Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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bevacizumab 25mg/mL concentrate for solution for infusion (Avastin®)

SMC No. (1135/16)

Roche Products Ltd

08 April 2016

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 NHS 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 and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix.

Restriction: for use in combination with cisplatin and paclitaxel.

In an open-label, randomised, phase III study, the addition of bevacizumab to combination chemotherapy increased overall survival.

This 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 patient access scheme in NHS Scotland or a list price that is equivalent or lower.

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

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

In combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix.

Dosing Information

Bevacizumab 15mg/kg by intravenous infusion once every three weeks, in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin or paclitaxel and topotecan. It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

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

Product availability date

April 2015
Bevacizumab meets SMC ultra orphan and end of life criteria in this setting.

Background

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 vasculogenesis and angiogenesis, and neutralising its activity thereby inhibiting tumour growth.[1,2] Bevacizumab is licensed for use in colorectal, breast, non-small cell lung, renal and ovarian cancers. The marketing authorisation has been extended to include use of bevacizumab in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, for the treatment of adult patients with persistent, recurrent, or metastatic cervical cancer. Bevacizumab meets SMC ultra orphan and end of life criteria in this setting.

The submitting company has requested that SMC considers bevacizumab when positioned for use in combination with cisplatin and paclitaxel.

Nature of condition

At the Patient and Clinician Engagement Meeting (PACE), participants highlighted that persistent, recurrent or metastatic cervical cancer is an incurable and life shortening, terminal disease which also disproportionately affects younger women. Patients are currently treated with palliative chemotherapy, which in this setting offers only modest response rates. Median survival has been shown to be 15 months with cisplatin-paclitaxel treatment.[1,2] There have been no new medicines licensed for over ten years.

Bevacizumab is the first anti-angiogenic medicine to be licensed for use with combination chemotherapy for the treatment of cervical cancer, which is the fourth most common cancer in women. Locally advanced disease is initially managed by chemoradiation (cisplatin plus radiotherapy). Patients with persistent, recurrent or metastatic disease have a very poor outcome and treatment is often

palliative with dual agent chemotherapy. The optimal chemotherapy combination has not been identified and options depend on previous treatment and tolerability. Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area for a treatment that improves outcomes.

Impact of new technology

Summary of evidence on comparative efficacy

Evidence comes from one open-label, randomised, phase III study (Gynaecology Oncology Group [GOG] 240) which compared the efficacy and safety of chemotherapy plus bevacizumab with chemotherapy alone in 452 patients with advanced cervical cancer.[1,2,3] The study used a 2x2 factorial design and eligible patients were randomly assigned to one of the four treatment arms: chemotherapy (cisplatin plus paclitaxel or topotecan plus paclitaxel) plus bevacizumab, or chemotherapy (cisplatin plus paclitaxel or topotecan plus paclitaxel) alone. The study included two efficacy objectives: firstly, to determine if adding bevacizumab to chemotherapy improved overall survival, and secondly, to determine if the use of paclitaxel and topotecan improved overall survival compared to cisplatin and paclitaxel. Eligible patients had metastatic, persistent or recurrent cervical cancer which was not amenable to curative treatment with surgery and/or radiation. They had measurable disease, GOG performance status score of 0 or 1 and adequate renal, hepatic, bone marrow function and blood coagulation parameters. Patients were to have recovered from surgery (≥ six weeks previously), radiation therapy (≥ three weeks previously) or chemoradiotherapy (≥ six weeks previously). Patients were randomised equally to receive one of the following four treatments:

- cisplatin (50mg/m^2 on day one or two, at investigator's discretion) plus paclitaxel (135 or 175mg/m^2 at investigator's discretion) plus bevacizumab 15mg/kg on day one (n=115)
- cisplatin (50mg/m^2 on day one or two, at investigator's discretion) plus paclitaxel (135 or 175mg/m^2 at investigator's discretion) on day one (n=114)
- topotecan (0.75mg/m^2) on days one to three plus paclitaxel (135 or 175mg/m^2 at investigator's discretion) on day one plus bevacizumab 15mg/kg on day one (n=112)
- topotecan (0.75mg/m^2) on days one to three plus paclitaxel (135 or 175mg/m^2 at investigator's discretion) on day one (n=111)

Randomisation was stratified by the disease stage (persistent/recurrent versus Stage IVB), performance status (0 versus 1) and prior platinum therapy (yes versus no). Study treatment was continued until disease progression or unacceptable toxicity. If a patient achieved a complete response, she could receive an additional two to three cycles of treatment at the investigator's discretion.

