National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Bevacizumab in combination with paclitaxel and carboplatin for the first-line treatment of ovarian cancer

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from **Southampton Health Technology Assessment Centre (SHTAC)** to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by **5pm** on **1st November 2012** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

29th October 2009

Issue 1 Current clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	SHTAC response
Page 8 and throughout report The report makes a number of erroneous references to current clinical practice which suggest that "In clinical practice bevacizumab is given to patients with Stage III residual disease only which is a subset of patients within the key trial."	It should be made clear that most CDF listings for bevacizumab in this indication specify patients with FIGO Stage III and IV disease.	The current wording suggests a more restricted patient population and is not reflective of clinical practice in England as observed in the CDF listings. The CDF listings reflect the population for which clinicians have requested bevacizumab over the past 10 months.	The SHTAC comment was informed by our local clinical expert. No action (not a factual error).

Issue 2 Treatment duration

Description of problem	Description of proposed amendment	Justification for amendment	SHTAC response
Page 8 and throughout the report. The ERG is mistaken in thinking that the economic evaluation of GOG-0218 limits treatment with bevacizumab to 12 months. "The treatment duration used within the model has been underestimated by using a maximum of one year, rather than 15 months as stated in the Summary of Product Characteristics (SPC) for bevacizumab and for the GOG-0218 trial, and therefore the cost of bevacizumab has been underestimated."	This assertion, and all references to related amendments of the economic evaluation, should be removed from the report.	We provided the survival curve for these patients on page 164 of our submission (Fig 22) which makes it clear that the duration of treatment for patients randomised to bevacizumab in GOG-0218 is based on observations from the trial.	The ERG refers the manufacturer to the GOG-0218 model, Bevacizumab + Chem! Worksheet, cells u59-u70 which clearly show no cost for bevacizumab after 12 months. No action (not a factual error).

Issue 3 Use of CA-125 in UK clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	SHTAC response
Page 16 and throughout the report. "The ERG notes, however, that CA-125 measurement is commonly used in the UK for disease progression. "	The assertion that alternative data for PFS should be used to establish clinical and cost effectiveness should be removed from the report.	In GOG-0218 CA-125 alone could be used to indicate progression and cause a change of therapy. Although CA-125 is commonly monitored in the UK, it is rarely used on its own to determine a change of therapy. In general in the UK therapy is changed only when disease progression is confirmed by imaging or clinical symptoms. This has been confirmed through discussions with a panel of clinical experts.	The SHTAC comment was informed by our local clinical expert. No action (not a factual error).

Issue 4 Use of external patient characteristics

Description of problem	Description of proposed amendment	Justification for amendment	SHTAC response
Page 34. The ERG claims the following: "No explanation is provided for why the patient characteristics used in the model were not taken from the GOG-0218 trial."	This sentence should be removed from the report.	We explain (in Section 7.5.5.2 of the manufacturer submission) our rationale for using an external source for patient characteristics relating to dosing calculations and show that the mean weight of patients in GOG trial was 10kg more than mean weight of UK patients. We also include a full sensitivity analysis on this assumption.	No action. (This sentence is not a factual error.)

Issue 5 Inclusion of inoperable patients

Description of problem	Description of proposed amendment	Justification for amendment	SHTAC response
Page 35. The ERG states that this population may not be fully within the scope because it includes a group of inoperable patients.	This sentence should be removed from the report.	Neither the scope of the decision problem, nor the licensing authorisation, specify that patients needed to have had surgery to be eligible for treatment with bevacizumab.	The ERG notes that one of the inclusion criteria for the licensing trial (GOG-0218) was '1-12 weeks after debulking surgery' and that there could be an implicit assumption that patients would have had surgery. Also bevacizumab is licensed in combination with paclitaxel and carboplatin as chemotherapy usually after surgery. No action (interpretation not a factual error).

Issue 6 Critique of PFS curves in the economic model

Description of problem	Description of proposed amendment	Justification for amendment	SHTAC response
Page 36 "A gamma model provided the best fit to the treatment arm, while a log-logistic model provided the best fit to the comparator arm (MS section 7.3.1.1, Table 40, p.135)."	It should be clarified that we state in the submission that the gamma model provides the best statistical fit to the data.	The report's current wording is ambiguous.	This is a useful clarification. No action required as not a factual inaccuracy.

Issue 7 Sensitivity analyses of PFS curves

Description of problem	Description of proposed amendment	Justification for amendment	SHTAC response
Page 37 "The MS examines a gamma model in a deterministic sensitivity analysis for which results are presented (MS table 63, p.186) and discussed (MS section 7.7.10, p.192)."	It should be clarified that we explored both log-logistic and gamma model for PFS in deterministic sensitivity analyses.	The report's current wording implies only one parameter curve was explored in our sensitivity analyses.	This is a useful clarification. No action required as not a factual inaccuracy.

Issue 8 Quality assessment of ICON7

Description of problem	Description of proposed amendment	Justification for amendment	SHTAC response
Page 51. With regards to unexpected imbalances in drop-outs between groups (table 15), the ERG states that: "Proportionally more patients in the CPB7.5+ arm than in the CP arm were withdrawn from treatment (26.2% and 9.8%, respectively, MS p76). Reasons are not provided for all patient withdrawals in the MS, but are provided in the trial paper.1. The MS states that the proportion of patients withdrawn due to insufficient therapeutic response or death was higher in the CPB7.5+ arm than in the CP arm (12.8% of patients in the CPB7.5+ arm and	We suggest that this is re-written to reflect the fact that the imbalances in drop-outs are not unexpected in an un-blinded study without a placebo control and with prolonged maintenance therapy.	These imbalances in safety data are not 'unexpected' in a study without a placebo control and with prolonged maintenance therapy. We discuss this on page 113 of our submission.	This is a useful clarification. There are imbalances in drop-outs between groups and whether these are unexpected is a matter of interpretation. No action (not a factual error).

2.4% of patients in the CP arm; one patient in the CPB7.5+ arm died and two patients in the CP arm died). The trial paper shows that more patients in the CPB7.5+ arm than in the CP arm withdrew due to an AE or intercurrent illness. This was adjusted for by use of ITT analyses of the PFS and OS outcomes.”			