Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Jonathan G Fox

bevacizumab 25mg/mL concentrate for solution for infusion, (Avastin®)
SMC No. (1063/15)

## Roche Products Limited

07 August 2015

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 Scotland. The advice is summarised as follows:

**ADVICE**: following a full submission considered under the end of life and ultra-orphan medicine process

**bevacizumab (Avastin®)** is accepted for restricted use within NHS Scotland.

**Indication under review:** in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor-targeted agents.

**SMC restriction:** to use in combination with paclitaxel.

The addition of bevacizumab to chemotherapy improved progression free survival in patients with platinum-resistant ovarian cancer in an open-label phase III randomised study.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of bevacizumab. 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**



Published 07 September 2015

## Indication

Bevacizumab in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor-targeted agents.

## Dosing Information

Bevacizumab is administered in combination with one of the following agents - paclitaxel, topotecan (given weekly) or pegylated liposomal doxorubicin. The recommended dose of bevacizumab is 10mg/kg of body weight given once every two weeks as an intravenous infusion. When bevacizumab is administered in combination with topotecan (given on days 1-5, every 3 weeks), the recommended dose of bevacizumab is 15mg/kg of body weight given once every 3 weeks as an intravenous infusion. It is recommended that treatment be continued until disease progression or unacceptable toxicity.

Bevacizumab must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products.

## Product availability date

July 2014. Bevacizumab meets SMC end of life and ultra-orphan criteria.

## Summary of evidence on comparative efficacy

Bevacizumab is a recombinant humanised monoclonal antibody that inhibits angiogenesis by neutralising vascular endothelial growth factor (VEGF) and blocking binding to its receptors. VEGF is involved in vasculogenesis and angiogenesis and is often over-expressed in epithelial ovarian cancer. Bevacizumab is already indicated, in combination with carboplatin and paclitaxel, for the front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics [FIGO] stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer and in combination with carboplatin and gemcitabine, for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.[1] SMC has issued not recommended advice for both of these indications. A recent licence extension allows the use of bevacizumab in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.

The submitting company has requested that SMC considers bevacizumab when positioned for use in patients who are eligible to receive paclitaxel for the treatment of their disease.

Evidence to support the use of bevacizumab in this indication comes from AURELIA, an open-label randomised phase III study in 361 patients with platinum-resistant recurrent ovarian cancer.[2] Women with histologically confirmed epithelial ovarian, fallopian tube or primary peritoneal cancer that had progressed within six months of completing at least four cycles of platinum-based chemotherapy, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of at least 2 and adequate

liver, renal and bone marrow function were enrolled in the study. All patients had received a maximum of two prior anticancer regimens. Investigators selected one of the following single-agent chemotherapies on an individual patient basis: paclitaxel 80mg/m$^2$ intravenously (IV) on day 1, 8, 15 and 22 every four weeks; pegylated liposomal doxorubicin 40mg/m$^2$ IV on day 1 every four weeks; or topotecan 4mg/m$^2$ IV on day 1, 8 and 15 every four weeks or 1.25mg/m$^2$ on day 1 to 5 every three weeks. Patients were then stratified according to selected chemotherapy, prior anti-angiogenic therapy and platinum-free interval, and randomised to receive either chemotherapy alone or in combination with bevacizumab 10mg/kg IV every two weeks (or 15mg/kg IV every three weeks if receiving the three-weekly topotecan schedule). Patients allocated to the chemotherapy alone group could receive bevacizumab single-agent after disease progression.[2]

The primary outcome was investigator assessed progression free survival (PFS) by RECIST (Response Evaluation Criteria In Solid Tumors) version 1.0, defined as the interval between random assignment and first radiologically documented disease progression or death.[2] Median follow up was 13.9 months in the chemotherapy alone group and 13 months in the bevacizumab plus chemotherapy group at the primary analysis data cut-off.[2] The median PFS was 6.7 months in patients allocated to bevacizumab plus chemotherapy compared with 3.4 months in patients allocated to chemotherapy alone, hazard ratio (HR) 0.48 (95% confidence interval [CI]: 0.38 to 0.60, p<0.001).[2]

In patients with measurable disease at baseline (n=286), the overall response rate (measured by RECIST) was higher in the bevacizumab plus chemotherapy group compared with the chemotherapy group, 28% (40/142) versus 12% (18/144), stratified p<0.001.[3] In patients who achieved an objective response (n=58), the median duration of response was 9.4 months and 5.4 months respectively.[3]