The primary efficacy outcome was overall survival defined as the time from randomisation to death from any cause. Two timepoints were initially planned for analysis, including an interim analysis after approximately half the required number of deaths (cut-off 6 February 2012 after 174 deaths) and a final analysis after 346 deaths had occurred. However, a further unplanned analysis (cut-off 12 December 2012, after 78% of the total required deaths) was performed at the request of the Data Safety Monitoring Board (DSMB) and was considered the final analysis. Data analyses were performed by GOG (with resulting peer reviewed publications)[3,4] and by the submitting company (with results used for regulatory authorities). The company submission is based on the analyses performed by the company and presented in the summary of product characteristics (SPC) and European Public Assessment Report (EPAR).[1,2] There were no important differences in the results of the different analyses.

At the final analysis (cut-off date 12 December 2012), after a median follow-up of 20.8 months and a median of seven cycles of treatment with bevacizumab plus chemotherapy and six cycles of chemotherapy alone, 62% (141/227) chemotherapy plus bevacizumab patients had died compared with 65% (147/225) chemotherapy alone patients. The median overall survival was 16.8 months versus 12.9 months in the chemotherapy plus bevacizumab (n=227) and chemotherapy alone (n=225) groups respectively: hazard ratio (HR) 0.74 (95% confidence interval [CI]: 0.58 to 0.94), p=0.0132. In the cisplatin plus paclitaxel subgroup, the median overall survival was 17.5 months in patients treated with bevacizumab and 14.3 months in those without: HR 0.72 (95% CI: 0.51 to 1.02), p=0.0609.[1,2]

Results of an updated analysis (cut-off date 7 March 2014) found median overall survival of 16.8 months in the chemotherapy plus bevacizumab group versus 13.3 months in the chemotherapy alone group: HR 0.76 (95% CI: 0.62 to 0.94), p=0.0126. In the cisplatin plus paclitaxel subgroup, median overall survival was 17.5 months and 15.0 months with and without bevacizumab respectively (HR 0.75 [95% CI: 0.55 to 1.01], p=0.0584).[1,2] The economic model, described later in this document predicts a mean survival gain of 7.8 months.

The key secondary outcomes were progression-free survival (PFS, defined as the time from randomisation to first documented disease progression, assessed according to the GOG Response Evaluation Criteria In Solid Tumours [RECIST] v1.0, or death) and objective response rate (ORR, defined as the proportion of patients with a complete or partial response assessed by the investigator on two consecutive visits at least four weeks apart in patients with measurable disease at baseline). At the primary analysis, PFS in the overall population was 8.3 months in chemotherapy plus bevacizumab treated patients, compared with 6.0 months in chemotherapy alone treated patients: HR 0.66 (95% CI: 0.54 to 0.81), p<0.0001. In the cisplatin plus paclitaxel subgroup, median PFS was 9.1 months with bevacizumab and 6.9 months without (HR 0.57 [95% CI: 0.42 to 0.78], p=0.0003). In the overall population, ORR was achieved by 45% (103/227) of chemotherapy plus bevacizumab patients compared with 34% (76/225) chemotherapy alone patients (difference of 12% [95% CI: 2.4% to 21%], p=0.0117) and included a complete response in 8.4% (19/227) and in 4.0% (9/225) of patients respectively. In the cisplatin plus paclitaxel subgroup, ORR was achieved by 47% (54/115) of those treated with bevacizumab and 43% (49/114) of those without (difference of 4.0% [95% CI: -9.4% to 17%], p=0.55).[1,2]

