MIFAMURTIDE FOR OSTEOSARCOMA:

ADDENDUM CRITIQUING THE REVISED SUBMITTED ECONOMIC MODEL INCORPORATING A PATIENT ACCESS SCHEME

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This report should be referenced as follows:

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List of abbreviations

CEAC	Cost effectiveness Acceptability Curve
CI	Confidence Interval
ERG	Evidence Review Group
ICER	Incremental Cost Effectiveness Ratio
MS	Manufacturer's Submission
NICE	National Institute for Health and Clinical Excellence
PAS	Patient Access Scheme
PSA	Probabilistic Sensitivity Analyses
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial

1 SUMMARY

1.1 Scope of the submission [a]

The manufacturer's submission (MS) generally reflects the scope of the appraisal issued by the National Institute for Health and Clinical Excellence (NICE), and is appropriate to the NHS. The majority of the MS reflects the use of mifamurtide in individuals with osteosarcoma who have undergone surgical resection; however, it does not reflect the broader population outlined in the NICE scope (individuals with osteosarcoma related to Paget's disease, individuals with metastatic disease and individuals with relapsed osteosarcoma). The MS defines the intervention as mifamurtide as an add-on treatment to post-operative multi-agent adjuvant chemotherapy (3- or 4- agent adjuvant chemotherapy using high dose methotrexate, doxorubicin, cisplatin with/without ifosfamide). The decision problem defines the population and the intervention in relation to the proposed licensed indication (mifamurtide is indicated as a combination therapy with post operative multi-agent chemotherapy in children (from two to 12 years), adolescents (from 12 to 18 years) and young adults for the treatment of high-grade resectable, non-metastatic osteosarcoma after macroscopically complete surgical resection), a more tightly defined group than that stated in the NICE scope. The MS considered post-operative multi-agent chemotherapy as the most relevant comparator, as reflected in the scope. The outcome measures identified in the scope were all relevant and included overall survival, disease-free survival, adverse effects and health related quality of life. The results provided are presented in terms of cost per quality adjusted life year (QALY) with a time horizon of 60 years with the perspective of costs taken from an NHS and Personal Social Services perspective.

[a] Copied from the original ERG submission. The ERG note that the population in the scope not evaluated in the submission are outside of the marketing authorisation.

1.2 Summary of submitted clinical effectiveness evidence [b]

- The evidence in the submission is derived from one head-to-head, phase III, four-arm (Regimen A, methotrexate, doxorubicin and cisplatin; Regimen A+, Regimen A plus mifamurtide; Regimen B, methotrexate, doxorubicin, cisplatin and ifosfamide; Regimen B+, Regimen B plus mifamurtide), multi-centre, randomised, open-label, active controlled, two by two factorial design (INT-0133) trial comparing mifamurtide in addition to multi-agent chemotherapy (Regimens A+ and B+) with multi-agent chemotherapy alone (Regimens A and B) in individuals with high grade, resectable, non metastatic osteosarcoma (primary analysis). Additional supplementary data (requested by the Evidence Review Group (ERG)) also compared individual mifamurtide containing regimens (Regimen A+) to chemotherapy regimens most commonly used in the UK (Regimen A).

- The results of the randomised controlled trial (RCT) suggest that after a median follow up of 7.9 years, the addition of mifamurtide to multi-agent chemotherapy (Regimens A+ and B+ combined) increased overall survival (hazard ratio, 0.72; 95% CI, 0.53 to 0.97; p=0.0313) and disease-free survival (hazard ratio, 0.78; 95% CI, 0.61 to 1.01; p=0.0586) in patients (less than 30 years age) with high grade, resectable, non metastatic osteosarcoma compared with chemotherapy alone (Regimens A and B combined). Additional post hoc analysis that compared the addition of mifamurtide to Regimen A (Regimen A+) with chemotherapy alone (Regimen A) showed non-significant improvements in overall survival (hazard ratio, 0.75; 95% CI, 0.49 to 1.16; p=0.1949) and disease-free survival (hazard ratio, 0.96; 95% CI, 0.67 to 1.38; p=0.8357).

- Although the adverse event profile was generally similar in those receiving mifamurtide (in combination with multi-agent chemotherapy) compared with those receiving multi-agent chemotherapy alone, more mifamurtide recipients discontinued treatment prematurely (the

[b] Copied from the original ERG submission

statistical analysis comparing the rates of discontinuation between the treatment groups were not reported in the MS or in the requested supplementary data). Although no reasons were given, the MS assumes that many parents withdrew subjects (or patients withdrew) from mifamurtide treatment since it was an investigational drug of unproven benefit and was uncomfortable or inconvenient when added to an existing multi-agent chemotherapy.