At the final overall survival analysis data cut-off, 72% and 75% of patients had died in the bevacizumab plus chemotherapy group and chemotherapy alone group respectively. Median overall survival was 16.6 months versus 13.3 months in the bevacizumab plus chemotherapy and chemotherapy alone groups, HR 0.85 (95% CI: 0.66 to 1.08), p=0.174.[2]

Exploratory analysis for the subgroup of patients who received paclitaxel (n=115) found that the median PFS was 9.2 months in patients allocated to bevacizumab plus paclitaxel compared with 3.9 months in patients allocated to paclitaxel alone, HR 0.47 (95% CI: 0.31 to 0.72).[3] The overall response rate (measured by RECIST, CA-125 criteria or both) in this subgroup was 52% versus 29% in the bevacizumab plus paclitaxel group versus the paclitaxel alone group.[4] At the final overall survival analysis cut-off, the median overall survival was 22.4 months in the bevacizumab plus paclitaxel group compared with 13.2 months in the paclitaxel alone group, HR 0.65 (95% CI: 0.42 to 1.02).[5]

Patient-reported outcomes were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Ovarian Cancer Module 28 (EORTC QLQ-OV28) and Functional Assessment of Cancer Therapy – Ovarian Cancer symptom index (FOSI) at baseline and every two or three cycles (eight or nine weeks) until disease progression. Of the 317 patients who completed the baseline questionnaire, significantly more patients in the bevacizumab plus chemotherapy group reported a ≥15% improvement in abdominal/gastrointestinal symptoms at week 8/9, (22% [34/155] versus 9.3% [15/162]), difference 13% (95% CI: 4.4 to 20.9, p=0.002). Subgroup analyses of patients with sufficient symptoms at baseline (65% of the study population) and patients with ascites at baseline (27% of the study population) favoured bevacizumab. As information was only collected until progressive disease, there was a substantial amount of missing data in the primary analysis; 21% (33/155) of patients in the bevacizumab plus chemotherapy group were classed as non-responders due to missing data compared with 48% (78/162) of patients in the chemotherapy group.[6,5]

## Summary of evidence on comparative safety

The safety population included 360 patients. One patient in the bevacizumab plus chemotherapy group did not receive any treatment (and was therefore excluded from the analysis), and one patient in the chemotherapy group received bevacizumab plus chemotherapy.[2]

Adverse events of at least grade 2 occurring in more than 10% of the bevacizumab plus chemotherapy treated patients were neutropenia (31% versus 25%), anaemia (20% versus 27%), hypertension (19% versus 5.5%), peripheral sensory neuropathy (18% versus 7.2%), mucosal inflammation (13% versus 5.5%), proteinuria (12% versus 0.6%), infection (11% versus 4.4%) and palmar plantar erythrodysaesthesia (11% versus 5%) versus chemotherapy alone.[3]

Adverse events of special interest occurred in 57% of bevacizumab plus chemotherapy treated patients versus 40% of patients treated with chemotherapy alone. These included hypertension ≥grade 2 (20% versus 6.6%), thromboembolic events ≥grade 3 (5% versus 4.4%), gastrointestinal perforation ≥grade 2 (2.2% versus 0) and proteinuria ≥grade 3 (1.7% versus 0) reported in patients receiving bevacizumab plus chemotherapy versus patients receiving chemotherapy alone.[2]

More patients treated with bevacizumab plus chemotherapy discontinued treatment due to adverse events compared with patients treated with chemotherapy alone (44% versus 8.8%) although this may be partly explained by the increased progression free survival in this group. Bevacizumab treatment was discontinued mainly due to neutropenia, gastrointestinal disorders, fatigue, neuropathy, pulmonary embolism, palmar plantar erythrodysaesthesia and hypertension.[3]

A slightly higher proportion of patients in the bevacizumab plus paclitaxel group reported adverse events of at least grade 2 and discontinued treatment due to adverse events compared with the other combination groups.[3]

## Summary of clinical effectiveness issues

Ovarian cancer has a significant detrimental impact on patients' quality of life with symptoms including abdominal bloating, persistent pelvic abdominal pain, fatigue, indigestion, urinary frequency and/or incontinence, unexplained weight loss, vaginal bleeding, nausea and diarrhoea.[7] Patients with platinum-resistant recurrent ovarian cancer, defined as disease that recurs within six months of chemotherapy, have a poor prognosis. Patients usually receive single-agent chemotherapy and have a median overall survival of less than 12 months.[3] Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely the poor response to current treatments. The submitting company has requested that SMC considers bevacizumab when positioned for use in patients who are eligible to receive paclitaxel for the treatment of their disease. Bevacizumab meets SMC end of life and ultra-orphan criteria for this indication.