Quality of life was assessed prior to cycle 2 and cycle 5, and six and nine months after cycle 1. The completion rate decreased from 94% (426/452) at baseline to 43% (193/452) at 9 months after cycle 1, with no difference between treatment groups. There were no statistically significant differences between the groups in the Functional Assessment of Cancer Therapy-Cervix (FACT-Cx) Trial Outcome Index (TOI), the FACT/GOG-Neurotoxicity four-item subscale (FACT/GOG-Ntx-4) and the Brief Pain Inventory (BPI) single item which assessed worst pain in the previous 24 hours.[4]

Summary of evidence on comparative safety

In the GOG 240 study, any adverse event was reported in 99% (216/218) of chemotherapy plus bevacizumab and in 99% (219/222) of chemotherapy alone patients: serious adverse event in 51% (111/218) and 37% (81/222) respectively; adverse event of grade ≥3 in 76% (165/218) and 57% (127/222) respectively and discontinuation due to adverse event in 26% (56/218) and 18% (40/222) respectively. The most common adverse events were those related to chemotherapy in general eg nausea, fatigue, constipation, peripheral neuropathy and alopecia with slight differences depending on the chemotherapy backbone. The safety results in the chemotherapy plus bevacizumab and chemotherapy alone groups were as expected. However, gastrointestinal perforation (including vaginal fistulae), grade ≥3 venous thromboembolism and grade ≥3 bleeding rates in patients treated with bevacizumab were higher than those observed in previous bevacizumab clinical studies.[2]

Hypertension of any severity occurred in significantly more patients treated with chemotherapy plus bevacizumab than with chemotherapy alone (29% versus 6.3%). There were also more cases of hyperglycaemia (26% versus 19%), hypomagnesaemia (24% versus 15%), hyponatraemia (19% versus 9.9%), fatigue (80% versus 75%), epistaxis (17% versus 1.8%), decreased weight (21% versus 6.8%), infections (9.6% versus 4.5%), neutropenia (13% versus 6.3%) and pelvic pain (14% versus 8.1%) in the chemotherapy plus bevacizumab group than the chemotherapy alone group.[2]

The frequency of fistula was reported in a higher proportion of patients in the chemotherapy plus bevacizumab than the chemotherapy alone group: gastrointestinal perforation, excluding gastrointestinal vaginal fistula (3.2% versus 0%), gastrointestinal vaginal fistulae (8.3% versus 0.9%) and non-gastrointestinal vaginal, vesical, or female genital tract fistulae (1.8% versus 1.4%).[2] The SPC notes that bevacizumab treated patients may be at an increased risk of developing gastrointestinal perforation and that patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab are also at increased risk of gastrointestinal-vaginal fistulae. The only predictor is previous radiation therapy and all patients who developed gastrointestinal perforation or gastrointestinal vaginal fistulae had a history of prior pelvic radiation.[1,2]

In the cisplatin plus paclitaxel subgroup (ie the population relevant to the positioning proposed by the submitting company), any adverse event was reported in 100% (109/109) of cisplatin plus paclitaxel plus bevacizumab and in 99% (112/114) of cisplatin plus paclitaxel alone patients: serious adverse event in 46% (50/109) and 39% (44/114) respectively; adverse event of grade ≥3 in 78% (85/109) and 59% (67/114) respectively and discontinuation due to adverse event in 33% (36/109) and 25% (29/114) respectively. Detailed safety results for the cisplatin plus paclitaxel subgroup were not reported in the EPAR.[2]

