AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

One Wales Medicines Assessment Group Recommendation: Bevacizumab at a dose of 7.5 mg/kg in combination with carboplatin and paclitaxel for the front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer at high risk for progression (OW01)

April 2025

ONE WALES INTERIM DECISION

Bevacizumab 7.5 mg/kg dose in combination with carboplatin and paclitaxel for the front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer at high risk for progression

Date of original advice: June 2019
Date of review: March 2025

The following One Wales Medicines Assessment Group (OWMAG) recommendation has been noted by the All Wales Medicines Strategy Group (AWMSG) and ratified by Welsh Government.

Bevacizumab 7.5 mg/kg dose in combination with carboplatin and paclitaxel can be made available within NHS Wales for the front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer at high risk for progression. High risk is defined as: International Federation of Gynaecology and Obstetrics [FIGO] stage III debulked but residual disease more than 1.0 cm or stage IV disease, or stage III disease at presentation and requiring neoadjuvant chemotherapy due to low likelihood of optimal primary surgical cytoreduction.

Bevacizumab 7.5mg/kg dose is not licensed to treat this indication and is therefore ‘off-label’. Each provider organisation must ensure all internal governance arrangements are completed before these medicines are prescribed in combination.

The risks and benefits of the off-label use of bevacizumab for this indication should be clearly stated and discussed with the patient to allow informed consent.

Providers should consult the relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice has been reviewed annually by OWMAG since its issue in 2019 with no new evidence identified to affect the current recommendation. Therefore, this advice will no longer undergo review by OWMAG unless new evidence becomes available.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Medicines Assessment Group decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Medicines Assessment Group decisions and ensuring that a process is in place for monitoring clinical outcomes.

One Wales advice promotes consistency of access across NHS Wales.

Starting and stopping criteria for bevacizumab at a dose of 7.5 mg/kg in combination with carboplatin and paclitaxel for the front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer at high risk for progression

Prescribers should note that front-line treatment with bevacizumab is available for patients with stage III and IV homologous recombination deficiency (HRD)-positive disease who are eligible to receive olaparib plus bevacizumab maintenance therapy in line with the National Institute for Health and Care Excellence (NICE) guidance TA946 and should refer to this for full eligibility criteria[1].

These criteria are adapted from the NHS England National Cancer Drugs Fund List[2].

Starting criteria:
Patients with newly diagnosed epithelial ovarian, fallopian tube or primary peritoneal cancer with sufficient performance status to undergo treatment with carboplatin, paclitaxel and bevacizumab in one of the following groups:

- patients with FIGO stage III disease debulked but residual disease more than 1 cm
- patients with FIGO stage III disease and unsuitable for debulking surgery
- patients with FIGO stage IV disease
- patients with FIGO stage III disease at presentation and requiring neoadjuvant chemotherapy due to low likelihood of optimal primary surgical cytoreduction.

Patients who satisfy the eligibility criteria will be prescribed bevacizumab following consultation with the patient and/or carer taking into account potential adverse effects, cautions and contraindications. This consultation should be recorded in the patient's notes.

Bevacizumab is prescribed at a dose of 7.5 mg/kg every three weeks up to a maximum of 18 cycles. Bevacizumab should be given with the:

- first or second cycle of chemotherapy following primary debulking surgery
- first or second cycle of chemotherapy for those patients with inoperable stage IV disease or inoperable stage III disease or who are unable to undergo surgery due to increased risk during COVID19
- first or second cycle of chemotherapy following interval debulking surgery performed after three to four cycles of non-bevacizumab-containing neoadjuvant chemotherapy
- first or second cycle of neoadjuvant chemotherapy.

Stopping criteria:

- radiological or clinical evidence of disease progression
- toxicity
- patient request
- after 18 cycles of bevacizumab.

References:

1. National Institute for Health and Care Excellence. Technology Appraisal TA946. January 2024. Available at: https://www.nice.org.uk/guidance/ta946. Accessed April 2025.
2. NHS England. National Cancer Drugs Fund. April 2025. Available at: https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/. Accessed April 2025.

