Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

bevacizumab, 25mg/mL, concentrate for solution for infusion (Avastin®)

SMC No. (778/12)

Roche Products Ltd.

06 April 2012

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

bevacizumab (Avastin®) is not recommended for use within NHS Scotland.

Indication under review: bevacizumab in combination with capecitabine is indicated for first-line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate.

In a double-blind, multicentre, randomised, placebo-controlled phase III study in patients with locally recurrent or metastatic breast cancer, treatment with bevacizumab plus capecitabine was associated with an extended median progression-free survival of 2.9 months compared with capecitabine monotherapy. However, there was no overall significant improvement in survival.

The submitting company did not present a sufficiently robust economic analysis and, in addition, their justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by the SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Bevacizumab in combination with capecitabine is indicated for first-line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with bevacizumab in combination with capecitabine.

Dosing Information

Intravenous infusion of 10mg/kg once every two weeks, or 15mg/kg once every three weeks. Treatment should be continued until progression of the underlying disease or until unacceptable toxicity occurs.

In the pivotal phase III study the dose of bevacizumab was 15mg/kg every three weeks and capecitabine 1,000mg/m^2 orally twice daily for two weeks of a three-week cycle.

Product availability date

June 2011

Summary of evidence on comparative efficacy

Bevacizumab interferes with the biological activity of vascular endothelial growth factor (VEGF) by binding to it and preventing interaction with its receptors on endothelial cells. Neutralisation of VEGF activity leads to inhibition of tumour growth.[1]

Bevacizumab has had a marketing authorisation for use in the first-line treatment of metastatic breast cancer (in combination with paclitaxel) since 2007. SMC issued not recommended advice for bevacizumab in this indication in July 2007 as the sponsor company did not make a submission. The marketing authorisation for bevacizumab has now been extended to permit use in combination with capecitabine in this setting. SMC accepted the use of capecitabine monotherapy in metastatic breast cancer after the failure of taxanes and an anthracycline-containing regimen in 2003 (and in combination with docetaxel in those previously treated with an anthracycline).

The marketing authorisation specifies that bevacizumab in combination with capecitabine should be used as first-line chemotherapy in patients with metastatic breast cancer only when treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. It is indicated for first-line chemotherapy in these patients although treatment with radiotherapy or hormonal therapy may have been given in the metastatic setting. It also stipulates that patients with metastatic disease who have received taxanes and anthracyclines in the adjuvant setting within the previous 12 months are not eligible for treatment with bevacizumab plus capecitabine.

The submitting company has requested that SMC considers the use of bevacizumab in patients with metastatic breast cancer who have failed on previous treatment with taxane and anthracycline-containing regimens. Although the terms of the marketing authorisation are broader, supporting use in patients in whom these agents are not considered appropriate, the

company has positioned bevacizumab in patients who reflect a sub-population in the pivotal RIBBON-1 study that also conforms to the licensed indication for capecitabine.

Evidence to support the use of bevacizumab in combination with capecitabine is from the RIBBON-1 study, a multi-centre, randomised, double-blind, placebo-controlled, phase III study with two patient cohorts, defined by the investigator-selected chemotherapy regimen assigned pre-randomisation: either capecitabine, or anthracycline-/taxane-based chemotherapy. Adults ≥18 years with locally recurrent or metastatic breast cancer, and Eastern Co-operative Oncology Group performance status 0 or 1 were recruited to the study. Patients with HER2-positive status were excluded from the study, unless they had progressed while on trastuzumab, or trastuzumab was contraindicated or unavailable. In the capecitabine cohort, relevant to the indication under review and reported hereafter, patients received capecitabine 1,000mg/m^2 orally on days one to 14 of a three week cycle, in combination with either bevacizumab 15mg/kg intravenous infusion every three weeks (n=409) or placebo (n=206). Patients were randomly assigned in a 2:1 ratio with stratification for disease-free interval (≤12 or >12 months), history of prior (neo)adjuvant chemotherapy (yes or no), and number of metastatic sites (<3 or ≥3 sites). Combination treatment continued until there was progressive disease, unacceptable toxicity, investigator decision to stop or death, whichever came first. Bevacizumab or placebo could be continued for up to 48 months. Patients with documented disease progression during the blinded phase of the study could choose to receive second-line chemotherapy (at investigator's discretion and excluding anthracycline-based chemotherapy) with open-label bevacizumab (5mg/kg per week equivalent dose).[2]