Summary of clinical effectiveness issues

The submitting company has requested that SMC considers bevacizumab when positioned for use in combination with cisplatin and paclitaxel. The evidence to support this positioning comes from a subgroup analysis of the pivotal GOG 240 study. The primary outcome, overall survival, is a direct health outcome and results found a statistically significant survival benefit when bevacizumab was added to chemotherapy in the overall study population. The addition of bevacizumab increased median overall survival by 3.9 months and this was considered clinically relevant. However, in the relevant subgroup, the addition of bevacizumab to cisplatin plus paclitaxel increased median overall survival by 3.2 months which did not reach statistical significance, although the study was not sufficiently powered for this subgroup analysis. Although the survival benefit with cisplatin plus paclitaxel plus bevacizumab was numerically greater than with topotecan plus paclitaxel plus bevacizumab, the number of responders was similar and the European Medicines Agency (EMA) concluded that the combination of topotecan plus paclitaxel plus bevacizumab is a valuable alternative for patients that cannot be treated with cisplatin.[2] The addition of bevacizumab to cisplatin plus paclitaxel numerically improved overall survival. This was supported by improved PFS and there was no deterioration in quality of life.[2,3,4] The study was open-label and the secondary outcomes of PFS and ORR were investigator assessed so this could have led to bias. The final analysis was a second unplanned analysis of the data performed at the request of the DSMB which included 78% of the total required deaths.[3]

The majority of study patients had squamous cell carcinoma, persistent/recurrent disease, one or two metastatic sites, lymph node involvement, and more than six months of platinum-free interval. However, subgroup analyses indicated that the overall survival results were generally consistent with the overall study population.[2] Since study patients were not amenable to curative surgery or radiation, evidence from the pivotal study supports the palliative use of bevacizumab.

The safety profile of bevacizumab in combination with chemotherapy is established and treatment-related adverse events were as expected. Although no new safety signals were observed, the addition of bevacizumab was associated with a higher incidence of hypertension, serious thromboembolic events and gastrointestinal fistula in the GOG 240 study than in previous bevacizumab studies.[1,2,3]

Although the submitting company has requested that SMC considers bevacizumab when positioned for use in combination with cisplatin and paclitaxel, they suggest that carboplatin plus paclitaxel is the standard of care in Scotland. Clinical experts have indicated that both doublet combinations may be used. The company presented results of a Bayesian network meta-analysis (NMA) to allow indirect comparison of cisplatin plus paclitaxel with carboplatin plus paclitaxel in patients with persistent, recurrent or metastatic cervical cancer. The NMA included 25 studies (two of which linked the comparison of interest: GOG 240 and JCOG0505 [which directly compared cisplatin plus paclitaxel with carboplatin plus paclitaxel]) and assessed overall survival and PFS.[3,5] However, results of the updated analysis of the GOG 240 study were used in the NMA rather than the primary analysis which would have been more appropriate and comparable with the results of JCOG0505. The resulting hazard ratios and credible intervals (which included 1) indicated no real difference between cisplatin plus paclitaxel and carboplatin plus paclitaxel but the comparison is limited by comparing outcomes after different durations of follow-up and differences in the study populations, including previous treatment. However, the NMA results were very similar to direct comparison results from JC0505.

Clinical experts consulted by SMC considered that bevacizumab is a therapeutic advancement due to the improvement in survival. Bevacizumab is not licensed for use with carboplatin plus paclitaxel. Any change from using carboplatin plus paclitaxel to bevacizumab plus cisplatin plus paclitaxel may have some minimal service implications to allow for administration of infusions and to continue treatment until disease progression. Clinicians at PACE reported that the additional survival time was of good quality with a small impact on quality of life. Side effects in addition to the usual standard chemotherapy regimens are manageable and usually not detrimental to patients' quality of life.

Patient and clinician engagement (PACE)

A Patient and Clinician Engagement (PACE) meeting with a patient group representative 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:

- Persistent, recurrent or metastatic cervical cancer is an incurable and life shortening, terminal disease, and a diagnosis can have a catastrophic effect on a patient and their family. The women affected are often young and this is therefore a deeply distressing time for the patient and their families.

- Patients are currently treated with palliative chemotherapy which in this setting only offers modest response rates. There have been no other medicines licensed for at least ten years and bevacizumab is considered a significant breakthrough.