1.3 Summary of submitted cost effectiveness evidence

- The decision analytic model structures and assumptions are based on Markov model methodology, which is an appropriate modelling strategy for the problem outlined in the submission.

- The functionality to conduct probabilistic sensitivity analyses (PSA) is contained within the mathematical model. The analyses undertaken by the ERG show that the results from the PSA are slightly favourable to mifamurtide, although often the manufacturer reports the deterministic results in preference. The manufacturer's base case cost per QALY is £56,683, which assumes that efficacy is calculated from Regimen A+/B+ compared with Regimen A/B. The cost per QALY increases to £130,814 if Regimen A+ is compared with Regimen A and falls to £36,913 when Regimen B+ is compared with Regimen B. Besides these subgroups the discount rate used for outcomes was shown to markedly influence the cost per QALY.

1.4 Commentary on the robustness of submitted evidence [c]

Strengths

- The MS conducted adequate systematic searches for clinical- and cost-effectiveness studies of mifamurtide for the treatment of osteosarcoma. It appears unlikely that any additional trials would have met the inclusion criteria had the search been widened to include conference proceedings.

[c] Partially copied from the original ERG submission

- The RCT is of reasonable methodological quality (with some limitations), and measured a range of outcomes that are as appropriate and clinically relevant as possible.

- The submitted mathematical model incorporates the major health states for patients with osteosarcoma, who may or may not receive mifamurtide in a RCT setting. Following the ERG clarification questions and subsequent amendment of the model, the model is unlikely to have coding issues that would materialistically alter the cost effectiveness of mifamurtide in the context of the Patient Access Scheme (PAS) in place on the 12th of February 2010, where the first 7 vials of mifamurtide is provided free.

Weaknesses

- The processes undertaken by the manufacturer for data extraction and applying quality criteria to included studies are not explicitly clear in the MS. These factors limit the robustness of the systematic review.

- The ERG has substantial concerns regarding the selection of the base case. Where there appears to be a debate on parameters that should be entered into the model, (for example, which is the most appropriate comparator; whether the effects of hearing loss should be incorporated; whether general population mortality rates should be used if a patient has five years without recurrence; whether amputation or limb salvage costs should be used; whether age-related utilities should be used and whether 100% of patients should start the model in disease free state) the manufacturer has chosen the option most favourable to mifamurtide. As a result, the base case incremental cost effectiveness ratio (ICER) is likely to be substantially greater than that reported, particularly if it were considered that the efficacy results from comparing regimen A+ with regimen A were the most appropriate to UK clinical practice.

- The ERG has concern regarding the lack of face validity of the model. The modelled survival rates are greater than the observed data with

increases in the range of 3-4 percentage points. It is not known whether this discrepancy favours or disfavours mifamurtide but is likely to increase the uncertainty in the results.

Areas of uncertainty

- Although it is probable that the addition of mifamurtide to multi-agent chemotherapy (Regimens A+ and B+ combined) increases overall survival and disease-free survival compared with multi-agent chemotherapy alone (Regimens A and B combined), the size of the actual treatment effect of mifamurtide is uncertain, given the trial design limitations (open label design, delayed adminstration and failure to receive mifamurtide after randomisation, imbalance of histological response to neoadjuvant therapy and disparity of survival events in the subset of patients who did not enter the maintenance phase) and the interpretation of the statistical analyses (wide confidence intervals (CI) with similar point estimates for efficacy). The clinical advice provided to the ERG indicated that it is likely that a more clinically relevant assessment for a UK population would be derived from an analyses comparing Regimen A+ with Regimen A. The mathematical model submitted by the manufacturer also estimates that, on average, a patient being treated with Regimen A would accrue more QALYs at a lower cost than a patient receiving Regimen B.

- Importantly, the addition of mifamurtide to multi-agent chemotherapy may be substantially reduced if it is assumed that Regimen A represents current UK practice hold, rather than a combination of Regimen A and Regimen B.

- There is uncertainty associated with the ICER due to the patients being grouped based on the number of doses received, with the midpoint of the range used in the model. For example, patients who had received between 21 and 25 doses were assumed homogenous and all assumed to have 23 doses. If the true average number of doses was 22.1 the costs of mifamurtide would be overestimated; conversely if the average number of doses was 23.7 the costs would

be underestimated. It is unclear why the manufacturers did not use the raw data to calculate the ICER, although the inaccuracy is unlikely to be substantial.