The primary endpoint was progression-free survival (PFS) defined as the time from randomisation to first disease progression, based on investigator tumour assessment using the Response Evaluation Criteria in Solid Tumours (RECIST) 1.0 protocol, or death from any cause in the intent-to-treat (ITT) population. At the pre-specified clinical cut-off after 407 events, after a median follow-up time of 15.6 months, treatment with capecitabine plus bevacizumab was associated with a prolonged investigator-determined PFS of 2.9 months compared with treatment with capecitabine plus placebo. The median PFS was 8.6 months versus 5.7 months, respectively, with an associated hazard ratio (HR) of 0.69 (95% confidence interval [CI]: 0.56 to 0.84, p<0.001).[2]

Key secondary endpoints were overall survival, and objective response rate. There was no statistically significant difference between the groups in terms of overall survival, HR=0.85 (95% CI: 0.63 to 1.14), or in one year survival rate (81% versus 74% for capecitabine plus bevacizumab and capecitabine plus placebo groups, respectively).[2] The results had not changed significantly in an updated analysis conducted seven months later: HR for OS was 0.88 (95% CI: 0.69 to 1.13), and one year survival rates were 81% versus 75% respectively.[3] The objective response rate in patients with measurable disease was significantly greater in patients treated with capecitabine plus bevacizumab (35%, n=115/325) compared with capecitabine plus placebo (24%, n=38/161), p=0.0097, responses predominantly meeting partial response criteria only. In those who responded to treatment, median duration of objective response in the capecitabine plus bevacizumab group was 9.2 months (95% CI: 8.5 to 10.4 months) compared with 7.2 months (95% CI: 5.1 to 9.3 months) for the capecitabine plus placebo group.[2]

Pre-specified analysis of PFS across clinically relevant sub-groups yielded hazard ratios numerically in favour of capecitabine plus bevacizumab, which reached statistical significance in most cases. Sub-groups in which there was not a significant benefit with capecitabine plus bevacizumab included patients with a disease-free interval ≤12 months (HR=0.81, 95% CI: 0.54

to 1.21), and those who had not had prior adjuvant chemotherapy (HR=0.80, 95% CI: 0.54 to 1.18). The sub-group of patients used in the health economic analysis comprised patients with a history of taxane-based chemotherapy (n=245/615, 40% of the ITT population). PFS in this sub-group was 8.7 months for patients treated with capecitabine plus bevacizumab compared with 4.2 months if treated with capecitabine plus placebo, a 4.5 month PFS benefit, (HR=0.62, 95% CI: 0.45 to 0.84).[2]

Summary of evidence on comparative safety

Adverse events (AEs) were reported in 39% (157/404) of patients in the bevacizumab group compared with 25% (51/201) of patients in the placebo group. AEs of severity grades three to five were reported in a greater proportion of patients in the bevacizumab group compared with the placebo group: 35% versus 22%, respectively. A similar proportion of patients discontinued bevacizumab or placebo because of an AE: 12% in each group.

Treatment with bevacizumab was associated with a higher incidence of hypertension (10%) and proteinuria (2.2%) compared with placebo (1% and 0%, respectively). Sensory neuropathy was reported in 3% of bevacizumab-treated patients compared with one placebo patient (0.5%). There were no reports of febrile neutropenia or gastro-intestinal perforation, and similar incidences of neutropenia (approx 1%) and venous thromboembolic events (3.5 to 5%) in the treatment groups. The majority of deaths in the study were related to disease progression; however, there were 11 fatal AEs, six (1.5%) in the bevacizumab group, and 5 (2.5%) in the placebo group.[2] The safety profile was consistent with previous studies of bevacizumab in oncology.[3]