- The additional vital survival time may allow patients to be more independent, adjust to what is happening and to plan for their family's future. The financial impact of advanced cervical cancer can be significant and the opportunity for patients to continue working, or their carers/partners to continue to work has important financial benefits.

- PACE participants highlighted that the most challenging symptoms for patients with advanced cervical cancer can be those caused by locally recurrent and uncontrolled pelvic disease; pain, urinary and faecal incontinence, fistulas, stomas etc. Patients may require nephrostomies which are extremely difficult and uncomfortable for patients to live with. Managing these unpleasant symptoms requires prolonged inpatient ward admissions and can be very uncomfortable and distressing for the patient. Clinicians described how in practice, bevacizumab has been seen to delay progression of these complications.

- There are no additional hospital or clinic visits needed with bevacizumab so service implications are expected to be negligible.

Additional Patient and Carer Involvement

A patient group submission was received from Jo's Cervical Cancer Trust which is a registered charity. The patient group has received 3% pharmaceutical company funding in the past two years, including from the submitting company. A representative from the patient group participated in the PACE meeting. The key points of their submission have been included in the full PACE statement.

Value for money

The submitting company presented a cost-utility analysis of bevacizumab in combination with cisplatin and paclitaxel compared to standard therapy with carboplatin and paclitaxel alone for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix. An assessment of the cost-effectiveness of the bevacizumab regimen versus cisplatin and paclitaxel alone was also provided. SMC clinical experts have indicated both carboplatin and cisplatin in combination with paclitaxel are used in clinical practice. An area-under-the-curve economic model was used consisting of 3 health states of PFS, progressive disease (PD) and death, with a lifetime time horizon consisting of 20 years.

The clinical data used in the model were taken from the sub-group of patients from the GOG 240 study where bevacizumab plus cisplatin plus paclitaxel was compared to cisplatin plus paclitaxel alone. PFS was extrapolated by fitting the Gamma parametric function to the observed data for each treatment arm. Overall survival extrapolation consisted of fitting the log logistic function to the observed data for the treatment arms, but due to a potential underestimation of longer term survival based on the GOG 240 data this was adjusted from year 5 in the model by fitting a parametric function to published observational survival data (US SEER database) in patients with distant/stage IV cervical cancer.

In order to enable a comparison with carboplatin plus paclitaxel, a non-inferiority study in advanced cervical cancer of cisplatin plus paclitaxel versus carboplatin plus paclitaxel (study JCOG 0505) was identified from a systematic review and included in an NMA. The resulting hazard ratios were 1.039 for PFS and 0.994 for overall survival for the carboplatin regimen versus the cisplatin regimen and these results were applied to the cisplatin plus paclitaxel extrapolations in the economic analysis.

As utility estimates were not directly available from data in the GOG 240 study, EQ 5D derived utilities for the PFS health state were derived through a mapping of FACT-G data from the study to EQ 5D values. A mean utility of 0.79 was derived using a mapping algorithm from a Canadian study in patients with a range of cancers (breast, lung and colorectal).[6] Due to a lack of post progression patient reported outcome data in GOG 240, a simple 20% decrement in PFS utility was applied to reflect utility in the PD health state (i.e. 0.63). The impact on quality of life of differences in grade 3 and 4 adverse events between treatment arms was assumed to be negligible, and any disutility was

assumed to be captured within the FACT-G to EQ 5D derived PFS utility estimate (applied to both arms).

Costs covered drug acquisition and administration costs for bevacizumab, carboplatin or cisplatin, 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 palliative care costs. No costs were included for post progression anti-cancer treatment, as it was stated that the likelihood of additional treatment was low due to the poor prognosis of patients at this disease stage. The dose of bevacizumab was as per the GOG 240 study at 15mg/kg delivered by IV infusion. The actual doses from GOG 240 for IV infusion with bevacizumab, cisplatin plus paclitaxel were used in the economic analysis, but for the comparison with carboplatin plus paclitaxel, the planned dose of carboplatin according to the label was used in the base case. Treatment durations were estimated directly from the GOG 240 subgroup time to off treatment (TTOT) data for the intervention and comparator arms, with extrapolation of this based on fitting parametric functions. The carboplatin plus paclitaxel versus cisplatin plus paclitaxel PFS hazard ratio of 1.039 was applied to the TTOT estimates for cisplatin plus paclitaxel in order to provide an estimate of treatment duration for carboplatin plus paclitaxel. Incidence and costs of treating adverse events for carboplatin were assumed to be the same as for cisplatin.

