bevacizumab, 100mg and 400mg vials (Avastin®) No. (469/08)
Roche

09 May 2008

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

bevacizumab (Avastin®) is not recommended for use within NHS Scotland in combination with fluoropyrimidine-based chemotherapy for treatment of patients with metastatic carcinoma of the colon or rectum.

In a randomised trial standard chemotherapy plus bevacizumab showed a small benefit over standard chemotherapy alone in terms of progression-free survival. However, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum.

Dosing information

Bevacizumab 5mg/kg or 10mg/kg given once every 2 weeks, or 7.5mg/kg or 15mg/kg given once every 3 weeks.

Product availability date

25 January 2008

Summary of evidence on comparative efficacy

The manufacturer of bevacizumab has asked that SMC consider the regimen including bevacizumab in combination with capecitabine and oxaliplatin (B-Cape Ox) only, and has submitted clinical and economic data for this regimen compared with fluorouracil plus folinic acid plus oxaliplatin (FOLFOX-4).

Bevacizumab is a recombinant humanised monoclonal IgG1 antibody that binds to human vascular endothelial growth factor (VEGF), inhibiting its binding to receptors on endothelial cells and thereby neutralising the physiological activity of VEGF. This reduces development of blood vessel within tumours and inhibits tumour growth.

A phase III open label study recruited adult patients with an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1 and a histologically confirmed adenocarcinoma of colon or rectum with metastatic disease (mCRC) not previously treated. Patients were randomised to oral capecitabine plus intravenous (IV) oxaliplatin (Cape Ox, n=317) every 3 weeks or fluorouracil IV plus folinic acid IV plus oxaliplatin IV (FOLFOX-4, n=317) every 2 weeks (see the cost table for relevant comparators for complete regimens). Following randomisation of 634 patients the open label study was amended to include a 2x2 partially blinded design. Bevacizumab 7.5mg/kg or placebo IV was added to Cape Ox (B-Cape Ox [n=350] or P-Cape Ox [n=350]) and bevacizumab 5mg/kg or placebo IV was added to FOLFOX-4 (B-FOLFOX-4 [n=349] or P-FOLFOX-4 [n=351]).

The first of the two co-primary endpoints was the non-inferiority of FOLFOX-4 regimens (FOLFOX-4 / B-FOLFOX-4 / P-FOLFOX-4) versus Cape Ox regimens (Cape Ox / B-Cape Ox / P-Cape Ox) for progression free survival (PFS); non-inferiority was concluded if the upper limit of the 97.5% confidence interval (CI) for the hazard ratio was ≤ 1.23. The second co-primary endpoint was superiority of bevacizumab plus chemotherapy (B-FOLFOX-4 / B-Cape Ox) over placebo plus chemotherapy (P-FOLFOX-4 / P-Cape Ox) for PFS. Superiority was concluded if $p \leq 0.025$ for the difference between treatments. The Intention to Treat (ITT) population was used for the superiority analyses and the Eligible Patient Population (EPP), which excludes patients from the ITT population who had violated major protocol inclusion and exclusion criteria or who did not receive at least one dose of study medication, for the non-inferiority analysis. Secondary endpoints included overall survival (OS).

Cape Ox regimens were non-inferior to FOLFOX-4 regimens (Hazard Ratio [HR] 1.05, 97.5% CI 0.94 to 1.18) in terms of PFS. Bevacizumab plus chemotherapy (n=699) was superior to placebo plus chemotherapy (n=701); the median PFS was 9.4 months versus 8.0 months (HR 0.83, 97.5% CI 0.72 to 0.95,).

In treatment subgroup comparisons the median PFS for B-FOLFOX-4 and P-FOLFOX-4 was 9.4 and 8.6 months respectively (HR=0.89, 97.5% CI 0.73 to 1.08) and for B-Cape Ox and P-Cape Ox was 9.3 and 7.4 months respectively (HR=0.77, 97.5% CI 0.63 to 0.94).

There was a trend for OS being longer for the chemotherapy plus bevacizumab group compared with the chemotherapy plus placebo group although the difference was not significant; (median OS 21.2 months versus 19.9 months; HR 0.89, 97.5% CI 0.76 to 1.03,).

A second study comparing FOLFOX-4 (n=292) versus FOLFOX-4 + bevacizumab (n=293) versus bevacizumab (n=244) for second-line use in patients with advanced or metastatic colorectal cancer has been conducted and is included for completeness. This phase III, randomised, open-label, multi-centre study recruited adult patients with a histologically confirmed adenocarcinoma of the colon or rectum with metastatic disease, an ECOG PS of 0 to 2 and previously treated with a fluoropyrimidine-based and irinotecan-based regimen. The doses of drugs used in the FOLFOX- 4 regimen are as described previously. The dose of bevacizumab was 10mg/kg every 2 weeks and patients were treated until disease progression. The primary efficacy endpoint was duration of survival (DS), defined as the time from randomisation to death from any cause. All reported deaths were included in the analysis. DS was significantly longer for patients in the FOLFOX-4 + bevacizumab arm compared with patients in the FOLFOX-4 arm (13.0 months versus 10.8 months, stratified HR = 0.751 [95% CI 0.63 to 0.89]).

