14th January 2010

NHS
National Institute for
Health and Clinical Excellence

NICE
Midcity Place
71 High Holborn
London
WC1V 6NA

Dear [redacted]

Re: Single Technology Appraisal – Mifamurtide for osteosarcoma

The Evidence Review Group (School of Health and Related Research [ScHARR], University of Sheffield) and the technical team at NICE have now had an opportunity to take a look at submission received on the 10th December by Takeda UK. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the PAS and the cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports, and you may want to respond to the points raised 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, 28th January 2010**. 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.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in red, and all information submitted under 'academic in confidence' in yellow.

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

Yours sincerely

[redacted]
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on cost effectiveness data

Patient access scheme (PAS)

A1. **Priority Question**: Please provide a copy of the PAS as submitted to the Patient Access Scheme Liaison Unit at NICE.

A2. **Priority Question**: Please clarify the following details of The PAS

I. At present it appears that in the model a patient would receive unlimited free vials of mifamurtide after completing 38 doses, however in the submission it appears that a patient would receive 10 free vials of mifamurtide after completing the 38 doses. Please clarify the number of free vials of mifamurtide provided through the PAS.

II. Please confirm that no administration charges for the PAS have been incorporated.

A3. **Priority Question**: Clinical advice suggests that often patients who develop complications may be treated at their local hospital which might provide logistical problems in administering the PAS scheme. Please amend the economic model to allow a variable administrative cost per mifamurtide dose to be incorporated.

A4. Often patients recruited to RCTs are healthier and/or more compliant with medication than those seen in clinical practice. If the patients seen in UK clinical practice were significantly less healthy or less compliant with medication, fewer patients would receive more than 38 doses. This would affect the effect of the PAS scheme on the cost effectiveness. Please comment on this hypothesis and provide evidence relating the severity of the condition in patients in the trial to that observed in routine practice.

Economic model

A5. **Priority Question**: There appears to be a discrepancy with the face validity of the model. The base case used in the new submission is associated with a survival rate of 77% without mifamurtide and 83% with mifamurtide; however, the data from the trial give these values to be 70% and 78% respectively. This suggests that the model does not produce the survival rates from the trial that it is simulating. Please provide an explanation as to why this happens in the model and why it may be justifiable.

A6. **Priority Question**: There appears to be a discrepancy between the report of the health economic model in the new submission and the model itself. The submission discusses the relative risk of events associated with mifamurtide use. However the Excel model does not use relative risks but appears to use raw data (presumably from the relevant trials). It is currently unclear which dataset has been used. Please provide a full description of the data used in the Excel model and its source. This is particularly pertinent to the use of Beta trees where the variables used within the model (S1 to S6) have not been defined.

A7. **Priority Question**: With respect to the Beta Trees, a number of issues have been identified:

I. There appears to be no uncertainty associated with a transition probability where all patients remained in the same state. Ideally an uninformative prior would be used to allow the possibility of transitions to other states. Please consider including an uninformative prior to incorporate the uncertainty in the economic model.

II. The modelled population due to reside in S4 from S2 have been reapportioned between disease free and recurrence in the ratio of [those that stay in S2 +those that moved to s5 or S6]: [those that were to have moved to S1 or S3]. This ratio appears subjective. Please provide justification for this ratio and an exploration of its effects.

III. Those that have a recurrence but were supposed to move into S4 have been reapportioned between progressed disease and disease free in the ratio of [Recurrence with liver metastases * (1-Surgical Remission with lung metastases) + Recurrence without liver metastases * (1-Surgical Remission without lung metastases): Recurrence with liver metastases * (Surgical Remission with lung metastases) + Recurrence without liver metastases * Surgical Remission without lung metastases). This ratio appears subjective. Please provide justification for this ratio and an exploration of its effects.

A8. The following issues have been identified relating to the Excel model:

I. Please update the model with the most recent version of the life tables available.

II. Please clarify whether cell E278 of the 'ME-No_Mepact' worksheet j25 should be j27. In addition, please confirm whether the reference to cell BY218 is redundant or is a mistyped cell reference.

III. Please confirm whether the use of j43 in the 'ME-Mepact' worksheet Cells E278 and F278 is now redundant or whether they are mistyped cell references.

IV. Please confirm that the distributions used in the PSA relate to the uncertainty in the average costs for the procedure rather than the range of individual observations.

V. Please clarify why no uncertainty was assumed around the disutility of hearing loss.

VI. The AgeUtil parameter does not appear to be used correctly and it appears to square the utility of a person. Please clarify the purpose of this functionality.

VII. Deaths in the Post-Recurrence Disease Free States (Column DA of the 'ME-Mepact' and 'ME-No_Mepact' Worksheets) automatically have a half cycle correction. Please clarify why the remaining parameters have the option for half cycle correction not to be undertaken.

VIII. The formula used to calculate the discount factor is incorrect as (cycle number / 2) incorrectly assumes that the duration of the first cycle was

0.5 years rather than 0.75. Please correct the formula in the economic model.