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 of bevacizumab. With the PAS the base case result was an incremental cost-effectiveness ratio (ICER) of £43,624 per quality-adjusted life-year (QALY) gained for bevacizumab plus cisplatin plus paclitaxel versus carboplatin plus paclitaxel. This is based on a discounted incremental cost of £16,547 and incremental QALYs of 0.38 (non-discounted incremental life years of 0.65 or 7.8 months).

The key cost driver was the higher drug acquisition cost for bevacizumab, with some additional costs for IV drug administration, adverse event management and PFS/PD health state costs. The life years and QALY gains for bevacizumab are associated with additional PFS time (0.26 LYs and 0.205 QALYs gained), but also with additional time and QALYs in PD (0.275 LYs and 0.174 QALYs gained). The base case results were most sensitive to use of alternative parametric functions and extrapolation methods for overall survival producing an ICER range of £39k/QALY to £51k/QALY. The company also performed a scenario analysis assuming a hazard ratio of 1 for carboplatin plus paclitaxel versus cisplatin plus paclitaxel PFS and overall survival producing a marginal impact on the ICER (£43,188/QALY). There was some sensitivity to the PFS and PD utility estimation as adopting the lower PFS value in the range identified from published FACT-G to EQ 5D mapping studies (0.68) increased the ICER (£51k/QALY). The results were reasonably insensitive to variation in treatment duration, drug dose, and cost parameters, and varying the time horizon had a modest impact on the ICERs.

The ICER for the comparison with cisplatin plus paclitaxel was £45,950/QALY with PAS. As carboplatin and cisplatin have comparable efficacy, the difference in ICER from the base case analysis is associated with the lower drug acquisition cost for cisplatin. Sensitivity analysis was requested from the company and indicated some sensitivity to alternative parametric functions and extrapolation methods with an ICER range of £41k to £54k/QALY. Applying a lower PFS utility of 0.68 increased the ICER to £53k/QALY.

There were a number of issues with the economic analysis as follows:

- A limitation of the clinical data was that overall survival in the subgroup of the GOG 240 study used in the economic analysis did not show statistical significance between bevacizumab plus

cisplatin plus paclitaxel and cisplatin plus paclitaxel. The company highlighted that the study was underpowered to detect a statistically significant difference in this subgroup and that the upper 95% CI for the hazard ratio only just exceeded one. Despite this limitation, the comparison with cisplatin plus paclitaxel can be considered relatively robust as it was based on direct data from the GOG 240 study. There were also limitations in the NMA performed to facilitate comparisons between bevacizumab plus cisplatin plus paclitaxel versus carboplatin plus paclitaxel, although it should be noted that a NMA was not entirely necessary to support an assumption of equivalence of carboplatin plus paclitaxel versus cisplatin plus paclitaxel in patients with late stage cervical cancer as direct evidence existed for this (Study JCOG 505).

- There are some uncertainties with the extrapolation of survival beyond the GOG 240 study based on observational data. As a consequence of the approach used, the mean survival gain predicted by the model is 7.8 months (not discounted) compared to a much shorter median survival benefit estimated with the model at 3.5 months (not discounted). Sensitivity analysis with survival extrapolation performed by fitting a parametric function to the GOG 240 data alone resulted in an ICER of £47k/QALY versus carboplatin plus paclitaxel, and £49k/QALY versus cisplatin plus paclitaxel.