- It is unclear whether the loss of hearing observed when mifamurtide was added to chemotherapy regimens is representative of actual events or whether these were chance events associated with cisplatin use.

1.5 Key issues

The lack of clarity around whether the clinical evidence from the RCT used in the MS should be pooled according to mifamurtide/non-mifamurtide treatment is a major issue.

The main drivers of the ICERs are:

- The choice of treatment regimens, which lead to markedly different estimates of effectiveness.
- The rate of hearing loss assumed to be associated with the addition of mifamurtide to a current chemotherapy regimen.
- Whether all patients begin the model in the 100% disease free state, whether age-related utilities are employed and whether mortality rates reduce to that associated with the general population after 5-years without recurrence.

These elements combine to introduce substantial variability in the model outputs and consequently raise the level of uncertainty considerably. This uncertainty is increased due to the fact that the raw data was not used to calculate the ICER, with a midpoint of a band preferred instead.

2 BACKGROUND

This document was written in response to a re-submission from the manufacturer following the incorporation of a PAS. In the interim period a new economic model was constructed to provide information regarding the estimated ICER of mifamurtide, which was also submitted to the ERG. This model was coded in Microsoft Excel (© Microsoft Corp) in contrast to the initial model that was constructed in TreeAge (© TreeAge Software Inc). The model was reviewed (by a different person to that who reviewed the initial model) and clarification questions were sent to the manufacturer. The manufacturer's response was provided in a supplementary document (Takeda Clarification Response), and a number of changes were made to the economic model in response to the ERG clarification questions. The manufacturer's re-submission was concerned solely with the estimation of the ICER associated with the use of mifamurtide and excluded any additional details on the expected clinical effectiveness. Accordingly, this report will not critique the clinical effectiveness and the reader is referred to the initial ERG report. Clinical issues will be discussed only when they have direct implications for the resultant ICER, for example, in discussing whether the efficacy for mifamurtide is best represented by the pooling of Regimens A+ and B+ compared with Regimen A and B, or whether the efficacy from Regimen A+ compared with Regimen A is more appropriate.

The PAS initially proposed was subsequently altered to allow doses to be provided free to the NHS at the beginning rather than the end of the patient's simulated treatment. This had the effect of reducing the manufacturer's base case deterministic ICER from £58,246 in the re-submission to £56,683.

The ERG comment that in the final version of the model supplied to the ERG on the 5th of February 2010, the mathematics concerning the initially proposed PAS is incorrectly coded, and thus the previous model is required to verify these results. However, for clarity, the ERG will concentrate its ultimate critique of the robustness of the presented cost per QALY assuming that the latest PAS (7 free doses at the start of treatment) is accepted.

2.1 Critique of manufacturer's description of underlying health problem

Refer to the original ERG report.

2.2 Critique of manufacturer's overview of current service provision

Refer to the original ERG report.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF THE DECISION PROBLEM

Refer to the original ERG report.

4 CRITIQUE OF CLINICAL EFFECTIVENESS DATA

Refer to the original ERG report.

5 ECONOMIC EVALUATION

5.1 Overview of manufacturer's economic evaluation

Natural history

The major disease stages of osteosarcoma have been identified and modelled via health states representing Disease Free, Recurrence, Post Recurrence Progressed Disease, Post Recurrence Disease Free and Death.

Treatment effectiveness within the submission

The decision analytic model structure is based on Markov model methodology, which is an appropriate modelling strategy for the problem outlined in the submission provided that the model is correctly populated and the time horizon is appropriate.

The probabilities of moving between health states were taken from the transitions observed within the trial for 604 patients who entered the maintenance phase. However, the estimated probabilities of survival at six 6 years differ between the model and that observed within the trial. The manufacturer has attempted to explain the discrepancy in their response to the clarification questions (contained in the response to question A5 in the Takeda Clarification Response document); however, the ERG is not satisfied with these reasons. If the length of the time cycles produce an answer that does not match the known data, then a more appropriate duration for the time cycle should be chosen. The explanation provided regarding patients who were censored because of a recurrence is unclear, the ERG would expect that patients with a recurrence that are retained in the model would have a greater mortality rate. The ERG believe that it is more likely that the cause of the discrepancy is the subjective redistribution of patients who entered states not contained within the model (see clarification question A7 in the Takeda Clarification Response document). The ERG is not satisfied with the justification for the redistribution which appears to be only that this was how the original model was constructed. Whilst the lack of face validity is a cause of uncertainty, it is unclear in which direction the ICER would move were the mortality rates observed in the RCT replicated in the model.

