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[redacted]

16 March 2009

Dear [redacted]

Trabectedin for the treatment of advanced metastatic soft tissue sarcoma

The Evidence Review Group (School of Health and Related Research, University of Sheffield) and the technical team at NICE have now had an opportunity to review the submission document and economic model submitted by PharmaMar.

There are a number of issues relating to the clinical and cost effectiveness data on which we are seeking clarification at this stage.

The ERG have specified key issues for clarification, referring to the submission where applicable. These points for clarification are provided in sections labelled A–C of this clarification letter. Included in the clarification are requests to:

- provide further description of the identification and selection of evidence for the submission;
- confirm confidentiality status of trial data;
- provide further explanation, access to patient level data and specified re-analyses of the economic evaluation.

Both the ERG and the NICE technical team will be addressing these points in their reports. As there will not be any consultation on these reports prior to the Committee Meeting you may want to address the points below and provide further discussion from your perspective at this stage.

We request you to provide a written response to this letter to the Institute by 17:00, **30 March 2009**.

Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

If you present data that are not already referenced in the main body of your submission and that data are seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

If you have further queries on the technical issues raised in this letter, please contact Whitney Miller or Ruaraidh Hill. Procedural questions should be addressed to Jeremy Powell in the first instance.

Regards

Meindert Boysen
Associate Director - Appraisals
Encl. checklist for in confidence information

A: Literature search

Ref	Clarification Point
A1	Please provide a search strategy for the clinical effectiveness searches in MEDLINE, EMBASE and COCHRANE.
A2	Please explain the choice to search MEDLINE and EMBASE together via EMBASE.com, rather than to search each separately. Please clarify whether EMBASE.com can ensure consistency when mapping MeSH terms to EMTREE terms? Please clarify whether searching EMBASE and MEDLINE separately give the same results minus MEDLINE duplicates as searching EMBASE.com?
A3	Searching conducted by the ERG on EMBASE alone provided 521 results searching for 'Trabectedin' as an index term and a free text term, whereas in the submission it states 360 results when searching both MEDLINE and EMBASE for this term (on EMBASE.com). Please provide details of the limits used to yield only 360 results.
A4	Some index terms are used where no index term exists on EMBASE, for example 'Yondelis' and 'soft part sarcoma'. Please explain the choice of these terms.
A5	Please explain why searching on MEDLINE was omitted. MEDLINE *in process* is a core database to search for the clinical effectiveness evidence.

B: Confidentiality status

Ref	Clarification Point
B1	Please note that some study details provided in the submission (referenced from the clinical study reports) are only available in the Academic-in-Confidence paper, not the published abstracts or EMEA documents (notably TTP rates at 3 months and 6 months). Please confirm the status (AIC, CIC or not confidential) of these data. (It is noted that Figure 2 is marked as 'In Confidence').

C: Economic evaluation

Ref	Clarification Point
C1	The model currently assumes a body surface area (BSA) of 1.7 m^2. Please use the BSA observed in study STS-201. If this information is not available, please use referenced sources. In addition, please explore the impact of BSA in one-way sensitivity analysis and in the probabilistic sensitivity analyses (PSA).
C2	Transition probabilities in the model are based on survival curves. It is assumed that

Ref	Clarification Point
	the survival curves were estimated independently please confirm whether this is the case. Please provide the rationale for not maintaining the correlation between these outcomes and, if it is not possible to undertake this analysis, give an indication of the likely effect on the incremental cost-effectiveness ratio.
C3	It is noted that the extrapolation of the survival curves has been carried out using Weibull functions. Please confirm whether any other statistical forms (for example, gompertz or log-logistic) were tested. It is noted that visually the Weibull appears a reasonable fit. Please provide details of the patient level data if possible.
C4	A key concern is the potential non-comparability between patients in the treatment and BSC arms. It is noted that the populations may not be comparable, since the treatment arm includes only patients with liposarcomas and leiomyoscarcoma, while the BSC arm includes other sarcoma types (and treatment was shown to be more effective in the L-sarcoma population. Further to that, page 63 of the submission indicates that patients are less severely affected (in terms of the WHO performance status) in the treatment arm than in the BSC arm. Please re-analyse taking measures to address population comparability and provide details and results of these re-analyses.
C5	It is unclear why only hospitalisations due to nausea and vomiting were included. In the submission, it is stated that almost 47% of patients develop grade 3/4 neutropenia and other severe adverse events. Please consider the cost and utility impact of all events graded 3/4, regardless of whether they were associated with hospitalisation, and please make explicit the sources of these data.
C6	In the submission it states that outcomes are half-cycle corrected, but this does not appear to be correct. Please review and clarify.
C7	It appears that it has been assumed that all treatment costs occur at baseline (which overestimates the treatment cost). Please apply the treatment costs based on the schedule observed in the trial.
C8	For patients in the progression-free state treated with trabectedin, the model assumes that no costs are involved. The omission of follow-up costs may have been driven by the fact that these apply to both the treatment and best supportive care arms; however, it is suspected that where there are differences in the mortality rates, this approach may underestimate the costs associated with treatment. Please provide details of the patient cost data.
C9	Please clarify the mean dosage considered in the model per BSA. Currently the model assumes a mean dosage of 1.22 mg/m^2, based on trial data. However, it is likely that this value was calculated not taking into account the potential wastage (that is, open vials that were not used completely). Please provide the mean number of vials (of both sizes) used by patients within the STS-201 study.

Ref	Clarification Point
C10	Some inconsistencies between the report and the model have been noted. The submission states the *mean* number of cycles, while the model reports the *median* number of cycles. Please clarify which is correct.
C11	In the submission it is assumed that utilities for lung cancer are a good proxy for the utilities in STS patients. The model assumes that the utilities remain constant over time. It is felt that this is unlikely, as in lung cancer, the quality of life generally decreases with time for individuals in the progressive state. Please provide validation of the assumption used, and explore the impact of varying utilities on the incremental cost-effectiveness ratio in sensitivity analyses,
C12	Please provide clarification on how the cost for the progressive state was estimated.
C13	The references appear to be incorrect. Please review and correct referencing for ease of understanding.