Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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2nd Re-Submission

bevacizumab, 25mg/mL, concentrate for solution for infusion (Avastin®)
SMC No. (806/12)

Roche Products Limited

9 October 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 second resubmission assessed under the end of life and orphan equivalent process

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

Indication under review: In combination with carboplatin and paclitaxel, for the front-line treatment of advanced (International Federation of Gynaecology and Obstetrics (FIGO) stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.

SMC restriction: In patients with FIGO stage IV disease

Addition of bevacizumab to standard chemotherapy with carboplatin and paclitaxel increased progression-free survival.

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

Chairman,
Scottish Medicines Consortium

Indication

In combination with carboplatin and paclitaxel, for the front-line treatment of advanced (International Federation of Gynaecology and Obstetrics (FIGO) stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Dosing Information

15mg/kg intravenous infusion once every three weeks, in addition to carboplatin and paclitaxel for up to six cycles of treatment, followed by continued use as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier.

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

Product availability date

December 2011

Bevacizumab meets SMC orphan equivalent and end of life criteria.

Summary of evidence on comparative efficacy

Bevacizumab is a recombinant humanised monoclonal antibody that inhibits angiogenesis by neutralising vascular endothelial growth factor-A (VEGF) and blocking binding to its receptors. VEGF is involved in angiogenesis and is often over-expressed in epithelial ovarian cancer. Bevacizumab is the first anti-angiogenic medicine licensed for first-line treatment of advanced epithelial ovarian, fallopian-tube or primary peritoneal cancer and it is indicated for women with International Federation of Gynaecology and Obstetrics (FIGO) stage III or IV disease.[1] This is the second resubmission to SMC for the indication under review. The submitting company has requested that SMC considers bevacizumab when positioned for use in patients with FIGO stage IV disease.

A double-blind phase III study (GOG-0218) recruited 1,873 women who had undergone debulking surgery for newly diagnosed FIGO stage III (incompletely resectable) or stage IV (growth involving one or both ovaries with distant metastases) epithelial ovarian, primary peritoneal or fallopian-tube cancer and had a Gynaecologic Oncology Group (GOG) performance status score of 0 to 2.[2,3] Patients were randomised, with stratification for GOG performance status (0 versus 1 or 2) and disease stage (FIGO stage III with maximum lesion diameter ≤1cm, stage III with maximum lesion diameter >1cm, stage IV) to bevacizumab 15mg/kg intravenous (IV) infusion in cycles 2 to 22 (bevacizumab-throughout) or in cycles 2 to 6 followed by placebo to cycle 22 (bevacizumab-initiation) or to placebo in cycles 2 to 22. All patients received IV carboplatin (dosed to area under the concentration/time curve [AUC]) and IV paclitaxel (175mg/m^2) in cycles 1 to 6. The primary outcome was investigator-assessed progression-free survival (PFS), defined as time from enrolment until cancer progression shown by radiography according to Response Evaluation Criteria in Solid Tumours (RECIST), an

increase in CA125 level according to Gynaecologic Cancer InterGroup criteria, global deterioration of health or death from any cause (CA125 was permitted as the sole basis of progression only if chemotherapy had been completed). This was compared between the groups via a log-rank test.[2,3] Only the results of the bevacizumab licensed dose regimen (bevacizumab-throughout) are reported in this document.

At data cut-off on 29 September 2009 (PFS primary analysis), PFS events had occurred in 51% (317/623) versus 60% (375/625) of women in the bevacizumab versus placebo groups. In the overall population; median PFS was significantly longer in the bevacizumab group compared with the placebo group, 14.1 versus 10.4 months, respectively; stratified hazard ratio (HR) versus placebo, 0.71 (95% confidence interval [CI]: 0.61 to 0.83), p<0.0001. Similarly, in an exploratory updated analysis up to unblinding date of 25 February 2010 when 67% of women had experienced an event, median PFS in the respective groups was 14.7 versus 10.6 months, HR (95% CI) 0.70 (0.61 to 0.81), p<0.0001. Sensitivity and subgroup analyses by disease stage and debulking status demonstrated the robustness of the PFS analyses. Maximum separation of the PFS survival curves for the bevacizumab versus placebo groups occurred at 15 months with convergence approximately nine months later.[2,3] In protocol-specified analysis on the stage IV subgroup (n=483) of investigator-assessed PFS (without censoring for CA125 or non-protocol cancer therapy), at the 25 February 2010 cut-off, median PFS was significantly longer in the bevacizumab group (12.8 months) compared with placebo (9.5 months); stratified HR (95% CI) 0.64 (0.49 to 0.82).[3]