The open-label design of the AURELIA study could have biased the primary end point investigator assessed PFS; however, assessment by an independent review committee supported the investigator PFS results.[3] The patient-reported outcomes could have been biased by the open-label design and the missing data.[3] Patients assigned to the chemotherapy alone treatment group could cross over to single-agent bevacizumab at disease progression, and 40% of patients in the chemotherapy alone group received bevacizumab post-progression. Patients in the bevacizumab plus chemotherapy group could receive standard of care treatment without bevacizumab on disease progression.[2] In the small subgroup of patients who had received prior anti-angiogenic treatment, the results favoured the

chemotherapy alone group; therefore, the eligible population has been restricted to patients who have not received prior therapy with any anti-angiogenics.[1,3]

Differences in the results between the three chemotherapy cohorts suggest that outcomes are not the same, and paclitaxel-treated patients seem to derive a substantial benefit from the addition of bevacizumab.[3] Paclitaxel is licensed as a three-weekly IV infusion; however, use as a weekly IV infusion (outwith the marketing authorisation) is established clinical practice for treating patients with platinum-resistant disease.[9]

Strict exclusion criteria limited the incidence of gastrointestinal perforation in the pivotal study.[2] It is unknown if patients who have had a bowel resection as part of their debulking surgery are at a higher risk of gastrointestinal perforations as this information was not collected.[3] Only 4.4% of the study population were over 75 years old so evidence is limited for these patients.[1,3]

Clinical experts consulted by SMC considered that bevacizumab is a therapeutic advancement due to the improvement in progression free survival demonstrated in the AURELIA study. They considered that the introduction of bevacizumab had the potential to impact on the patient and on service delivery because of the additional IV infusions required.

## Summary of patient and clinician engagement

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

The key points expressed by the group were:

- Relapsed ovarian cancer is a devastating diagnosis and has a poor prognostic outcome with many patients being in their last year of life. The condition is highly symptomatic with frequent complications such as malignant ascites and bowel obstruction which require frequent and prolonged hospitalisation. These symptoms are difficult to palliate and impact hugely on quality of life.

- There is a paucity of treatment options in platinum-resistant disease. Chemotherapy is given with the predominant aim of improving symptoms and quality of life.

- Bevacizumab, in combination with paclitaxel, offers a significantly improved rate of response compared to chemotherapy alone and this has been linked to improvements in quality of life. Treatment has been shown to double progression free survival in this group of highly symptomatic patients, and is also associated with an overall survival benefit. Such improved symptom control and delay in progression of the disease is greatly valued by patients and their families.

- Bevacizumab is generally well tolerated, allowing patients to return to a more ‘normal’ life. Hospital attendance for IV infusions once every two weeks is far preferred by patients than a similar rate of attendance for palliative management of symptoms such as draining of ascites which is associated with considerable disutility.

- Clinicians noted an equity issue that can impact on NHS Scotland’s ability to participate in clinical research.

- The PACE group felt strongly that this medicine should be made available in NHS Scotland and that this should be in line with the company's positioning where the evidence indicated that clinical benefit was greatest - in combination with weekly paclitaxel.

## Summary of ultra-orphan decision-making framework

Bevacizumab has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines. Relevant factors under each of the criteria are summarised below:

**Nature of the condition**
Patients with platinum-resistant recurrent ovarian cancer have a poor prognosis. Patients receiving single-agent chemotherapy have a median overall survival of less than 12 months. It is a highly symptomatic disease and common complications such as malignant ascites and bowel obstruction require hospitalisation and have a major impact on a patient's quality of life.

At the PACE meeting, attention was drawn to the psychological effect of the anxiety and uncertainty surrounding frequent hospitalisations, impactful symptoms and poor prognosis and the influence this had on the ability to plan family life.