IX. Please clarify why, in column CV in the 'ME-Mepact' and 'ME-No_Mepact' worksheets, the part of the formulae that deal with half cycle correction is omitted, even though this is contained in the other columns for transitions.

X. It is unclear why from the 'ME No_Mepact' worksheet cycle 1 (cell e280) onwards for the costs of disease progression there is a reference to the transition rate between Progressed Disease and Progressed Disease. Please clarify whether this was meant to refer to the costs of hearing loss.

XI. Please confirm whether cell F39 in the Drug Costs Worksheet should be 38 (as was used in the model base case).

XII. Please confirm whether cell D29 in the Mortality Worksheet should be 2 (as was used in the model base case).

XIII. Please confirm whether cell D12 in the Utility Worksheet should be 0.85 (as was used in the model base case).

XIV. The maximum and median ICER on the 'PSA Calcs' worksheet is incorrect as 'dominated' values are excluded. Please consider the inclusion of dominated values.

Model inputs and assumptions

A9. **Priority Question**: Please explain why the 'other model assumptions' contained in 3.9.6 (page 30 of the new submission) are not deemed to be part of the base case analyses.

A10. The number of Mepact Doses (Column D of the 'Drug Cost' Worksheet) are all integers. Please confirm whether the raw data was used to calculate these numbers. If not, please provide an explanation

A11. Please clarify the number of patients who may need more than 1 vial (page 37 of the new submission). Please also confirm whether this occurrence has been included within the model, and if necessary justify why these additional costs have been excluded.

Utility values

A12. Please clarify whether the multiplication factor of 75/85 used to adjust utility values in Table 3.4 (page 20 of the new submission) is still appropriate given that the utility of the disease-free state has been increased from 0.75 to 0.85. It may be the case that in Table 3.4 the utility for disease progression was initially reduced from 0.44 to 0.39, but now needs to be reset to 0.44.

Probabilistic sensitivity analysis

A13. **Priority Question**: The cost effectiveness of treatment in the probabilistic sensitivity analyses has not been presented as a summary cost per QALY value. Such an estimate is required as it produces a more accurate estimation

of mean cost effectiveness in the presence of non-linear models. The calculation of this value in the 'PSA Calcs' worksheet (Cell P8) is incorrect as it uses the mean of the individual ICERs rather than the formula of mean incremental cost / mean incremental QALYs. Please provide the ICER derived from the PSA for all combinations of regimen type.

Reporting of results

A14. **Priority Question:** Please confirm that the base case results compare regimens A/B with regimens A+/B+.

A15. **Priority Question:** Please provide estimates for regimen A compared with regimen A+, which may be more representative of UK practice.

A16. Please provide all relevant ICERs for the pooled chemotherapy regimens and the individual regimens included within the model (incorporating the requested amendments contained in this document).

A17. Please clarify the number of patients who may receive more than 1 vial (page 37 of the new submission) and whether this occurrence has been included within the model.

A18. Table 3.1 (page 16 of the new submission) indicates that anomaly 5 strongly favours no mifamurtide whereas anomaly 6 favours mifamurtide. This appears to contradict the results in Table 3.9 (page 24 of the new submission) where the combination of anomaly 5 and anomaly 6 result in an increased ICER. Please explain the reason for this apparent discrepancy.

A19. For completeness, please add the results for anomaly 2 and anomaly 3 to Table 3.9 (page 24 of the new submission) and disaggregate anomaly 5 and 6.

A20. Please explain why the 6-month mortality rates quoted on page 17 of the new submission are assumed to apply until the end of the time horizon.

A21. Please clarify whether it is a coincidence that the values in Tables 3.6 and 3.7 (pages 21 to 22 of the new submission) rise by 5 in both tables as the range of the number of doses is increased (which implies in Table 3.7 that all additional doses of mifamurtide beyond 40 were associated with additional outpatient visits).

A22. Please clarify whether the raw data from the trial were used in Table 3.7.

Section B: Textual clarifications and additional points

B1. Please confirm that Figure 3.1 (page 16 of the new submission) is correct. There appears to be a large number of variables where the lower bound is not below the value produced by the deterministic analysis.

B2. Please confirm that the values reported in the text of 3.9.3 (page 26 of the addendum) correspond with values in Figure 3.1 (page 16 of the new submission).

B3. Please provide the rationale for not incorporating ‘other model assumptions’ (contained in 3.9.6) within the base case.

B4. Please clarify why in Table 4.1 (page 35 of the new submission) the potential population falls even though the total UK population is increasing.

B5. Please clarify whether the labels on tables 4.1 and 4.2 (page 35 of the new submission) should read ’48 doses’ or ‘38.4 doses’. Please also explain why the values in these tables differ from the previous submission.

B6. It appears that an assumption has been made that all patients have resectable osteosarcoma but no account has been taken for those patients with resectable primary tumours e.g. of the pelvis or vertebra or those with craniofacial tumours, for whom there is no evidence that mifamurtide is appropriate. Please provide the justification for the assumption.

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