At disease progression, treatment allocation was unblinded and women in the placebo group could subsequently receive treatment with bevacizumab. There was no significant difference between the groups in overall survival. In the initial analysis, when 76% of women were still alive, with a median follow-up of 17.4 months, Kaplan-Meier estimate of median overall survival was 39.7 and 39.3 months in the bevacizumab and placebo groups respectively. In the final analysis (cut-off 26 August 2011) when 47% of women had died, Kaplan-Meier estimate of median overall survival was 43.8 and 40.6 months in the respective groups. In the final analysis of overall survival, in the prespecified stage IV subgroup, 49% (81/165) of patients in the bevacizumab group had died compared with 61% (93/153) of patients in the placebo group; unstratified HR (95% CI) for death 0.72 (0.53 to 0.97). This equates to median overall survival of 40.6 months and 32.8 months, respectively.[4]

There was no significant difference between treatment groups in objective response rate (complete or partial response on RECIST): 66% (266/403) for bevacizumab and 63% (251/396) for placebo in the overall study population.[2,3]

A supportive open-label phase III study (ICON7) recruited 1,528 women with histologically confirmed epithelial ovarian, primary peritoneal or fallopian-tube cancer that was high-risk early stage (FIGO stage I or IIA and clear cell or grade 3 tumours) or advanced (FIGO stage IIB to IV) and had an Eastern Cooperative Oncology Group performance status of 0 to 2 with adequate coagulation values, and renal, hepatic and bone marrow function. Enrolment of high-risk early disease was restricted to 10% of the study population. All patients received IV carboplatin (AUC 6) plus IV paclitaxel 175mg/m^2 every three weeks for six cycles and were randomised equally to addition or not of bevacizumab 7.5mg/kg IV infusion every three weeks for five or six cycles (if chemotherapy was started within four weeks of surgery, bevacizumab was omitted from cycle 1). Bevacizumab was then continued for up to 12 additional cycles or until disease progression. Randomisation was stratified by FIGO stage and residual disease (stage I to III with ≤1cm residual disease versus stage I to III with >1cm residual disease versus stage III [inoperable] or IV) and interval between surgery and initiation of chemotherapy (≤4 or >4 weeks). The primary

outcome was PFS, defined as time from randomisation to death or disease progression according to RECIST on the basis of radiologic, clinical or symptomatic indicators. This was compared using an unstratified log-rank test in the intention-to-treat (ITT) population, which included all randomised patients.[3,5]

At the study cut-off date, 28 February 2010 (PFS primary analysis), PFS events had occurred in 48% (367/764) and 51% (392/764) women in the respective bevacizumab and control groups in the ITT population. PFS was significantly longer in the bevacizumab group with an unstratified HR (95% CI) of 0.79 (0.68 to 0.91), p=0.0010. Median PFS was 18.3 and 16.0 months in the respective groups. In an updated analysis (cut-off date 30 November 2010), when 62% (470/764) and 61% (464/764) of women in the bevacizumab and control groups respectively had experienced a PFS event, PFS was significantly longer in the bevacizumab group with a HR (95% CI) of 0.86 (0.75 to 0.98), p=0.0185. Median PFS was 19.3 and 16.9 months in the respective groups. Maximal separation of the PFS survival curves occurred around 12 months, with convergence by 24 months.[1,3,5] In protocol-specified analysis of the stage IV subgroup (n=201), at the 10 November 2010 cut-off, there was no significant difference in median PFS: 13.5 months in the bevacizumab group and 10.1 months in the control group HR (95% CI) 0.74 (0.55 to 1.01).[3]