**Impact of the new technology**
Current treatment includes a variety of chemotherapy regimens including paclitaxel, liposomal doxorubicin and topotecan. Response rates to current treatments are low at 10-20%.

Addition of bevacizumab to standard chemotherapy has been shown to offer a significant increase in median PFS of 5.3 months, a considerable increase in overall response rate and a numerical increase in median overall survival of 9.2 months in the sub-group of patients who received paclitaxel. This overall survival benefit is confounded due to substantial cross over (40%). The economic model predicts a mean survival gain of 0.863 years (10.4 months).

At the PACE meeting, it was noted that improvement in response rate, delay in progression and its associated symptoms and reduction in procedures to manage symptoms (e.g. paracentesis to relieve ascites) have been shown to lead to genuine improvements in quality of life. Any treatment which can improve symptoms, reduce the likelihood of hospitalisation and delay the progression of the disease is highly valued by patients and their families and has the potential to allow patients to return to a more normal life.

**Value for money**
The submitting company presented a cost-utility analysis comparing bevacizumab plus paclitaxel with paclitaxel alone for the treatment of platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. The positioning requested by the company is in the sub-group of patients who are eligible for treatment with paclitaxel. SMC clinical experts have confirmed that bevacizumab would be used in addition to paclitaxel.

An area under the curve economic model was used consisting of three health states (PFS, progressed disease (PD) and death) over a 10-year time horizon. Patients begin in the PFS state and after weekly cycles either remain in that state or transition to the PD health state or death. PFS and overall survival were estimated by fitting parametric functions to Kaplan-Meier data from the paclitaxel sub-group of the pivotal AURELIA study described above. In the base case analysis for PFS, the log-normal parametric function was used to extrapolate the Kaplan-Meier data. To extrapolate the overall survival data, again the log-normal parametric function was used by fitting the curve to the tail of the Kaplan-Meier data using the median time half of the patients were still alive in each treatment arm as

the cut-off point. The overall survival results were confounded by 38% of patients in the paclitaxel alone arm crossing over to receive bevacizumab after disease progression. The rank preserving structural failure time (RPSFT) method was used to adjust for crossover.

Utility estimation instruments were collected in the AURELIA study. However, the utility values used in the base case analysis were derived from a separate published source that elicited the utility values from a study comparing trabectedin plus pegylated liposomal doxorubicin versus pegylated liposomal doxorubicin alone in patients with recurrent ovarian cancer. The utility value for the PFS health state was 0.718 and for the PD health state was 0.649.

Costs were included in the model for drug acquisition and administration. Costs associated with the management of adverse events and paracentesis procedures for the management of ascities were also included. Costs associated with routine care of patients in the PFS health state included a monthly oncology visit and a bimonthly CT scan. Costs relating to continuous palliative care were included for the PD health state.

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. Under the PAS a confidential discount was offered for this indication only which takes the form of a rebate on the list price. With the PAS, the company estimated a cost per quality adjusted life year (QALY) of £55,090 based on an incremental cost of £32,574 and an incremental QALY gain of 0.591.

The submitting company provided a range of deterministic and probabilistic sensitivity analyses. The results were most sensitive to assuming a 5 year time horizon and using an alternative parametric function to extrapolate overall survival data from the AURELIA study. The results were also sensitive to modelling the utility values collected from the study data and using these values assuming no treatment effect, and estimating the time to off-treatment (TTOT) by applying different parametric functions.

In addition to the high base case incremental cost-effectiveness ratio (ICER) the following weaknesses were noted;

- In the AURELIA study, quality of life data were collected using the EORTC-QLQ-C30 instrument, which was then mapped to EQ-5D to estimate utility values for the patients in the study. These were not used in the base case, but when they were applied in the sensitivity analysis using separate utility values in each arm of the model for the PFS state, the ICER increased to £58k per QALY. When these utility values from the study were modelled and the same PFS utility value applied in both arms the ICER increased to £63k per QALY. While it is usually preferable to use trial-based quality of life data in the economic model, it should be noted that the mapping algorithm used to derive the utility values from the trial quality of life data had a number of important limitations and therefore the base case approach may be considered more appropriate.
- The overall survival results were confounded by 38% of the paclitaxel alone group crossing over to the bevacizumab plus paclitaxel arm after disease progression. When no crossover adjustment was applied, the ICER increased to £58k per QALY. However, the approach used to adjust for crossover was appropriate.
- The increase in overall survival associated with the bevacizumab plus paclitaxel arm was not statistically significant. The company argued that the difference in survival should not be ignored due to a non-significant result. While the arguments against removing the non-significant differences are noted, it is nevertheless helpful for SMC to see the results of the analysis in order to explore the uncertainty in this parameter. Removing the non-significant differences is one way of doing this, particularly given that the analysis is based on a sub-group and is confounded by crossover, both of which introduce further uncertainty. The company subsequently provided an analysis which assumed no difference in overall survival between the treatment arms beyond the