Following a recommendation by the ERG, the model includes uninformative priors where all the patients remained in the same state. This allows uncertainty to be incorporated in the PSA and is welcomed; although no justification was given for the value of the uninformative prior used (0.1).

The base case model assumes a 60 year time-horizon which is appropriate as there are survival differences between those patients who received mifamurtide and those that did not. However, due to the trial being constrained to a shorter time length (12.25 years) it is necessary to extrapolate transition probabilities beyond this time point. Whilst the ERG does not believe that the method used is incorrect it is noted that there will be some uncertainty in the estimated ICER over the 60-year time horizon.

The rate of limb salvage used in the manufacturer's model (75%) is based on UK rates which are slightly higher than the rates in the INT-0133 trial (64%). However, this rate does not vary appreciably across treatment arms, so that the impact on cost effectiveness estimates should be minimal.

Health related quality of life

The original ERG report describes in detail the potential limitations of the utility estimates used within the model; these are not repeated here due to the small impact utility effects have on the ICER (see Table B1 in the Takeda Clarification Response document). The ERG additionally believe that the utility values used in the model are internally inconsistent as the value for progressed disease was estimated based on the value of the disease free state, which was increased in the new model. However, the ERG agrees that there is minimal impact on the ICER if the suggested values are used (see clarification question A12 in the Takeda Clarification Response document).

It is commented that there is no uncertainty associated with the disutility of hearing loss, which is fixed at a value of 18% of the underlying utility. Given the arbitrary (and incorrect) Gamma distributions (see Resources and Costs section) assigned to costs within the model, there appears no reason not to investigate the uncertainty in hearing loss. However, the ERG does not

believe that this would noticeably alter the ICER, but would increase the level of uncertainty in this value.

The model only includes the adverse events associated with infusion, which are associated with a relatively minor cost (£1.65) but no disutility, within the base case. A clear, and statistically significant, difference between hearing-loss rates in the primary trial (15% for mifamurtide arms versus 8% for non-mifamurtide arms) was omitted. The reasons for this omission based on clinical advice that the most likely cause is the platinum-based treatment (cisplatin) in the combination therapy (MS, Section 7.2.7.4, p74), and that the rates were consistent with current evidence. While the ERG recognises that this serious adverse event is known to be associated with platinum-based treatment, it is not clear that the observed data should be ignored with the base case assuming no hearing loss. The model allows the effects of including hearing loss to be incorporated as a sensitivity analysis. Incorporating a greater incidence of hearing loss associated with mifamurtide treatment increases the ICER.

Resources and costs

The uncertainty in the costs of resources has been assumed to be a Gamma distribution with the assumption that the distribution had the same standard error as the mean. The ERG believes that this is incorrect for calculating the average cost, which should be used in the model. This is illustrated by using the cost for an MRI scan, which has a mean value of £241, but is varied within the PSA and can take values for the mean of £20 or £700. Given the number of MRI scans undertaken per year, it is not plausible that the average cost could be so far from the reported £241. Whilst this is an error, the impact of costs is not marked (as will be shown in the results section) and the associated increase in uncertainty due to inappropriate distributions is not expected to be large.

Discounting

A discount rate of 3.5% per annum was used in accordance with the NICE base case.[1] Other discount rates for utility were explored by the manufacturer, which noticeably changed the resultant ICER, although the ICER was

insensitive to the discount rate for costs. Using a discount rate of 0% for utility decreased the manufacturer's base case cost per QALY to £22,254; using a discount rate 6% for utility increased the manufacturer's base case cost per QALY to £92,806.

Sensitivity analyses

The manufacturer conducted a serious of one-way sensitivity analyses on their base case results (Fig 2.1 contained within Takeda UK Submission of Evidence 080210). This showed that the model was sensitive to the discount rates used for outcomes.

Model validation

The ERG notified the manufacturer of suspected coding errors (n>5) within the model. With the exception of one, which the ERG agree was originally correct, the manufacturer concurred that these represented errors and amended the model. The ERG is satisfied that the final model reasonably represents the calculations that the manufacturer wished to perform, with the largest limitation being the lack of face validity. The ERG note that there are errors in the final model relating to the old PAS, but that these are not relevant to the critique of the new PAS.

5.2 Critique of approach used

The following is a summary of the approach used:

- The Markov model methodology is an appropriate modelling strategy for the problem outlined in the submission. The methodology applied provides a fair assessment of the cost effectiveness of mifamurtide, but is limited in that the model does not estimate the same results as that observed in the trial.