- There are uncertainties associated with the utility estimates used in the economic model, as none are based on mapping algorithms in cervical cancer. The company chose a higher PFS utility from the range of published algorithms identified. A PFS utility of 0.73 represents a mid-point estimate derived from the mapping studies identified and so maybe more plausible as a base case. In addition, a simple decrement of 20% was applied to derive the PD health state utility. Whilst simplistic, this may be plausible. However, a scenario analysis was provided for the comparison with carboplatin plus paclitaxel assuming a 0.73 utility for PFS and applying a 20% decrement to this value for PD (i.e. 0.584). As greater time is estimated to be spent in both PFS and PD states with bevacizumab this increased the ICER to £47k/QALY (£50k for the comparison with cisplatin plus paclitaxel). In addition, no additional disutilities for adverse events experienced in the bevacizumab group were included, despite a higher incidence of fistula, hypertension and supraventricular tachycardia than the comparator arm in GOG 240. Including a further 2% utility decrement whilst on treatment (and using more conservative utility values as in the scenario described above) resulted in an ICER of £48k/QALY versus carboplatin plus paclitaxel.

- No post progression active treatment costs have been included in the analysis on the grounds that post progression survival is poor and additional treatment is unlikely to be provided. However, the duration of post progression survival in the economic analysis was estimated to be over 1.3 years so this assumption may not hold, and due to the longer time spend in the PD state for bevacizumab patients could introduce a bias in favour of the bevacizumab regimen.

- There is potential uncertainty associated with the estimates of carboplatin plus paclitaxel duration and dose as these were derived by proxy methods, although sensitivity analysis indicates this is not a major driver of cost-effectiveness.

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 life expectancy in the patient population targeted in the submission 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.

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

Impact beyond direct health benefits and on specialist services

Discussions at the PACE meeting emphasised that the addition of bevacizumab to standard chemotherapy regimens may allow patients to have more independence, work if they choose, spend time with family and care for children and parents. The financial impact of an advanced cervical cancer diagnosis on patients and their families can be huge and the opportunity for patients to continue working, or their carers/partners to continue to work has important financial benefits for the families. Survival gains seen in the GOG-0240 trial with the addition of bevacizumab were not associated with any clinically meaningful deterioration in quality of life. This allows patients to continue with family life and contribute to wider society where possible.

Clinicians at the PACE meeting considered that bevacizumab is well tolerated and no additional clinic time is needed. Side effects in addition to the standard chemotherapy regimens are minimal, and can be easily managed by clinicians if necessary. The treatment schedule does not incur additional hospital or clinic visits so service implications are expected to be negligible. There is no expected impact on NHS staffing, infrastructure or training requirements.

Costs to NHS and Personal Social Services

The submitting company estimated the population eligible for treatment to be 67 patients, with an estimated uptake rate of 20% (13 patients) in year 1 and 60% (40 patients) in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

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

Additional information: guidelines and protocols

The National Comprehensive Cancer Network (NCCN) published guidelines for the treatment of cervical cancer in 2015.[7] This guideline notes that cisplatin is considered the most effective agent for metastatic disease but since most patients have received cisplatin with radiotherapy as primary treatment, they may no longer be sensitive to single-agent platinum. Cisplatin-based combination treatments have been extensively studied and the guideline recommends a number of combinations for the first-line treatment of metastatic cervical cancer including: cisplatin plus paclitaxel plus bevacizumab, cisplatin plus paclitaxel, topotecan plus paclitaxel plus bevacizumab, carboplatin plus paclitaxel (for patients who have received prior cisplatin), carboplatin plus paclitaxel plus bevacizumab, cisplatin plus topotecan, topotecan plus paclitaxel and cisplatin plus gemcitabine.

