian tube, or primary peritoneal cancer. 3. In combination with paclitaxel, topotecan or pegylated liposomal doxorubicin for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer.	SDL (1 Apr 2022)	$600 (1 Sep 2022)
Bevacizumab reference biologic (Avastin) 100 mg/4 mL and 400 mg/16 mL concentrate for solution for infusion		Not recommended for subsidy	$600 (1 Sep 2022)
Maintenance treatment of newly diagnosed ovarian cancer			
Olaparib 100 mg and 150 mg tablets	1. As maintenance monotherapy for patients with advanced BRCA-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Treatment should be continued until disease progression or unacceptable toxicity or for a maximum of 24 months.	MAF (1 Sep 2022)	$1600 (1 Sep 2022)

	2. In combination with bevacizumab biosimilar (subsidised brand) as maintenance treatment of patients with advanced homologous recombination deficiency (HRD) positive high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy in combination with bevacizumab biosimilar. Treatment with olaparib should be continued until disease progression or unacceptable toxicity or for a maximum of 24 months.	MAF (1 Sep 2022)	$1600 (1 Sep 2022)
	3. In combination with bevacizumab (non-subsidised brand) as maintenance treatment of patients with advanced homologous recombination deficiency (HRD) positive high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy in combination with bevacizumab. Treatment with olaparib should be continued until disease progression or unacceptable toxicity or for a maximum of 24 months.	Not recommended for subsidy	$1600 (1 Sep 2022)
Niraparib 100 mg tablet	As maintenance monotherapy for patients with advanced epithelial high-grade ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Treatment should be continued until disease progression or unacceptable toxicity or a maximum of 36 months.	Not recommended for subsidy	$1600 (1 Sep 2022)
Maintenance treatment of relapsed ovarian cancer			
Olaparib 100 mg and 150 mg tablets	As maintenance monotherapy for patients with platinum-sensitive relapsed BRCA-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy. Patients must not have received prior treatment with a PARP inhibitor for ovarian cancer. Treatment should be continued until disease progression or unacceptable toxicity.	MAF (1 Sep 2022)	$1600 (1 Sep 2022)

Niraparib 100 mg tablet	As maintenance monotherapy for patients with platinum-sensitive relapsed BRCA-mutated high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy. Patients must not have received prior treatment with a PARP inhibitor for ovarian cancer. Treatment should be continued until disease progression or unacceptable toxicity.	Not recommended for subsidy	$1600 (1 Sep 2022)

Abbreviations: BRCA, breast cancer gene; HRD, homologous recombination deficiency; MAF, Medication Assistance Fund; PARP, poly adenosine diphosphate-ribose polymerase; SDL, Standard Drug List.

VERSION HISTORY

Guidance on PARP inhibitors and bevacizumab for treating advanced ovarian cancer

This Version History is provided to track any updates or changes to the guidance following the first publication date. It is not part of the guidance.

1. **Publication of guidance**

   Date of Publication 1 Apr 2022

2. **Guidance updated with the MediShield Life claim limits for bevacizumab and niraparib**

   Date of Publication 12 Jul 2022

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government subsidy decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is based on the evidence available to the MOH Drug Advisory Committee as at 16 March, 2 July 2021 and 16 June 2022. It is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at www.ace-hta.gov.sg/about

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