- The various identified parameters used in the model are generally appropriate estimates of the modelled quantities. However, the calculation of average costs for resources such as an MRI scan is inappropriate, as the average can vary dramatically. Modifications

made by the ERG to adjust for this error show that it has little impact on the ICER.

- The base case assumptions selected by the manufacturer generally favoured mifamurtide (and consistently reduced the ICER). As a result, the ICER presented by the manufacturer (a deterministic value of £56,683) represents an optimistic evaluation of mifamurtide

5.3 Results included in manufacturer's submission

A description of the analyses undertaken by the manufacturer were provided to the ERG on February 8th 2010, and are contained in the supplementary document (Takeda Submission of Evidence 080210).

The ERG ran analyses on the 6th and 7th of February 2010, and where these were also run by the manufacturer, the deterministic results were identical and the PSA results similar. Key results provided by the manufacturer are given in Table 1. For clarity, the assumptions used to populate the manufacturer's base case are listed:

- Efficacy taken from Regimens A+/B+ combined compared with Regimens A/B combined
- All patients starting in the disease free state
- No amputation or limb salvage costs
- Hearing loss adverse events excluded
- Mortality risk reverting to that of the general population after a determined time in the disease free state not included
- Age related utility weights not included
- Discount Rates of 3.5% per annum for both costs and outcomes
- PAS employed

Table 1: Key results provided by the manufacturer.

Scenario	Cost Per QALY (£) (Deterministic : PSA)
Manufacturer's Base Case (MBC) as detailed above	56,683 : 54,830
MBC but no PAS	68,734 : Not Reported
MBC but Regimen A+ compared with Regimen A	130,814 : Not Reported
MBC but Regimen B+ compared with Regimen B	36,913 : 35,181
MBC but discount rate for outcomes set to 0% per annum	22,262 : Not Reported
MBC but discount rate for outcomes set to 6% per annum	92,806 : Not Reported
MBC but amputation and limb salvage costs included	59,231 : Not Reported
MBC but hearing losses possibly associated with mifamurtide incorporated	71,065 : Not Reported
MBC but the mortality rate of the general population used for patients who had been disease free for 5 years	61,580 : Not Reported
MBC but age-related utility values applied	62,112: Not Reported
'Most pessimistic' scenario	91,442: Not Reported

The manufacturer defined their 'most pessimistic' scenario as their base case with the following alterations: amputation and limb salvage costs were included; hearing losses possibly associated with mifamurtide incorporated; the mortality rate of the general population used for patients who had been disease free for 5 years and age-related utility values applied. The ERG comment that this may be a misnomer as the cost per QALY when regimen A+ is compared with regimen A is greater than that for the 'most pessimistic' scenario.

It is commented that the final mathematical model has calculation errors in calculating the results with the initially proposed PAS (where any vials over 38 were free) and that the previous model would be needed if these results were considered of interest.

The manufacturer's base case is summarised in Table 2. For ease of reference this Table also indicates with which parameters the ERG have undertaken sensitivity analyses and a set of parameters that the ERG would consider to be a plausible base case.

Table 2 Describing the manufacturer's base case, the sensitivity analyses undertaken by the ERG and the ERG base case

Manufacturers base case	Sensitivity analyses performed by the ERG (using the functionality of the supplied model unless stated)	ERG base case	Reason for difference, where appropriate, between the two base cases.
Calculation method is deterministic	This was altered to a probabilistic approach.	Calculation method is probabilistic.	A probabilistic approach. provides a better estimation of the ICER in non-linear models
Efficacy data assumed to be that from Regimens (A+/B+) compared with Regimens (A/B)	Efficacy data used only from Regimen A+ compared with Regimen A	Efficacy data used only from Regimen A+ compared with Regimen A	Clinical advice indicates that Regimen A is most predominantly used in the UK. Additional evidence is contained within the manufacturers model, which estimates that Regimen A dominates Regimen B.
No differential rate in hearing loss associated with mifamurtide use.	The differential rate in hearing loss associated with mifamurtide use observed in the trial was used.	No differential rate in hearing loss associated with mifamurtide use.	Not appropriate, although as this issue is a matter of genuine debate, sensitivity analyses were performed on the ERG base case
The assumption that all patients would enter the model in the disease free state	The assumption (as observed in the trial) that 0.66% of patients would enter with progressed disease.	The assumption that all patients would enter the model in the disease free state	Not appropriate, although this may be favourable to mifamurtide.
That the utilities assumed for	That the utilities assumed for	That the utilities assumed for	It is implausible that a patient in the disease