Women were not permitted to receive bevacizumab after disease progression. At the time of the primary analysis of PFS (28 February 2010), there had been 111 and 130 deaths in the bevacizumab and control groups respectively. There was no significant difference between the groups in overall survival with a HR (95% CI) of 0.81 (0.63 to 1.04), p=0.098.[3,5] In the final overall survival analysis (at cut-off 31 March 2013) when 47% of women had died, the HR was 0.99 (95% CI: 0.85 to 1.15), p=0.89, and median overall survival was 57.4 and 58.0 months in the bevacizumab and control groups respectively.[1,6] In the final overall survival analysis, there was no significant difference between treatment groups in the stage IV subgroup: 39.6 months in the bevacizumab group and 29.4 months in the control group; HR (95% CI) 0.76 (0.53 to 1.10).[6]

The European Medicines Agency noted that in both studies, changes in quality of life were small and differences between the groups were not clinically meaningful.[3] Another evaluation of the quality of life results in the ICON7 study using a lower threshold of clinical significance concluded that continuation of bevacizumab treatment after chemotherapy seems to be associated with a small but clinically significant decrement in quality of life compared with standard treatment for women with ovarian cancer. Overall, the mean global quality of life score improved during chemotherapy by 7·2 points (standard deviation [SD] 24·4) when analysed for all women with data at baseline and week 18. The mean global quality of life score at 54 weeks was higher in the standard chemotherapy group than in the bevacizumab group (76·1 [SD 18·2] versus 69·7 [19·1] points; difference 6·4 points, 95% CI 3·7–9·0, p<0·0001).[7]

Summary of evidence on comparative safety

Safety data from both studies were consistent with the present knowledge of the safety profile of bevacizumab, carboplatin and paclitaxel and no new safety concerns were identified.[3] Almost all women in the bevacizumab and control groups reported an adverse event and these were grade 3 to 5 severity (without laboratory data) in 55% and 46% of women in the respective bevacizumab and placebo groups of GOG-0218 study and in 54% and 65% of women in the respective bevacizumab and control groups of the ICON7 study.[3]

In GOG-0218, adverse events leading to discontinuation of study treatment occurred more often in the bevacizumab group, 16% (100/608), compared with the placebo group, 9.7% (58/601). This was also observed in the bevacizumab versus control groups of the ICON7 study: 17% (131/763) and 14% (107/746), respectively.[2,5]

The most common adverse events reported during the studies concerned the gastrointestinal system (abdominal pain, constipation, diarrhoea, nausea and vomiting) and the nervous system (headache and peripheral sensory neuropathy), with fatigue, alopecia and myalgia commonly reported.[3] Common adverse events associated with bevacizumab include epistaxis, stomatitis, nausea, diarrhoea, hypertension, dyspnoea, headache, arthralgia and fatigue. Less frequent, but more serious, and sometimes fatal, adverse events include gastrointestinal perforation, fistulae, haemorrhage, encephalopathy, arterial thromboembolism, congestive heart failure and infusion reactions.[1]

Summary of clinical effectiveness issues

Bevacizumab is the first anti-angiogenic medicine to be licensed in combination with the current standard of care chemotherapy for first-line treatment of advanced (FIGO stage IIIB, IIIC or IV) ovarian cancer.[1] Ovarian cancer tends to be asymptomatic in early stages or associated with vague symptoms so the majority of women present with advanced stage disease that is difficult to cure. Prolongation of survival is possible and delay in first recurrence is clinically meaningful. The standard of care for the past decade has been surgery plus platinum-based chemotherapy (eg carboplatin plus paclitaxel) and many women will respond to this. However, recurrence is common and most women will ultimately die of their disease.[3] Bevacizumab meets SMC orphan equivalent and end of life criteria.

The submitting company has requested that SMC considers bevacizumab when positioned for use in patients with FIGO stage IV disease. This is defined as growth involving one or both ovaries with distant metastases.[8] Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely improved treatment for patients with stage IV disease who have a very poor prognosis.