Summary of clinical effectiveness issues

The marketing authorisation specifies that the combination of bevacizumab with capecitabine may be used as first-line therapy in metastatic breast cancer when taxane- or anthracycline-based chemotherapy is not considered to be appropriate. The submitting company has requested, however, that SMC considers the use of this combination when positioned for use in a more restricted patient group i.e. only in those patients with metastatic breast cancer who have failed previous taxane- and anthracycline-containing regimens. This is in line with the licensed indication for capecitabine as monotherapy in locally advanced or metastatic breast cancer. There are very few treatment options available for this patient population, particularly those who are HER-2 and oestrogen receptor negative.

The primary outcome of the RIBBON-1 study was PFS, assessed using the accepted RECIST criteria. Bevacizumab in combination with capecitabine treatment resulted in a statistically significant, but modest, improvement in PFS of 2.9 months compared with capecitabine monotherapy treatment (8.6 months versus 5.7 months respectively). The effect on PFS was not supported by a significant improvement in overall survival. However the study was designed to allow crossover to open-label bevacizumab on disease progression, potentially confounding the results for overall survival. A potential additional problem is that the dose of capecitabine used (1,000mg/m^2 twice daily) was lower than the licensed dose for monotherapy in breast cancer, (1,250mg/m^2 twice daily); it is possible that this had an impact on the survival of the comparator group.

No quality of life data were reported.

Current treatment guidelines for metastatic breast cancer indicate that treatment options are dependent on previous adjuvant therapy and the interval since treatment. Anthracyclines and taxanes are considered more effective than capecitabine but may not be appropriate treatment options, for example due to previous therapy or poor performance status. RIBBON-1 did not recruit only patients for whom treatment with other chemotherapy options including taxanes or anthracyclines was not considered appropriate. The restriction in the marketing authorisation for use in patients for whom taxanes or anthracyclines are inappropriate was applied by the European Medicines Agency (EMA) since it considered the benefit/risk of bevacizumab plus capecitabine only to be positive in patients for whom these and other treatment options are not appropriate.[3] Investigators pre-selected the chemotherapy backbone prior to randomisation in RIBBON-1, so patients in the capecitabine cohort of the study may not have been considered by the investigator to be appropriate candidates for taxane and anthracycline-based chemotherapy.

For the economic case, the submitting company selected efficacy data from the sub-group of patients with prior history of treatment with taxane-based chemotherapy, a sub-group pre-specified in the study design. The majority of the patients in this sub-group (95%) had also been previously treated with anthracycline-based chemotherapy, so this was considered to be a reasonable approximation of the population relevant to the proposed restricted patient group.

Clinical guidelines for metastatic breast cancer published by the Scottish Intercollegiate Guidelines Network and by the National Institute for Health and Clinical Excellence (NICE), recommend that for patients for whom anthracyclines, taxanes, and trastuzumab are inappropriate, oral capecitabine or vinorelbine (orally or via the intravenous route) are treatment options. Clinical experts consulted by SMC have indicated that they are the treatment options used in Scotland. No comparative data were presented for vinorelbine since the submitting company did not consider this a common comparator following market research.

Bevacizumab requires to be administered by intravenous infusion over 30 to 90 minutes every three weeks. Compared with the requirements for weekly intravenous infusion of vinorelbine, this is potentially more convenient, but is disadvantageous compared with oral administration of capecitabine or vinorelbine.

Summary of comparative health economic evidence

A cost-utility analysis was presented by the submitting company comparing bevacizumab and capecitabine combination therapy with capecitabine monotherapy in patients with HER2 negative metastatic breast cancer who have relapsed after previous taxane and anthracycline therapy and for whom further anthracycline or taxane therapy is not considered appropriate. The model base case had a 15-year time horizon.

For this positioning, the clinical data used in the economic model was individual patient data for the sub-group of patients from the RIBBON-1 trial who had failed previous taxane-based chemotherapy, the majority of these also having failed prior antracycline therapy. Using these data (which represented 40% of the ITT population), time in PFS, and time in progressive disease states were modelled by extrapolating beyond the observed Kaplan-Meier data for the sub-group using an exponential function. In addition, as there was cross-over of patients from

capecitabine plus placebo to bevacizumab on disease progression, the Rank Preserving Structural Failure Time Model (RPSFT) approach was used to adjust for bias related to this.

