National Institute for Health and Clinical Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Breast cancer - bevacizumab with a taxane (1st line)

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from *CRD and CHE Technology Assessment Group, University of York,* to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 5pm, *27th May 2010* 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.

20th May 2010

Issue 1 Use of bevacizumab in clinical practice in the UK

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On the final paragraph of page 15 and in Table 15 on the top of page 66, it is stated that bevacizumab in combination with docetaxel wasn't formally considered despite being used in clinical practice in the UK.	Roche can confirm that bevacizumab in combination with docetaxel is not used in UK clinical practice.	This represents a factual inaccuracy.	Clinical advice to the ERG suggests that bevacizumab is not used in the NHS Yorkshire Cancer Network, but may be used in trusts or private practices elsewhere. The ERG does not have access to information that would confirm or refute the manufacturer's assertion that bevacizumab in combination with docetaxel is not used in UK clinical practice. However, the reasons to critique the exclusion of this regimen are still valid as this regimen was defined to be of interest in NICE's scope for the current evaluation. Consequently, the following change in wording has been made: p.15 "Specifically, bevacizumab in combination with docetaxel, and q3w paclitaxel were not formally considered despite being used in clinical practice in the UK. " should read "Specifically, bevacizumab in combination with docetaxel, and q3w paclitaxel were not formally considered despite the latter regimen being used in clinical practice in the UK." Table 15 "Not all relevant interventions (as defined by the scope and clinical practice) have been compared in the model." should read "Not all relevant interventions (as defined by the scope) have been compared in the model."

Issue 2 Patent expiry date of branded docetaxel

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
It is stated that the patent for docetaxel is soon to expire (May 2010). This appears on P. 16, 74, 82, 90, 102. The basic patent for docetaxel (EP 0 253 738) expires 26 November 2010. There is a high probability that a paediatric extension will be granted so that that the patent expires on 26 May 2011.	May 2010 should be removed and replaced by May 2011, or to reflect the uncertainty in this date, it could simply be stated that the patient is expected to expire in the next year.	This is an inaccuracy which should be corrected. The impact on the appraisal is that the potential for price decreases on docetaxel in the immediate future is not as large a concern as it is originally considered in the ERG report.	The manufacturer notes that the basic patent is going to expire in November 2010. Because the extension was not yet granted, the ERG will change the report to reflect the expiry date of the basic patent. **Erratum:** Page16, 74, 82, 90,102. "May 2010" should read "November 2010"

Issue 3 Selection of utility values for the base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 16, 55, 72 and 90, it is stated that the selection of utilities for the model seemed arbitrary.	Utility values were selected in accordance with the utility values used to inform NICE Clinical Guideline 81 (for Advanced Breast Cancer).	This provides further clarity for the utility values used in the base case analysis. (similarly, this is how the supportive care resource utilisation assumptions were determined).	The ERG does not consider that this sentence is inaccurate. The ERG knows that the values used are in accordance with previous clinical guidelines. However, it is unclear why the literature review was not used to inform the parameter values, and instead a specific study was selected.

			No amendment to be made.

Issue 4 Disregard of the analysis provided against paclitaxel monotherapy q3w (provided in the clarification response)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG highlights on several occasions (p.20 (x2), 50, and 117) that the manufacturer excluded paclitaxel monotherapy q3w from the evidence synthesis and model. However, this was provided in response to the clarification questions.	These statements should be adjusted to reflect the evidence synthesis and cost-effectiveness estimates were provided by the manufacturer upon request by the ERG.	This reflects a factual inaccuracy. It is also inconsistent within the text of the ERG report which highlights information provided from the clarification response throughout, however it ignores that this analysis against paclitaxel q3w was conducted.	The ERG has explicitly detailed in the beginning of Section 5 (page 47) that this Section would focus only in the initial manufacturer submission. It is in Section 6.1 that the ERG describes and critique's the additional work undertaken by the manufacturer following the request for clarifications. We have thus clearly acknowledged the manufacturer's evaluation of the use of paclitaxel monotherapy q3w in the report. No amendment to be made.

Issue 5 Inaccuracy in the text regarding toxicity of docetaxel versus paclitaxel

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the table summarising the manufacturer's economic evaluations (Table 4; page 48) in the Comparators row, it is stated that "PAC q3w was stated to be less effective and more toxic than PAC q1w".	In the MS, PAC q3w was stated as less effective as PAC q1w. However, the issue of toxicity was discussed in context of the comparison against docetaxel (DOC) q3w. Therefore this wording should be corrected.	No significant impact on the analysis or interpretation as this inaccuracy appears only in the description of the analysis.	**Erratum**: Page 48. "and PAC q3w was stated to be less effective and more toxic than PAC q1w." should read "and PAC q3w was stated to be less effective than PAC q1w."

Issue 6 PSA for duration of treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Table 14, on page 64, it is stated that the duration of treatment (extrapolated using a Weibull function) was not subject to uncertainty. This was an oversight by Roche when reporting the PSA parameters in the MS. These parameters were included in the PSA. The ERG is also aware of this as they have duplicated a table (Table 19) on page 75 reporting the duration of treatment resulting from running the PSA.	For the model variable – Duration of Treatment – it should be stated that this was subject to uncertainty and the parameters were varied in the PSA.	This is a factual inaccuracy due to incomplete reporting on behalf of the manufacturer.	**Erratum**: Page 64, Table 14, rows regarding the duration of treatment with PAC and with BEV. "Not considered uncertain" should read "Considered uncertain"

Further erratum

Section 6.2.4, Page 96. This error was identified by the ERG after the report was sent for consultation. The ERG report stated that the MS had not calculated the hazard ratios correctly. The hazard ratios in the MS are correctly calculated in accordance with the Bucher method. Therefore the following text (and cross reference on p.29) should be deleted from the ERG report:

"the hazard ratios are incorrectly calculated in the MS analysis. The MS calculated the mean hazard ratio (HR) according to the formula $E(HR) = \exp(\mu)$, where HR is assumed to take a lognormal distribution $\log(HR) \sim Normal(\mu,\sigma^2)$. This formula in fact estimates the median HR, not the mean. The correct formula is $E(HR) = \exp(\mu+\sigma^2/2)$. The difference can be substantial when the standard error is large. Fourth,"