Two studies have evaluated the addition of bevacizumab to standard treatment with paclitaxel and carboplatin. However, SMC has a remit to assess the clinical and cost-effectiveness of new medicines when used according to their marketing authorisation so advice cannot be issued based on the 7.5mg/kg dose used in the ICON7 study as this is not covered by the marketing authorisation. The primary outcome in both was PFS, which was significantly increased by a median of about four months in the GOG-0218 study and about two months in the ICON7 study.[2,3,5] In both studies, maximum separation of PFS curves occurred at around 12 to 15 months with convergence by 24 months.[2,5] In pre-specified subgroup analysis, median PFS in stage IV disease patients (corresponding to the proposed positioning) in both studies was more than three months longer in those who received bevacizumab throughout the study than in those who received placebo. [3,4]

There were no significant differences over control arm in overall survival, in the ITT populations of either the GOG-0218 study, which allowed crossover to active treatment after disease progression, or in the final analysis of the ICON7 study, which was not confounded by bevacizumab use after disease progression.[2,3,5,6] The final analysis of overall survival in the

stage IV disease subgroup of GOG-0218 demonstrated a median overall survival of 40.6 months in the bevacizumab group compared with 32.8 months in the placebo group.[4] However, statistical advice sought by SMC noted that statistical significance cannot be claimed as this was one of many subgroup analyses conducted and it was not the primary hypothesis. It does, however, suggest a survival benefit in this group.

When interpreting overall survival data for study GOG-0218, it should be noted that results are confounded by post-progression crossover to bevacizumab. These included bevacizumab for 15% and 28% of women in the bevacizumab and placebo groups at the final analysis for overall survival.[4] In the GOG-0218 study, more women discontinued study treatment because of adverse events in the bevacizumab group compared with the control group: 17% versus 12%. The 5% difference may be an overestimate, as more women in the control group discontinued study treatment due to disease progression, after which adverse event reporting ended.[3]

The evidence relevant to the proposed positioning, stage IV disease, is from subgroup analysis of the pivotal study; approximately 26% and 13% of the GOG-0218 and ICON7 study populations, respectively.[2,5]

Clinical experts consulted by SMC considered that bevacizumab is a therapeutic advancement due to improvements in PFS. The introduction of bevacizumab may impact on the patient and on service delivery as it is administered in addition to standard chemotherapy (carboplatin and paclitaxel for six cycles) then every three weeks to a maximum of 15 months.[1] The continuation of bevacizumab after chemotherapy has been completed would be associated with additional resource requirements for administration and monitoring of toxicity.

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 end of life/orphan equivalent medicine, in the context of treatments currently available in NHS Scotland, specifically in the front-line treatment of advanced ovarian cancer in patients who have stage 4 disease

The key points expressed by the group were:

- Advanced ovarian cancer has a very profound impact on physical and emotional health and is devastating for women and their families. It is heavily symptomatic so quality of life is generally very poor. Malignant ascites and bowel obstruction are particularly distressing complications that frequently lead to prolonged hospitalisation.

- Treatment often has a significant physical burden on the individual. Restarting chemotherapy for relapsed disease is associated with further health impairment so a longer interval off treatment can help the patient recuperate, making subsequent chemotherapy more feasible.

- Patients with stage 4 disease are suitable for treatment with bevacizumab since they have the worst prognosis and there was a strong trend in favour of both improved PFS and OS in this group. Statistical significance would not be expected given the relatively small number of patients included in the studies with stage 4 disease

- The extended survival and good quality of life achieved with bevacizumab was highly valued by patients and their families.

- PACE participants highlighted the evidence supporting the (off-label) 7.5mg/kg dose used in the ICON 7 study. They recognised that SMC can consider only the licensed dose but wished to stress that the off-label dose is being used in practice. It was believed that this would be more cost-effective with reduced toxicity.

- PACE participants expressed very strong support for this medicine, given the lack of effective treatment options for this devastating condition. They noted that there is an equity issue that can be distressing for patients and can impact on NHS Scotland's ability to participate in clinical research.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of bevacizumab in combination with standard chemotherapy (carboplatin and paclitaxel) compared to standard chemotherapy alone for the first-line treatment of patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer. The positioning proposed by the company was in the subgroup of patients with FIGO stage IV disease. An area-under-the-curve economic model was used consisting of 3 health states of PFS, progressive disease (PD) and death, and the model had a time horizon of 25 years.