The European Society for Medical Oncology (ESMO) published clinical practice guidelines for cervical cancer in 2012.[8] These guidelines state that in those with metastatic or recurrent disease, chemotherapy is palliative. Compared to those who are chemotherapy-naive, the response rates are

lower. Whilst cisplatin is the most active cytotoxic agent, the guidelines acknowledge that the objective response is low and that survival is only around seven months. The guidelines state that while cisplatin combination therapy has been investigated, only cisplatin-topotecan offers a survival advantage over monotherapy. The guidelines however state that in a phase III study comparing different cisplatin combination regimens, whilst there was no differences observed in overall survival, there was a trend suggesting cisplatin-paclitaxel may be referable in terms of response rate, progression and overall survival. The guidelines suggest this regimen may be preferable from a toxicity perspective.

The Scottish Intercollegiate Guidelines Network (SIGN) published guidelines for the management of cervical cancer in January 2008.[9] The guidelines state that the prognosis for patients with recurrent disease is six months to two years and with both recurrence and metastatic disease women may also experience substantial morbidity. Treatment options for women who have failed first line treatment include surgery, chemotherapy or palliative care. It was recommended that palliative chemotherapy should be offered to women with Féderation Internationale de Gynécologie et d'Obstétrique (FIGO) stage IVB or recurrent cervical carcinoma, after discussion of the relative benefits and risks, with either cisplatin 50mg/m^2 on day 1 plus topotecan 0.75mg/m^2 on days 1 to 3 every 3 weeks or cisplatin 50mg/m^2 on day 1 plus paclitaxel 135mg/m^2 every 3 weeks. Other recommendations included that cisplatin and topotecan combination be restricted to women who were cisplatin naive and also that it should be considered for patients of performance status 0 to 2.

Additional information: comparators

Since bevacizumab would be added to chemotherapy, there are no direct comparators in this indication.

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)	Cost per course (£)
Bevacizumab plus cisplatin plus paclitaxel	**Bevacizumab 15mg/kg intravenously on day 1 plus cisplatin 50mg/m^2 intravenously on day 1 plus paclitaxel* 175mg/m^2 intravenously on day 1 repeated every 3 weeks**	**3,294**	**23,058**
Carboplatin plus paclitaxel	Carboplatin 400mg/m^2 intravenously on day 1 plus paclitaxel 175mg/m^2 intravenously on day 1 repeated every 3 weeks	928	6,496
Cisplatin plus paclitaxel	cisplatin 50mg/m2 intravenously on day 1 plus paclitaxel 175mg/m^2 intravenously on day 1 repeated every 3 weeks	717	5,019

Costs from electronic British National Formulary accessed on 11 January 2016. Dose based on 70kg body weight and 1.8m^2 body surface area. It is recommended that treatment is continued until disease progression or unacceptable toxicity occurs. In the GOG 240 study, patients received a median of seven cycles of bevacizumab and therefore the cost per course is based on seven cycles but in practice this will vary.

References

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

1. Roche Products Ltd. Bevacizumab concentrate for solution for infusion (Avastin®) summary of product, last updated 19 November 2015.

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3. Tewari KS, Sill MW, Long HJ et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med 2014;370:734-43.

4. Penson RT, Huang HQ, Wenzel LB et al. Bevacizumab for adanced cervical cancer: patient-reported outcomes of a randomised, phase 3 trial (NRG Oncology-Gynecologic Oncology Group protocol 240). Lancet Oncol 2015;16:301-11.

5. Kitagawa R, Katsumata N, Shibata T et al. Paclitaxel plus carboplatin versus paclitaxel plus cisplatin in metastatic or recurrent cervical cancer: the open-label randomised phase III trial JCOG0505. J Clin Oncol 2015;33:2129-35

6. Teckle P, Taggart-Cowan H, Van der HK et al. Mapping the FACT-G cancer-specific quality of life instrument to the EQ-5D and SF-6D. Health Qual Life Outcomes 2013;11:203

7. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: cervical cancer. www.nccn.org (accessed 3 January 2016).

8. Colombo N, Carinelli S, Colombo A et al. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 Suppl 7:vii27-vii32.

9. Scottish Intercollegiate Guidelines Network (SIGN). Guideline number 99: Management of cervical cancer. January 2008

This assessment is based on data submitted by the applicant company up to and including 12 February 2016.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

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.