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

Summary of evidence on comparative safety

Grade 3/4 adverse events (AEs) that were more common in the bevacizumab plus chemotherapy groups compared with the placebo plus chemotherapy groups include; diarrhoea (17% versus 15%), palmar-plantar erythrodysesthesia (PPE) also known as hand-foot syndrome (7.1% versus 3.4%), venous thromboembolic events (7.8% vs. 4.9%) and hypertension (3.7% versus 1.2%). Grade 3/4 AEs that were more common for Cape Ox / P-Cape Ox groups compared with FOLFOX-4 / P-FOLFOX-4 groups include diarrhoea (20% versus 11%) and hand-foot syndrome (6.1% versus 1.2%). Grade 3/4 neutropenia was more common for FOLFOX-4 / P-FOLFOX-4 (44%) than Cape Ox / P-Cape Ox (7.0%) treated patients.

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

Summary of clinical effectiveness issues

In the pivotal trial all patients had an ECOG PS of ≤1 and were relatively young. This compares to Cancer Registry data from patients in Scotland in 2004 where 73% and 59% of patients diagnosed with colorectal cancer were aged at least 65 years and at least 70 years respectively. It is possible that the benefits observed with bevacizumab in the pivotal trial may be different to those observed in the Scottish population eligible for treatment.

The B-Cape Ox regimen, which includes capecitabine given orally, may offer an advantage over other chemotherapy regimens for mCRC that contain drugs administered solely by the intravenous route by allowing changes to service delivery.

The licensed doses for the indication under review are bevacizumab 5mg/kg or 10mg/kg given once every 2 weeks, or 7.5mg/kg or 15mg/kg given once every 3 weeks. In the first

trial the doses of bevacizumab studied were 7.5 mg/kg every 3 weeks (with Cape Ox) and 5 mg/kg every 2 weeks (with FOLFOX-4). In the second trial the dose of bevacizumab was 10 mg/kg every 2 weeks. The efficacy of the higher dose in first-line use and the lower dose in second-line use has not been studied.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing treatment with bevacizumab, capecitabine and oxaliplatin (B-Cape Ox) with fluorouracil, folinic acid, and oxaliplatin (FOLFOX-4) in patients with mCRC. A lifetime time horizon was used in the model and the clinical data source was the pivotal phase III clinical trial. Parametric survival analysis was used to extrapolate beyond the end of the Kaplan Meier data from the RCT. The manufacturer estimated a cost per QALY of £25,806 based on an increased cost of £3,568 and a QALY gain of 0.138.

The submission focused specifically on patients receiving first-line combination therapy and the comparison between B-Cape Ox and FOLFOX-4. The pivotal clinical trial also included a treatment arm where patients received bevacizumab plus FOLFOX (B-FOLFOX-4). However the manufacturer stated that a preliminary economic analysis of B-FOLFOX-4 compared with FOLFOX-4 showed that it was unlikely to be cost-effective; therefore this comparison was not included in the submission.

The issues relating to the choice of comparator were as follows:

- Expert replies from Scottish cancer centres indicate that current treatment for the majority of patients is Cape Ox. Therefore, FOLFOX-4 does not appear to be the treatment most likely to be replaced in Scotland. A comparison with Cape Ox would have been more appropriate.
- Patients currently receiving IV fluorouracil within the FOLFOX-4 regimen rather than oral capecitabine within the Cape Ox regimen may do so for a clinical reason due to the different toxicity profile and for this reason such patients may be unsuitable for treatment with B-Cape Ox.

The significance of this for the cost per QALY is that the cost of bevacizumab was largely offset by savings of £7k in drug administration and pharmacy costs from switching from IV fluorouracil to oral capecitabine. If this switch would not happen in practice then these savings would not be realised. Expert replies indicated that the shift from IV fluorouracil to oral capecitabine has largely already happened in Scotland.

Based on the choice of comparator the manufacturer has not presented a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Beating Bowel Cancer
- Bowel Cancer UK

Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) published technology appraisal 118, *bevacizumab and cetuximab for the treatment of metastatic colorectal cancer*, in January 2007. NICE advised that bevacizumab in combination with 5-fluorouracil plus folinic acid, with or without irinotecan, is not recommended for the first-line treatment of metastatic colorectal cancer. This guideline predates the change in indication that is currently being considered by SMC.

The NICE technology appraisal 93, *irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer* was published in August 2005. NICE recommended the use of irinotecan in combination with 5-fluorouracil and folinic acid as first-line therapy, and irinotecan alone in subsequent therapy as well as the use of oxaliplatin in combination with 5-fluorouracil and folinic acid as first-line or subsequent therapy.

The NICE technology appraisal 61, *guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer* was published in May 2003. Oral therapy with either capecitabine or tegafur with uracil (in combination with folinic acid) is recommended as an option for the first-line treatment of metastatic colorectal cancer.

A guideline titled *diagnosis and management of colorectal and anal cancer*, with an expected date of issue to be confirmed, is listed on the NICE website.