The clinical data used in the model were for the subgroup of stage IV patients from the GOG-0218 study of bevacizumab plus carboplatin and paclitaxel compared to carboplatin and paclitaxel alone, which used the licensed dose for bevacizumab of 15mg/kg. PFS and overall survival data were extrapolated by fitting a log-logistic and Weibull function respectively to the end of the tail of the observed Kaplan-Meier data. For the measurement of PFS, patients for whom progression was measured by rising serum CA125 levels alone without radiographic assessment were censored (representing 22% of events) as the company argued this more accurately reflects routine clinical practice of assessing progression by RECIST in Scotland. Overall survival estimates were confounded by cross-over of 23% of patients with stage IV disease from the comparator arm to bevacizumab on disease progression; therefore, these data were adjusted using the rank preserving structural failure time (RPSFT) approach resulting in a HR for overall survival of 0.63, (95%CI: 0.42, 0.95) compared to 0.72 (95%CI: 0.53, 0.97) without adjustment.

As utility estimates were not available from data in the GOG-0128 study, EQ 5D derived utilities for stage IV patients were obtained from the ICON7 open label phase III study of bevacizumab plus carboplatin/paclitaxel versus carboplatin/paclitaxel. From this source, utility estimates of 0.643 for the first 3 weeks, 0.715 for weeks 3-5 rising to 0.826 for week 54 and beyond were applied to the PFS state. As ICON7 lacked EQ 5D data beyond disease progression, for the PD state a utility value of 0.718 was applied based on a previous health technology assessment in second line/refractory ovarian cancer. In the base case, no disutility was applied for adverse events, although in scenario analysis utility decrements of 1% and 2% for the bevacizumab arm in the PFS state were applied.

Costs covered drug acquisition and administration costs for bevacizumab, carboplatin and paclitaxel, pharmacy preparation time costs, grade 3 and 4 adverse event management costs, and costs of routine care received in PFS and PD health states, and for palliative care. No costs were included for post progression treatment, although differences between treatment arms are not expected to be significant. Drug doses for IV infusion were based on patient body weight and body surface area (BSA), which were derived from the GOG-0218 study for stage IV patients and estimated to be an average of 70.6kg and 1.75m^2 respectively. Treatment durations were estimated directly from the GOG-0218 stage IV subgroup.

The base case result was an incremental cost-effectiveness ratio (ICER) of £50,538 per quality-adjusted life-year (QALY) gained for bevacizumab plus standard chemotherapy versus standard chemotherapy alone. This is based on a discounted incremental cost of £33,658 and incremental QALYs of 0.71 (discounted incremental life years of 0.85 or 10.2 months). The key cost driver was the higher drug acquisition and administration costs for bevacizumab, with some additional costs for adverse events and PFS health state costs. The life years and QALY gain for bevacizumab are primarily associated with additional PFS time (0.572 life years), but also with additional time in PD (0.279 life years).

A range of deterministic scenarios were performed using alternative parametric functions, fitting of parametric functions to the whole observed data, utility and cost scenarios, shorter time horizon of 10 years, varying drug doses, PD resource use estimates and varying the discount rate. The ICERs were not highly sensitive to the parameters tested with an upper ICER of £56.1k/QALY associated with fitting the Gompertz function to the whole observed overall survival data, and the lowest ICER estimated at £36k/QALY associated with use of a log-normal function fitted to the tail of the observed overall survival data. However, this function is associated with a long tail and had relatively poor statistical fit so is likely to have overestimated the survival benefit for bevacizumab. The base case ICER assumes the proportional hazards assumption holds for RPSFT-adjusted overall survival, which is uncertain. A sensitivity analysis was provided which assumed non-proportionality and resulted in an ICER of £43.6k/QALY. Applying plausible assumptions of a 2% decrement to the bevacizumab arm PFS utility and assuming a lower PD utility of 0.646 resulted in an ICER of £54.5k/QALY.

There were a number of uncertainties with the economic analysis:

- The evidence for the stage IV patient population was from a sub-group of the GOG-0218 study, with some limitations in the strength of this data for estimating overall survival outcomes.

- Measurement of PFS based on censoring of patients with CA125 defined progression alone is uncertain. Inclusion of these patients had a modest impact on the ICER, increasing it to £52.5k/QALY.

- The uncertainty around overall survival estimates may not have been fully explored in the sensitivity analysis. The company was requested to perform sensitivity analysis for the ICER range based on applying 95% confidence intervals for RPSFT adjusted overall survival (0.42 – 0.95). However, the company stated this was not possible as the model was not set up to enable such analysis.