end of the study period and this resulted in an ICER of £62k with the PAS. A further scenario analysis was explored which assumed no difference in overall survival and applied a 5% decrement to the utility values used in the base case analysis. This increased the ICER with the PAS to £65k.

**Patient and clinician engagement**
A Patient and Clinician Engagement (PACE) meeting was held for this submission. Participants at the PACE meeting indicated a range of potential impacts of the new technology for the patient and families/carers.

**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, symptomatic problems and terminal stage of cancer and hence the potential importance of bevacizumab in delaying progression. It was noted that progression of disease and the need for hospitalisation to manage symptoms can cause a significant burden on family members. By delaying progression and its associated symptoms, bevacizumab can offer patients a longer period of normal family life.

Bevacizumab is given as an IV infusion requiring some additional resources both for administration (chair time and pharmacy dispensing time) and monitoring of patients.

**Costs to NHS and Personal Social Services**
The submitting company has estimated that between 3 and 15 patients would be treated wih bevacizumab per year and this would be associated with a drug budget impact of £76k to £437k per year. The submitting company did not estimate any costs outside of the NHS.

The Committee also considered the benefits of bevacizumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in quality of life was satisfied. In addition, as bevacizumab is an ultra-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 bevacizumab for restricted use in NHS Scotland.

## Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups.

- Submissions were received from Target Ovarian Cancer, Ovacome and Ovarian Cancer Action, which are all registered charities.

- Both Ovarian Cancer Action and Ovacome have received pharmaceutical company funding in the past two years, with Ovacome having received funding from the submitting company. Target Ovarian Cancer has not received any pharmaceutical company funding in the past two years.

- Ovarian cancer is a devastating disease for patients and their families. For many, ovarian cancer has a significant impact on physical and emotional health, as well as posing a practical and financial challenge. Even after a seemingly successful course of treatment there is still fear and anxiety due to the possibility of a recurrence as recurrence rates for ovarian cancer are very high – approx. 70%. The prognosis for these patients is very poor.

- For patients with platinum resistant recurrent ovarian cancer there are very limited options when it comes to treatment and very few treatments that have evidence of improving overall survival or progression free survival.

- Bevacizumab has evidence of improving both overall survival and progression free survival. The possibility of these extra few months and of delaying chemotherapy is very meaningful for patients and their families. In addition, bevacizumab would give clinicians another treatment option, allowing them to tailor treatment to individual patients.

## Additional information: guidelines and protocols

Current National Institute of Health and Care Excellence (NICE) multiple technology appraisal guidance (TA91, May 2005) recommends a choice of paclitaxel, pegylated liposomal doxorubicin and topotecan. This advice is however currently being updated (ID468) and the final appraisal determination issued in December 2014 advises that paclitaxel in combination with platinum or as monotherapy and pegylated liposomal doxorubicin hydrochloride as monotherapy are recommended within their marketing authorisation as options for treating recurrent ovarian cancer. Topotecan is not recommended for use in patients with recurrent platinum-resistant or platinum-refractory ovarian cancer.[9]

The Scottish Intercollegiate Guidelines Network published SIGN 135: Management of epithelial ovarian cancer in November 2013. 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. For patients with platinum-resistant ovarian cancer the evidence is less clear and no specific recommendations are made.[7]

The European Society of Medical Oncology updated its clinical practice guidelines for newly diagnosed and relapsed epithelial ovarian carcinoma in 2013. 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 with platinum resistant disease treatment should be focused on quality of life and control of symptoms. No benefit has been shown with combination therapy so single agent therapy should be considered in these patients. Paclitaxel, topotecan, pegylated liposomal doxorubicin and gemcitabine have demonstrated modest activity in phase III studies and choice of therapy should be based on individual patient factors. There is information provided in the guideline regarding the primary outcome of the AURELIA study however the guideline predates the availability of the overall survival and quality of life analyses from this study.[10]

## Additional information: comparators

Current treatment options for patients with platinum-resistant ovarian cancer are paclitaxel, topotecan or pegylated liposomal doxorubicin.