Manufacturers base case	Sensitivity analyses performed by the ERG (using the functionality of the supplied model unless stated)	ERG base case	Reason for difference, where appropriate, between the two base cases.
each health state are independent of age.	each health state were dependent of age.	each health state were dependent of age.	free state at the age of 75 would have the same utility as a 25 year old in the same state.
That the mortality rate of a patient with osteosarcoma is always greater than that of the general age-matched population.	That if a patient is disease free for a period of 5 years the mortality rate equals that of the age-matched population	That if a patient is disease free for a period of 5 years the mortality rate equals that of the age-matched population	Clinical advice provided to the ERG indicates that if patients have lived for 5 years within the disease free state their prognosis would be similar to patients who have not experience the disease.
That costs associated with limb salvage and amputation are not included in the model.	That costs associated with limb salvage and amputation are not included in the model.	That costs associated with limb salvage and amputation are not included in the model.	Costs associated with the disease under consideration should be incorporated within the model.
That all patients only require 1 vial per dose.	That 8% of patients would require 2 vials per dose.	That 8% of patients would require 2 vials per dose.	Clinical advice given to the ERG suggests that over 8% of patients would have a surface area of > $2m^2$ which would require a second vial.
That the PAS is correctly applied,	1) That the PAS is not used	That the PAS is correctly applied, however it is likely that an	It is unlikely that the PAS could be employed without administrative charges.

Manufacturers base case	Sensitivity analyses performed by the ERG (using the functionality of the supplied model unless stated)	ERG base case	Reason for difference, where appropriate, between the two base cases.
without administrative charge.	2) That a cost of administering the scheme would be incurred	administrative charge would be incurred.	An indication of the increase in ICER per £1000 per patient is provided.
That the true average number of doses can be represented by a midpoint taken from patients banded into categories (0-5 vials, 6-10 vials etc)	That the true average may differ from the banded midpoint (either by an extra dose per category or one fewer dose)	That the true average number of doses can be represented by a midpoint taken from patients banded into categories (0-5 vials, 6-10 vials etc)	Not appropriate. However, without the raw data on the number of doses given to each patient the ERG cannot provide a more accurate estimate.
That the uncertainty in the average cost of inputs could be very large (using inappropriate Gamma formulae)	That there is no uncertainty in the average costs of input	That the uncertainty in the average cost of inputs could be very large (using inappropriate Gamma formulae)	Not appropriate. Whilst theoretically incorrect the effect on the ICER was minimal.

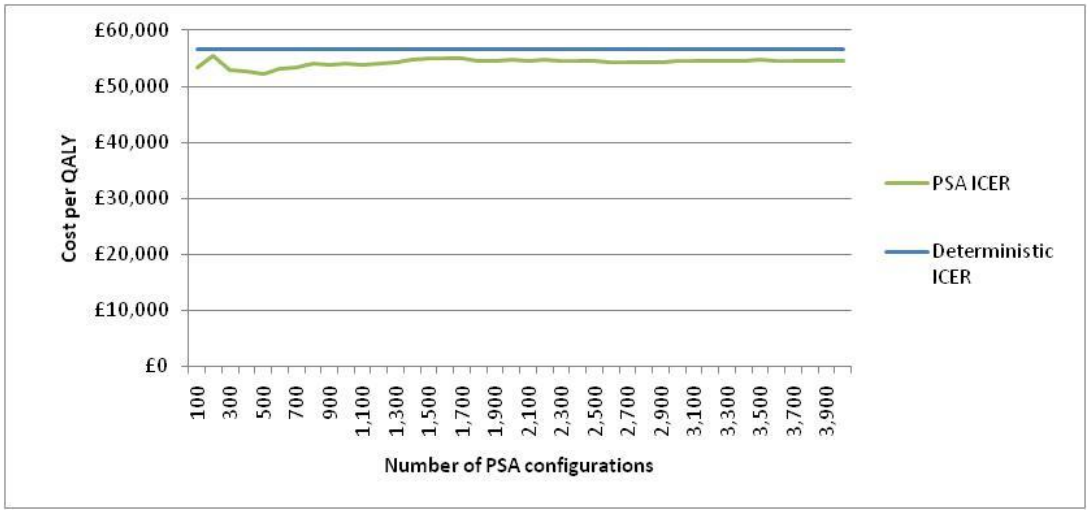
6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Additional sensitivity analyses

Note that these analyses were performed in the interim period between the model being delivered to the ERG (5th February 2010) and the final manufacturer's submission (8th February 2010) in order to meet the ERG deadline of 12th February 2010 for submission to NICE. The manufacturer's submission contains a number of these analyses, but this section has been left unaltered, to show that these results are identical for the deterministic analyses and very similar for results generated by the PSA.