Utility estimates were derived from a recent NICE multiple technology assessment report conducted in metastatic breast cancer, with the original source being a published vignette-based elicitation study in the UK general public. Values were derived for PFS with bevacizumab plus capecitabine (0.784), PFS with capecitabine (0.774), and progressive disease (0.496) states. It appeared that the PFS utilities did not take into account possible additional disutility associated with the addition of bevacizumab therapy, although the impact on the cost-effectiveness results is likely to be small.

Drug costs included drug acquisition and administration costs. Bevacizumab dosing was based on a patient weight of 72.1kg, and capecitabine dosing assumed a body surface area of 1.76m^2 derived from the sub-group characteristics. A lower dose for capecitabine than is recommended in the summary product characteristics (SPC) was used in the model (1000 mg/m^2 rather than the recommended 1,250 mg/m^2 per administration, the justification being the lower dose was used in the clinical trial and hence relates directly to efficacy). However, the potential use of higher doses in clinical practice has an unknown impact on relative costs and outcomes of bevacizumab and capecitabine vs capecitabine monotherapy. In estimating drug costs, account was taken of treatment discontinuation by fitting an exponential curve to observed data to estimate the time to off treatment for each treatment arm of the prior taxane sub-group. Costs associated with grade 3 or 4 adverse events with >2% incidence and considered by clinical experts to incur a treatment cost were also taken into account (this included only deep vein thrombosis and hypertension). Subsequent lines of therapy were not included in the model on the grounds that the treatment and cost would be the same for both treatment arms. Resource use estimates for PFS and progressive disease states were based on those reported in NICE clinical guideline 81 for advanced breast cancer.

The main result was an incremental cost per quality adjusted life year (QALY) for bevacizumab plus capecitabine of £77,318, based on an incremental cost of £38,924 per patient, and a gain of 0.86 life years and 0.5 QALYs. The life years/QALY gains with the use of bevacizumab were evenly spread through additional time in PFS and in progressive disease.

In sensitivity analysis, the best incremental cost-effectiveness ratio (ICER) achieved was £57.6K/QALY based on a 20% higher PFS/progressive disease utility than the base case values. The results were sensitive to variations in utility values, especially in progressive disease, with a range in the ICER of £62.3K to £101.8K when these were varied by ±20%. The ICER was moderately sensitive to higher patient weight, with weights greater than the base case of 72kg leading to reduced cost-effectiveness, and lower weight improving the ICER although still well above what would generally be considered acceptable levels. Shorter time horizons increased the ICER by a modest amount. From probabilistic sensitivity analysis, there was an estimated zero probability of bevacizumab plus capecitabine cost-effectiveness at willingness to pay thresholds below £30K/QALY.

There were a number of issues with the economic evaluation:

- There is uncertainty over the survival benefit associated with bevacizumab plus capecitabine. An advantage of using the prior taxane sub-group data is that a statistically significant overall survival result was found. In scenario analysis the submitting company attempted to fit parametric functions to the PFS and progressive disease survival probability. These did not provide a visually good fit to the data used,

and produced a variation in the ICER from £67K per QALY to over £100K/QALY depending on the function fitted. In addition, having to adjust survival outcomes for cross-over bias increases the uncertainty.

- There is uncertainty associated with the potential use of higher doses of capecitabine in clinical practice and thus the impact on relative costs and outcomes of bevacizumab plus capecitabine vs capecitabine monotherapy.
- In a small group of patients, SMC clinical experts have suggested vinorelbine may have been a relevant comparator treatment.

SMC considered the likely range of cost-effectiveness ratios for bevacizumab in this setting and the remaining uncertainties in the economic case. The committee considered the benefits of bevacizumab in the context of the SMC decision modifiers and was satisfied that that the modifier relating to whether a sub-group of patients may derive specific or extra benefit and the medicine can, in practice, be targeted at this sub-group was satisfied. The committee was, however, unable to accept bevacizumab due to the high cost per QALY with the additional upwards uncertainty.