- A probabilistic sensitivity analysis (PSA) was performed but demonstrated only limited uncertainty in the QALY estimates such that there appeared to be 0% probability of

bevacizumab being considered cost-effective at a ~£45k/QALY threshold but 100% probability at ~£55k/QALY threshold, which lacked plausibility. An additional analysis was requested whereby the base case parametric functions were fitted to the whole observed PFS and overall survival data, producing a potentially more plausible assessment of joint parameter uncertainty with a probabilistic ICER similar to the base case (at £48.5k/QALY) but 4% probability of bevacizumab cost-effectiveness at £30k/QALY and 90% probability at £100k/QALY. This provides some further information on the impact of uncertainty in the overall survival estimates in the absence of direct deterministic sensitivity analysis for the overall survival parameter.

The Committee 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 the absence of other treatments of proven benefit was satisfied. In addition, as bevacizumab is an orphan-equivalent 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 was able to accept bevacizumab for restricted use in NHS Scotland.

Summary of patient and public involvement

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

- A submission was received from Target Ovarian Cancer, which is a registered charity.
- Target Ovarian Cancer has not received any pharmaceutical company funding in the past two years.
- An ovarian cancer diagnosis is devastating 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. 70% of women will subsequently be diagnosed with recurrent ovarian cancer. Family and friends face a great deal of responsibility in supporting women with ovarian cancer. Women identify them as the main providers of practical support.
- Current front-line treatment for ovarian cancer available in NHS Scotland is typically a combination of carboplatin and paclitaxel. Introduction of bevacizumab in combination with paclitaxel and carboplatin would be the first time patients in Scotland had the opportunity to potentially improve progression free survival (PFS) in this setting. Most feel that side-effects of treatment are a small price to pay in order to achieve this.
- When making choices about treatment, women are primarily driven by a need to survive or improve progression free survival (PFS). Bevacizumab may improve PFS. Improvements in PFS are significant in allowing an extended time interval during which women can work on their physical and emotional recovery prior to their next phase of treatment starting.

Additional information: guidelines and protocols

In November 2013 the Scottish Intercollegiate Guidelines Network (SIGN) issued publication number 135: management of epithelial ovarian cancer. This recommends for advanced disease that first-line chemotherapy treatment should include a platinum agent either in combination or as a single agent, unless specifically contraindicated. Carboplatin is the platinum drug of choice in both single and combination therapy. Paclitaxel is recommended in combination therapy with platinum in the first-line post-surgery treatment of epithelial ovarian cancer where the potential benefits justify the toxicity of the therapy. In those unable to tolerate paclitaxel, pegylated liposomal doxorubicin or gemcitabine in combination with carboplatin can be used as an alternative. Patients who are unfit for combination therapy should be offered single agent carboplatin. A third cytotoxic agent should not be added to carboplatin and paclitaxel. Carboplatin AUC 6 (day 1 q21) and paclitaxel 80 mg/m^2 (day 1, 8, 15 q21) may be considered for the treatment of first-line ovarian cancer. The increased toxicity and frequency of visits need to be discussed with the patient.[9]

The European Society of Medical Oncology published "Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up" in October 2013. It notes that the risks of recurrence for disease spread beyond the ovary are significant, and chemotherapy is recommended for all patients with FIGO stage II–IV disease post surgery. Standard chemotherapy consists of a combination of paclitaxel 175 mg/m^2 and carboplatin AUC 6-5, both administered intravenously every three weeks. The addition of bevacizumab is recommended for patients with advanced ovarian cancer with poor prognostic features such as stage IV or suboptimal debulking as defined in the ICON7 trial. Bevacizumab should be given with paclitaxel or carboplatin with a treatment duration of one year.[8]

The National Institute for Health and Care Excellence (NICE) clinical guideline 122 Ovarian cancer: the recognition and initial management of ovarian cancer was published in April 2011.[10] It refers to the NICE Technology Appraisal Guidance no.55 for recommendations on first-line chemotherapy regimens for ovarian cancer.