The ERG initially determined an appropriate number of PSA parameter configurations to undertake. The manufacturer's base case was used and the number of PSA configurations plotted against the estimated ICER. This plot is shown in Figure 1.

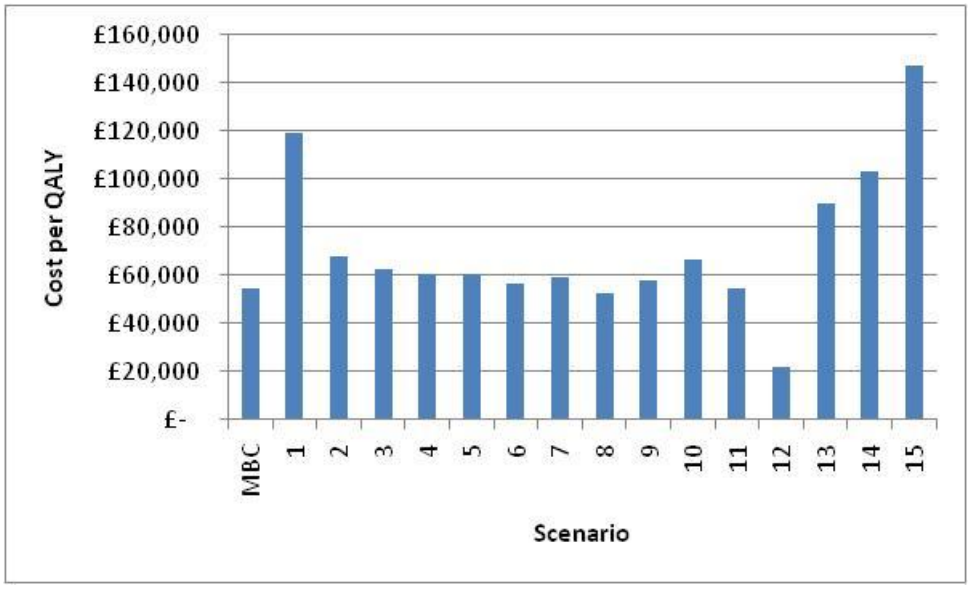
Figure 1 Comparing the ICER with the number of PSA runs undertaken



It appeared that a stable cost per QALY had been obtained when 4,000 parameter configurations were undertaken and this was used in the ERG PSA results. The computational time required was in the order of 5-15 minutes dependent on the processing speed of the computer used. In the manufacturer's submission 10,000 parameter configurations were used.

The results from the sensitivity analyses conducted by the ERG are shown in Table 3 and depicted graphically in Figure 2.

Figure 2 The cost per QALY values calculated by the ERG in sensitivity analyses



The scenarios are fully described in Table 2. All sensitivity analyses, (excluding that where the discount value for outcomes is set to 0%) increase the cost per QALY compared with the manufacturer's base case.

However, there is interactaction between the parameters, and the ERG base case (scenario 14), which combines scenarios 1,4,5,6 and 7, has a cost per QALY below scenario 1 alone. This interaction was between scenarios 1 and 5, where only patients with regimen A and A+ were analysed, and the mortality rates set to that of age-matched general population if the patient was disease free for 5 years. In this instance the cost per QALY was reduced to £90,327; the reason for this interaction is unclear.

Note that these numbers do not include administration costs, which increase the cost per QALY by £74 for every £100 spent per person in the manufacturer's base case and by £129 for every £100 spent per person in the ERG base case.

Additionally these sensitivity analyses do not attempt to adjust for the lack of face validity of the model, where the modelled results do not equate to those observed in the trial that it was trying to represent. More discussion on this has been provided in the ‘Treatment effectiveness within the submission’ of this report.

Table 3 The results from the ERG's sensitivity analyses

Scenario Code	Scenario Description (see Table 1 for more information)	Deterministic ICER (£)	Probabilistic ICER (£)	Proportion of PSA runs where ICER below £25,000	Proportion of PSA runs where ICER below £50,000	Proportion of PSA runs where ICER below £100,000
MBC	Manufacturer's base case (MBC)	56,638	54,516	1%	42%	82%
1	MBC, but efficacy data used only from Regimen A+ compared with Regimen A.	130,814	118,946	1%	17%	45%
2	MBC, but effects of observed hearing loss rates included	71,065	67,994	0%	27%	71%
3	MBC, but 0.66% of patients start in the progressed disease state	65,187	62,705	0%	32%	75%
4	MBC, but utilities dependent on age	62,112	60,704	0%	33%	79%
5	MBC, but mortality rates set to that of age-matched general population if the patient was disease free for 5 years.	61,580	60,637	0%	33%	80%
6	MBC, but limb salvage costs and amputation included.	59,231	56,863	1%	39%	80%