Summary of patient and public involvement

A Patient Interest Group Submission was received from: Breakthrough Breast Cancer.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guideline Network (SIGN) clinical guideline 84, Management of breast cancer in women was published in December 2005. It includes several recommendations for chemotherapy in patients with metastatic disease. Combination of taxane and trastuzumab is recommended in women with metastatic disease. Either capecitabine or vinorelbine should be considered for patients with advanced breast cancer.

The National Institute for Health and Clinical Excellence (NICE) clinical guideline CG81; Advanced breast cancer; diagnosis and treatment was published in February 2009. It includes a treatment algorithm for the use of chemo- or biological therapy. In patients who had contraindications to, or disease progression with anthracycline with a negative HER2 status should be considered for docetaxel first-line, either as a single agent, or when appropriate, in combination therapy. Combination chemotherapy is recommended in patients for whom the additional toxicity is likely to be tolerated, and a greater probability of response is important. Subsequent second and third-line options are vinorelbine or capecitabine.

The European Society for Medical Oncology (ESMO) has recently updated their guideline; locally recurrent or metastatic breast cancer; ESMO clinical practice guidelines for diagnosis, treatment and follow-up, in 2011. The guideline recognised that there are few proven standards of care in metastatic breast cancer. The main treatment goals are palliation: maintaining or improving quality of life, and improving survival. Choice of therapy should take into account the patient's preferences as well as other patient- and disease-related factors such as previous treatment, HER2 status, need for rapid control of symptoms, and co-morbidity. The guideline recommendation for bevacizumab relates to its licensed indication in combination with paclitaxel. Bevacizumab should be considered for carefully selected patients who have limited treatment options, taking into account the balance of benefit over side effects and cost.

The guidelines predate the licensing of bevacizumab in combination with capecitabine for first-line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate.

Additional information: comparators

Chemotherapy options in patients for whom anthracycline and taxane-based chemotherapy is not appropriate include oral capecitabine or vinorelbine (oral or intravenous).

Cost of relevant comparators

Drug	Dose Regimen	Cost per three-week cycle (£)
bevacizumab plus capecitabine	bevacizumab: 15mg/kg intravenous infusion every three weeks plus capecitabine: 1,000mg/m^2 orally twice daily for 14 days followed by a seven day rest period	£2,800
vinorelbine	60 to 80mg/m^2 orally once weekly	£726 to £924
vinorelbine	25 to 30mg/m^2 intravenous infusion once weekly	£420 to £509
capecitabine	1,250mg/m^2 orally twice daily for 14 days followed by a seven day rest period	£279

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS (January 2012) and from eVadis on 31 January 2012. Costs based on adult weighing 70kg with a body surface area of 1.8m^2 and do not include the costs of infusion fluids used.

Additional information: budget impact

The submitting company estimated the eligible patients to be 8 patients in year 1 and 41 patients in year 5, based on an estimated uptake of 10% in year 1 and 50% by year 5 of all eligible patients with HER2 negative metastatic breast cancer who have relapsed after prior taxane and anthracycline therapy. The impact of bevacizumab plus capecitabine on the medicines budget was estimated at £250K in year 1 and £1.3 million in year 5.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1) Roche Products Limited. Summary of Product Characteristics – Avastin 25mg/mL concentrate for solution for infusion. [online] Available from http://www.medicines.org.uk [Last updated 05 January 2012]

2) Robert NJ, Dieras V, Glaspy J, Brufsky AM et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol (2011); 29: 1252-60 http://dx.doi.org/10.1200/JCO.2010.28.0982

3) European Medicines Agency. Assessment report for Avastin (bevacizumab) Type II variation EMA/H/C/000582/II/0033. [online] Available from http://www.ema.europa.eu [Last updated 19 May 2011]

This assessment is based on data submitted by the applicant company up to and including **16 March 2012.**

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. 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.