The NICE Technology Appraisal Guidance No. 55: Guidance on the use of paclitaxel in the treatment of ovarian cancer was published in January 2003. It recommends that paclitaxel in combination with a platinum-based compound or platinum-based therapy alone (cisplatin or carboplatin) are offered as alternatives for first-line chemotherapy (usually following surgery) in the treatment of ovarian cancer. The choice of treatment for first-line chemotherapy for ovarian cancer should be made after discussion between the responsible clinician and the patient about the risks and benefits of the options available. In choosing between treatment with a platinum-based compound alone or paclitaxel in combination with a platinum-based compound, this discussion should cover the side-effect profiles of the alternative therapies, the stage of the woman's disease, the extent of surgical treatment of the tumour, and the disease-related performance status.[11]

In October 2013 NICE issued an 'Evidence summaries: unlicensed or off-label medicines (ESUOM21): Ovarian cancer (advanced): bevacizumab 7.5 mg/kg in combination with paclitaxel and carboplatin for first-line treatment.[12] This noted that one large (n=1528), open-label, randomised controlled trial (RCT; ICON7) that assessed the efficacy and safety of bevacizumab 7.5 mg/kg for treating ovarian cancer was identified; quality of life outcomes from this study

were also reported separately [7]. ICON7 found that interim analysis of overall survival data showed no benefit for adding bevacizumab to standard chemotherapy compared with standard chemotherapy alone, except in a subgroup deemed at high risk for progression. In this subgroup median results for progression-free survival after a median follow-up of 19 months were 10.5 months with standard chemotherapy and 15.9 months with standard chemotherapy plus bevacizumab. Adding bevacizumab to standard chemotherapy resulted in a small but clinically relevant reduction in quality of life.[12]

Additional information: comparators

There are no comparator treatments for this indication.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
bevacizumab	**15mg/kg every 3 weeks for up to 20 cycles**	**51,536**

Cost from MIMS online on 27.07.15. Doses based on 70kg body weight.

Additional information: budget impact

The submitting company estimated the population eligible for treatment with stage IV disease to be 134 patients. Based on an estimated uptake of 10% in year 1 and 50% in year 5, the impact on the medicines budget was estimated at £368k in year 1, rising to £1.95 million in year 5. As bevacizumab is added to current treatment of carboplatin and paclitaxel, the net medicines budget impact is equivalent to the gross impact reported above.

These estimates are based on the licensed dose of bevacizumab and treatment duration from the GOG-0218 study, and do not take account of concurrent carboplatin and paclitaxel.

References

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

1. Bevacizumab concentrate for solution for infusion (Avastin®) Summary of product characteristics Roche Products Limited Electronic Medicines Compendium Last updated 07/04/15
2. Burger RA, Brady MF, Bookman MA et al. Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer. N Engl J Med 2011; 365(26): 2473-83
3. The European Medicines Agency (EMA) European Public Assessment Report .Bevacizumab(Avastin®) 17/11/11, EMEA/H/C/000582/II/0041www.ema.europa.eu
4. *Commercial in Confidence**
5. Perren TJ, Swart AM, Pfisterer J et al. A Phase 3 Trial of Bevacizumab in Ovarian Cancer. N Engl J Med 2011; 365(26):2484
6. Oza A, Perren T, Swart A, et al. ICON7: Final overall survival results in the GCIG phase III randomised trial of bevacizumab in women with newly diagnosed ovarian cancer. 2013
7. Stark D, Nankivel M, Pujade-Lauraine E et al. Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: quality-of-life outcomes from the International Collaboration on Ovarian Neoplasms (ICON7) phase 3 randomised trial Lancet Oncol 2013; 14: 236–43 .
8. Ledermann JA, Raja FA, C. Fotopoulou C et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, on behalf of the ESMO Guidelines Working Group* Annals of Oncology 2013 24 (Supplement 6): vi24–vi32,
9. SIGN. Publication number 135. Management of epithelial ovarian cancer, November 2013
10. NICE clinical guideline 122 Ovarian cancer: the recognition and initial management of ovarian cancer, April 2011.
11. NICE Technology Appraisal Guidance No. 55: Guidance on the use of paclitaxel in the treatment of ovarian cancer, January 2003.
12. NICE 'Evidence summaries: unlicensed or off-label medicines' (ESUOM21): Ovarian cancer (advanced): bevacizumab 7.5 mg/kg in combination with paclitaxel and carboplatin for first-line treatment, October 2013.

This assessment is based on data submitted by the applicant company up to and including 3 August 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.

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.