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 67, *management of colorectal cancer; a national clinical guideline* in March 2003. A review report in 2007 indicated that the guideline requires revision in the light of new evidence.

Additional information: previous SMC advice

After review of a full submission the Scottish Medicines Consortium (SMC) issued advice on 9 January 2006 that bevacizumab (Avastin) is not recommended for use within NHS Scotland in combination with intravenous fluorouracil/folinic acid or intravenous fluorouracil/folinic acid/irinotecan for first-line treatment of patients with metastatic carcinoma of the colon or rectum. Bevacizumab, in combination with standard regimens containing fluorouracil and folinic acid or fluorouracil, folinic acid and irinotecan, improved overall and disease-free survival times compared to these standard regimens. However the economic case has not been demonstrated. The licence holder has indicated their decision to resubmit.

After review of a re-submission the Scottish Medicines Consortium (SMC) issued advice on 12 June 2006 that bevacizumab (Avastin) is not recommended for use within NHS Scotland in combination with intravenous fluorouracil/folinic acid or intravenous fluorouracil/folinic acid/irinotecan for first-line treatment of patients with metastatic carcinoma of the colon or rectum. Bevacizumab, in combination with standard regimens containing fluorouracil and folinic acid or fluorouracil, folinic acid and irinotecan, improved overall and disease-free survival times compared to these standard regimens. However, the economic case has not been demonstrated.

Additional information: comparators

NICE has recommended a number of different regimens for mCRC or advanced CRC including capecitabine, tegafur/uracil plus folinic acid, oxaliplatin/fluorouracil/folinic acid and irinotecan/fluorouracil/folinic acid. Experts, consulted by SMC regarding current treatment strategies for mCRC, suggested that Cape Ox, FOLFOX-4, and fluorouracil alone are being used in Scotland.

Cost of relevant comparators

Name of regimen	Dose regimen (where D1 = Day 1)	Cycle length	Cost per cycle (£)	Cost per 6 months (£)
B-Cape Ox	**Bevacizumab 7.5mg/kg IV D1 Oxaliplatin 130mg/m^2 IV D1 Capecitabine 1000mg/m^2 orally twice daily D1 to 14**	**3 weeks**	**2,484**	**19,872**
FOLFOX-4	Fluorouracil 400mg/m^2 IV bolus, 600mg/m^2 IV infusion D1, 2 Folinic acid 200mg/m^2 IV infusion D1, 2 Oxaliplatin 85mg/m^2 IV infusion D1	2 weeks	955	12,415
Cape Ox	Oxaliplatin 130mg/m^2 IV D1 Capecitabine 1000mg/m^2 orally twice daily D1 to 14	3 weeks	1074	8592
IFL, Saltz	Fluorouracil 500mg/m^2 IV D1, 8, 15, 22 Folinic acid 20mg/m^2 IV D1, 8, 15, 22 Irinotecan 125mg/m^2 D1, 8, 15, 22	6 weeks	1552	6208
Roswell Park	Fluorouracil 500mg/m^2 IV D1, 8, 15, 22, 29, 36 Folinic acid 500mg/m^2 IV D1, 8, 15, 22, 29, 36	8 weeks	1781	5343
-	Tegafur/uracil 100mg/m^2 / 224mg/m^2 three times daily D1 to 28 Folinic acid 30mg three times daily D1 to 28	5 weeks	929	4,645
-	Capecitabine 1250mg/m^2 orally twice daily D1 to 14	3 weeks	310	2,480
De Gramont	Fluorouracil 400mg/m^2 IV bolus, 600mg/m^2 IV infusion D1, 2 Folinic acid 200mg/m^2 IV D1, 2	2 weeks	295	3,835
Mayo	Fluorouracil 425mg/m^2 IV D1 to 5 Folinic acid 20mg/m^2 IV D1 to 5	4 weeks	110	660

Doses are for general comparison and do not imply therapeutic equivalence.
Costs obtained from BNF no 54 (September 2007) and eVadis (030308).
Costs are based on a body weight of 80kg and a body surface area of 1.8m^2. Costs per 6 months are the costs of compete cycles which would be administered during a 26 week period.

Additional information: budget impact

The manufacturer estimated a net budget impact of £493k in year 1 rising to £1.13m in year 5 based on 158 patients eligible for treatment in year 1 rising to 360 in year 5. The manufacturer assumed a 35% uptake in year 1 and 80% in year 5. These budget impact figures include drug acquisition and administration costs. The net drug budget impact alone would be expected to be considerably higher.

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.

This assessment is based on data submitted by the applicant company up to and including 18 April 2008.

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.

** 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/*

The undernoted reference was supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

Cassidy J, Clarke S, Diaz-Rubio E et al. First efficacy and safety results from XELOX-1/NO16966, a randomised 2 x 2 factorial Phase III trial of XELOX vs. FOLFOX4 + bevacizumab or placebo in first-line metastatic colorectal cancer (MCRC). Ann Oncol. 2006; 17: Abstract LBA3

European Medicines Agency. Assessment report for Avastin: Procedure No. EMEA/H/C/000582/II/0014. received 050308