Fifth Review of One Wales Decision – March 2025

Bevacizumab at a dose of 7.5 mg/kg in combination with carboplatin and paclitaxel for the front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer at high risk of progression.

This report was prepared by the All Wales Therapeutics and Toxicology Centre in February 2025. It summarises any new evidence available and patient outcome data collected since the last review in November 2023.

Background: Bevacizumab, at a 7.5 mg/kg dose, is an off-label use of bevacizumab and has not been appraised by NICE in this setting. However, NICE recommend a number of maintenance treatments, either as monotherapy or in combination with bevacizumab, following complete or partial response to first-line platinum-based chemotherapy plus bevacizumab as an induction treatment. As such, bevacizumab, at a dose of 7.5 mg/kg or 15 mg/kg is included in the Cancer Drugs Fund in England for patients with FIGO stage III who have debulked but with residual disease greater than 1.0 cm, stage IV disease, or stage III disease at diagnosis requiring neoadjuvant chemotherapy due to a low chance of optimal primary surgical cytoreduction. This includes use as both induction and maintenance therapy. To account for the absence of NICE advice for the off-label use of 7.5 mg/kg bevacizumab was assessed via the One Wales medicines process.

Current One Wales decision: Supported

Licence status: Off-label use for this licensed medicine.

Guidelines: In September 2024, the British Gynaecological Cancer Society updated its guidelines for ovarian, tubal, and primary peritoneal cancer and recommends administering 7.5 mg/kg of bevacizumab for 12 months alongside carboplatin and paclitaxel for patients with advanced ovarian cancer. The One Wales protocol is in accordance with this revision to the guideline.

Licensed alternative medicines or Health Technology Assessment advice for alternative medicines: Since the last report, TA946: olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer was published in January 2024.

Effectiveness: A repeat literature search conducted by AWTTC identified two retrospective cohort studies which analysed the clinical effectiveness of bevacizumab pertinent to the recommendation.

The retrospective cohort study by Tay et al (2023) reported overall survival in platinum-sensitive ovarian cancer patients undergoing different chemotherapy protocols and to assess patient tolerance, toxicity and efficacy with bevacizumab. The study included 95 patients with a median age of 55 (34-78) years and median follow-up of 39.7 (39.2 - 47.5) months. Most patients in the study were FIGO stage III (18 patients; 75%). However, only around a half of all patients went on to receive bevacizumab as maintenance treatment and when it was used, treatment was continued until progression, which differs to the protocol available through One Wales. Results showed no significant difference in overall survival (OS) between the three chemotherapy protocols (carboplatin-gemcitabine-bevacizumab, carboplatin-liposomal doxorubicin-

bevacizumab, and carboplatin-paclitaxel-bevacizumab), with median OS ranging from 37.9 to 41.3 months (p=0.173). Median progression-free survival (PFS) was also similar across three treatment groups: 10.8 months for carboplatin-gemcitabine-bevacizumab, 10.9 months for carboplatin-liposomal doxorubicin-bevacizumab, and 6.1 months for carboplatin-paclitaxel-bevacizumab, with no statistically significant difference (p=0.79). The OS and PFS for the lower dose of bevacizumab (7.5 mg/kg) was comparable to those reported in the literature for the higher dose (15 mg/kg) and had a lower frequency of toxicity.

The study conducted by Conic et al 2024 examined the impact of 7.5 mg/kg bevacizumab combined with carboplatin and paclitaxel chemotherapy on advanced ovarian cancer. The study included 71 patients with a mean age of 60.48 years (SD = 10.17) with FIGO stage IIIc (41 patients, 57.75%) and IV (30 patients, 42.25%) and compared their PFS and OS to a historical cohort of 30 patients with FIGO stage IIIc (19 patients, 63.33%) and IV (11 patients, 36.67%), with a mean age of 57.4 years (SD= 9.17) who received chemotherapy alone. Results showed that bevacizumab significantly improved median PFS (20 months versus 15 months, p = 0.02) and OS (58 months versus unknown upper limit), especially in patients <65 years and those without metastases or pleural effusion. Cox regression analysis revealed that younger patients had a reduced risk of disease progression.