Scenario Code	Scenario Description (see Table 1 for more information)	Deterministic ICER (£)	Probabilistic ICER (£)	Proportion of PSA runs where ICER below £25,000	Proportion of PSA runs where ICER below £50,000	Proportion of PSA runs where ICER below £100,000
7	MBC, but an assumption that 8% of patients would require 2 vials	61,148	59,447	0%	34%	80%
8	MBC, but midpoints used to calculate number of vials used are decreased by one	54,996	52,732	1%	45%	83%
9	MBC, but midpoints used to calculate number of vials used are increased by one	58,370	57,762	1%	38%	79%
10	MBC, but PAS excluded	68,734	66,730	0%	25%	75%
11	MBC, but cost inputs are assumed fixed	56,683	54,830	1%	42%	81%
12	Discount Rate for benefits set to 0%	22,262	21,753	59%	87%	94%
13	Discount Rate for benefits set to 6%	92,806	90,038	0%	5%	57%
14	ERG base case	109,296	103,494	0%	13%	48%
15	ERG base case but the observed rates of hearing loss incorporated	164,202	147,494	0%	7%	36%

7 DISCUSSION

7.1 Summary of clinical effectiveness issues[d]

The manufacturer's submission to NICE includes a systematic review of the clinical-effectiveness literature and narrative reporting of a single RCT that met the inclusion criteria of the review (INT-0133 trial). The ERG has two main areas of concern relating to clinical effectiveness issues in the manufacturer's submission; first, the limited evidence base and its relevance to the NHS, and second, the interpretation of the included RCT. Whilst the submitted evidence generally reflects the decision problem as defined in the manufacturer's submission, it is not totally representative of all patients with osteosarcoma in the UK (e.g. individuals with metastatic disease, recurrent disease, older patients and osteosarcoma related to Paget's disease or other primary sites), although these patients are outside of the intervention's marketing authorisation. The submitted evidence consists of the only published RCT concerning mifamurtide and as such may be helpful for answering some questions concerning osteosarcoma treatment that will impact on the NHS. The MS states that after a median follow up of 7.9 years the addition of mifamurtide to multi-agent chemotherapy (Regimens A+ and B+ combined) increased overall survival (hazard ratio, 0.72; 95% CI, 0.53 to 0.97; p=0.0313) and disease-free survival (hazard ratio, 0.78; 95% CI, 0.61 to 1.01; p=0.0586) in patients (less than 30 years age) with high grade, resectable, non metastatic osteosarcoma compared with chemotherapy alone (Regimens A and B combined). It is likely that a more clinically relevant assessment for a UK population would be derived from an analysis comparing individual mifamurtide containing regimens (Regimen A+) to chemotherapy regimens most commonly used in the UK (Regimen A). This additional post hoc analysis (requested by the ERG) that compared Regimen A+ with Regimen A showed a non-significant improvement in overall survival (hazard

[d] Partially copied from the original ERG report

ratio, 0.75; 95% CI, 0.49 to 1.16; p=0.1949) and disease-free survival (hazard ratio, 0.96; 95% CI, 0.67 to 1.38; p=0.8357).

7.2 Summary of cost effectiveness issues

The cost per QALY of mifamurtide is heavily dependent on which regimens are assumed to be most appropriate and whether the rates of hearing loss observed in the trial are influenced by the addition of mifamurtide to current treatment. The sensitivity analyses conducted by the ERG indicate that, with the PAS, it is very unlikely that the cost per QALY is below £50,000 and the ERG believes that the most plausible value will be greater than £100,000. It is commented that the discount rate applied to benefits does markedly change the ICER.

7.3 Implications for research

- Research is needed to determine the relationship (if any) between the addition of mifamurtide to current treatment and the rate of hearing loss. In the manufacturer's base case, it is assumed that there is no relationship, which was also assumed in the ERG base case. However, if hearing loss was caused by mifamurtide (and this possibility cannot be eliminated) the increase in cost per QALY is marked, increasing the ERG's base case ICER to £147,494.

- Further research is needed in other patient groups, namely in individuals with metastatic disease, recurrent disease, older patients and other osteosarcomas.

8. REFERENCE

1. Guide to the methods of technology appraisals. National Institute for Health and Clinical Excellence. 2008
http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf