[redacted]

Friday 23rd April 2010

[redacted]
Midcity Place
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BY E-MAIL

Re: Single Technology Appraisal – Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer

Dear [redacted]

Please find below our responses to the ERG clarification question 14.

We hope this feedback helps clarify the issues raised by the ERG. If you require any further clarification or information then please do not hesitate to contact us.

Yours sincerely,

[redacted]

B14. Please report the following:

- **The mean number of chemotherapy cycles (and SE) in the E2100 study for each treatment in each arm**

- **Descriptive statistics from the E2100 study reporting the proportion of patients receiving 0,1,2,3,4,5,… chemotherapy cycles for each treatment in each arm**

- **The mean number of cycles assumed in the economic model for each treatment of each regimen**

From the clinical study report, chemotherapy cycles and standard errors are reported by treatment arm only (therefore an aggregate mean chemotherapy cycle is provided for the Bev/Pac arm, not separately for Bev and Pac in the combination arm). It has only been possible to report the proportion of patients receiving 0,1,2,3,4,5 cycles by thirds (i.e. 1-3, 4-6, etc) as this is how it was reported within the CSR.

For the economic model, the number of cycles was not explicitly calculated but, for the purposes of the table below, cycles have been assumed to occur as per the E2100 protocol, that is, every 28 days from the beginning of the model. Thus the average number of cycles can be calculated based on the mean number of months of treatment (see Table 12 Mean time to off treatment provided in months in response to clarification question B4).

Table 1. Details on cycles of treatment by arm

Cycles received per patient	PAC (n=342)	PAC/BV (n=358)
Mean (SE) from E2100	6.8 (0.3)	10.8 (0.4)
Median from E2100	6	10
Proportion receiving the following cycles		
1–3	117 (34.2%)	57 (15.9%)
4–6	89 (26.0%)	70 (19.6%)
7–9	66 (19.3%)	48 (13.4%)
10+	70 (20.5%)	183 (51.1%)
Mean number of cycles calculated from economic model		
bevacizumab (based on 7.83 mths of treatment)	NA	8.51
paclitaxel (based on 5.35 or 7.16 mths of treatment)	5.82	7.78

We have also provided a similar breakdown below based on mean doses received. This additional information may provide improved granularity on the differences, with 3 doses of paclitaxel and 2 doses of bevacizumab provided in each cycle. Similarly, these figures are not explicitly required for the economic model but can be calculated based on the mean number of months of treatment.

Table 1. Details on doses of treatment by arm and treatment

Doses received per patient	PAC (n=342)*	PAC/BV (n=358)*	
		PAC	BV
Mean (SE) *	19.6 (0.8)	27.4 (0.9)	20.1 (0.7)
Median *	17	24	18
Range *	1 − 74	1 − 97	1 − 76
25th−75th ile *	9 − 27	14 − 40	10 − 30
Economic model (calculated from 5.35, 7.16, 7.83 months of treatment, respectively)	17.4	23.3	17.0

* non- Expanded Participation Project (EPP) patients receiving drug from the clinical study report

The economic model, which utilises a parametric extrapolation of treatment duration, assumes a smaller number of administrations (doses) than that reported within the clinical study. The rationale for this difference is partly due to the algorithm used to determine time to off treatment. This was provided in Section 7.2.1.2 of the Roche submission and reproduced below:

> To model actual and projected dose observed in the clinical trial by means of parametric extrapolation, it was necessary to develop an algorithm to either censor patients or to code patients as having had an event where "an event" was defined as:
>
> - Having not completed the protocol therapy due to disease progression,
> - Dying due to the disease,
> - Having been taken off drug prior to disease progression due to unacceptable toxicities, or
> - Refusing further treatment whilst not yet experiencing disease progression.
>
> Patients were censored if:
> - they were still considered progression free and on the protocol specified study drug at the time of the data cut-off (21 OCT 2006), or
> - they died for other than disease related reasons.
>
> To be consistent with the definition of progression free survival, this "time to off treatment" was calculated as the time from randomisation until censoring or experiencing an event.

By using this algorithm, a number of administrations which occurred in the clinical study after patients entered the post progression period have been removed. As post progression costs and outcomes are modelled under separate assumptions in order to minimise any potential confounding due to difference in post progression treatment, this was considered a reasonable approach.

It is worth noting that progression in our analysis is as defined by the independent review facility (IRF) using radiologic evidence to detect changes in tumour size. Therefore, if the investigator believed a patient was still progression-free they would continue to administer treatment (and this would be collected in the clinical study report), but if the IRF states the patient had already progressed at this point, then our algorithm would ignore this administration as the 'event' would have already occurred.