## Cost of relevant comparators

| Drug | Dose Regimen | Cost per course (£) |
|---|---|---|
| **Bevacizumab Plus Paclitaxel** | **10mg/kg IV on day 1 and 15 of a 28-day treatment cycle**<br><br>**80mg/m$^2$ IV on days 1, 8, 15 and 22 of a 28-day treatment cycle** | **27,041** |
| Topotecan | 4mg/m$^2$ IV on day 1, 8 and 15 of a 28-day treatment cycle | 9,416 |
| Pegylated liposomal doxorubicin | 40mg/m$^2$ IV on day 1 of a 28-day treatment cycle | 8,550 |
| Paclitaxel | 80mg/m$^2$ IV on days 1, 8, 15 and 22 of a 28-day treatment cycle | 7,212 |

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS online on 31/03/2015. Costs based on a bodyweight of 70kg and a body surface area of 1.8m$^2$. Costs based on six 28-day treatment cycles, the median duration of treatment in the bevacizumab plus chemotherapy group in the AURELIA study. For the other medicines licensed dosing schedules vary, six 28-day treatment cycles using the doses from the AURELIA study are for comparison only.

## Additional information: budget impact

The submitting company estimated there to be 29 patients eligible for treatment with bevacizumab in years 1 to 5 with an estimated uptake rate of 10% (3 patients) in year 1 and 50% (15 patients) in year 5. From SMC clinical expert responses, the number of eligible patients estimated is potentially underestimated.

Without the PAS, the gross medicines budget impact was estimated to be £76k in year 1 and £437k in year 5. As no other medicines were assumed to be displaced, the net medicines budget impact was estimated to be the same as the gross medicines budget impact. As the number of patients eligible for treatment may be underestimated, the gross and net medicines budget estimates may also therefore be underestimated.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.


1. Bevacizumab 25mg/mL concentrate for solution for infusion (Avastin®) Summary of product characteristics. Roche Products Limited. Electronic Medicines Compendium www.medicines.org.uk Last Updated 27/11/2014.

2. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol 2014;32(13):1302-8.

3. The European Medicines Agency (EMA) European Public Assessment Report. Bevacizumab (Avastin®). 26/06/2014, EMEA/H/C/000582/II/63. www.ema.europa.eu

4. Poveda A, Selle.F, Hilpert F, et al. Weekly paclitaxel, pegylated liposomal doxorubicin (PLD), or topotecan + bevacizumab in platinum-resistant recurrent ovarian cancer. Analysis by chemotherapy cohort in the GCIG AURELIA randomized phase III trial. ESMO Congress. Abstract LBA26. 2012

5. Witteveen P, Lortholary A, Fehm T et al. Final overall survival results from AURELIA, an open-label randomised phase III trial of chemotherapy with or without bevacizumab for platinum-resistant recurrent ovarian cancer. Presented at 2013 ESMO Congress.

6. Stockler MR, Hilpert F, Friedlander M, et al. Patient-reported outcome results from the open-label phase III AURELIA trial evaluating bevacizumab-containing therapy for platinum-resistant ovarian cancer. J Clin Oncol 2014;32(13):1309-16.

7. Scottish Intercollegiate Guidelines Network. Guidelines 135: Management of epithelial ovarian cancer: a national clinical guideline. 2013. www.sign.ac.uk

8. National Institute of Health and Care Excellence. TA91. Paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent treatment of advanced ovarian cancer: Review of Technology Appraisal Guidance 28, 45 and 55. May 2005 www.nice.ac.uk

9. National Institute of Health and Care Excellence. Final Appraisal Determination. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (including reviews of TA 91 and 222). ID468. 2014. www.nice.ac.uk

10. Ledermann JA, Raja FA, Fotopoulou C, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi24-vi32


This assessment is based on data submitted by the applicant company up to and including 15 May 2015.

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.*