Safety: No new relevant safety analyses identified in the repeat literature search.

Cost effectiveness: No relevant cost-effectiveness analyses identified in the repeat literature search.

Budget impact: Data received from clinicians indicate that 16 patients in South West Wales received 7.5 mg/kg bevacizumab over the two-year period spanning 2023-2024 and 8 patients in North Wales were treated during 2024. A retrospective review was conducted on 100 consecutive patients from the Chemocare records at Velindre Cancer Centre (VCC), all of whom began bevacizumab treatment (7.5mg/kg) in accordance with the One Wales start/stop criteria. The review covered the period from 1st August 2019 to 13th December 2023, averaging 23 patients per year for South East Wales. Fourteen patients had BRCA mutations or HRD, therefore swapped to 15 mg/kg bevacizumab in line with NICE guidance TA693 which came into effect in April 2021 and was superseded by TA946 in January 2024.

The original evidence status report from 2019 estimated an eligible population of 30 patients per year in Wales, excluding population growth. The average yearly uptake for the whole of Wales is about 39 patients which is around a third higher than the estimated annual uptake although these original figures did not take in to account population growth.

In the original estimates all patients were assumed to receive 18 cycles of bevacizumab. The median number of cycles administered for the 100 patients treated at VCC was 13, which would indicate that overall usage is comparable to the original estimates, however a total of 16 patients received more than 18 cycles. Bevacizumab continues to be available at a discounted price.

Impact on health and social care services: Minimal.

Patient outcome data: Of the 100 patients in whom we have outcome data, their median age was 69 years (range 24-86). At diagnosis, 50 patients were stage IV and 50 were stage III. Histologically, 90% had high-grade serous cancer, with the rest having adenocarcinoma, grade 3 adenocarcinoma, clear cell carcinoma, or no histology. Treatment indications included 12 patients with stage III debulked disease, 50 with stage IV, 37 with stage III requiring neoadjuvant chemotherapy, [confidential data removed], 14 patients had BRCA mutations/HRD and switched to 15 mg/kg bevacizumab per NICE guidance.

The median number of cycles received was 13 (range 1-54), with 36 patients receiving 18 or more cycles: 20 patients (20%) received exactly 18 cycles, while 16 patients (16%) received more than 18 cycles. Among these 16, 11 patients had BRCA mutations or HRD and were given additional cycles in accordance with NICE guidance. [Confidential data removed].

Treatment was stopped in 34 patients (34%) after completing their course, while 59 patients (59%) discontinued due to disease progression. [Confidential data removed]

The median progression-free survival was 10 months (95% CI: 9-12 months), with a median follow-up of 21 months. The median overall survival was 24 months (95% CI: 19-31 months). These figures are lower than the results reported in ICON-7 for the high-risk group but it is noted that patient characteristics differed, ICON-7 recruited younger patients (69 vs 60 years) with less stage IV disease (50% vs 42%).

Evaluation of evidence

No significant new evidence has been published which challenges the current One Wales advice. The outcome data show some patients have had a prolonged response to bevacizumab treatment with a varied number of cycles required. AWTTC recommends continuing access in Wales to low dose bevacizumab for the treatment of advanced ovarian cancer.

Next review date: This advice has been reviewed annually by OWMAG since its issue in 2019 with no new evidence identified to affect the current recommendation. Therefore, this advice will no longer undergo review by OWMAG unless new evidence becomes available.

References: A full reference list is available on request

This document includes evidence published since the last review or full assessment of this medicine for the indication under consideration. It does not replace the original full evidence status report. Any previous reviews and the original full evidence status report are available on the AWTTC website. Care has been taken to ensure the information is accurate and complete at the time of publication. However, the All Wales Therapeutics and Toxicology Centre (AWTTC) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC accept no liability in association with the use of its content.

An Equality and Health Impact Assessment (EHIA) has been completed in relation to the One Wales policy and this found there to be a positive impact. Key actions have been identified and these can be found in the One Wales Policy EHIA document.

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