

**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
FAD	Final Appraisal Determination
ICER	Incremental Cost Effectiveness Ratio
MBC	Manufacturer's Base Case
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 <sup>a</sup>

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.

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<sup>a</sup> 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 <sup>b</sup>

- 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

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<sup>b</sup> 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 <sup>c</sup>**

- 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 manufacturer presents a probabilistic base case cost per quality adjusted life year (QALY) of £56,677, and a deterministic value of £60,205. The base case assumes that efficacy is calculated from Regimen A+/B+ compared with Regimen A/B. Sensitivity analyses were conducted that show that the deterministic cost per QALY could be greater than £80,000 in a number of scenarios, yet only fell below £55,000 if the discount rate for outcomes was assumed to be low, with a 0% discount rate for outcomes resulting in a cost per QALY of £25,135. It is noted that a number of structural uncertainties were not evaluated by the manufacturer, in particular the cost-effectiveness of mifamurtide when Regimen A+ is compared with Regimen A alone, and in assessing the impact were hearing loss deemed to be associated with mifamurtide use. These changes, amongst others, have been undertaken by the ERG.
- The manufacturer reports that the deterministic ICER without the PAS is £84,364, which falls to £79,934 using a probabilistic methodology.

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<sup>c</sup> Contained in the Patient Access scheme submission from Takeda UK to NICE data October 2010

## 1.4 Commentary on the robustness of submitted evidence<sup>d</sup>

### *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.
- 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 which mifamurtide is discounted at ■ relative to the NHS list price.

### *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 notes that during the technology appraisal the manufacturers have amended their base case which is now more in agreement with the ERG base case. The model submitted to the ERG in November 2010 uses a base case reported to be that which reflects the base case of the appraisal committee following publication of the Final Appraisal Determination (FAD).<sup>e</sup> However, there are a number of salient uncertainties that the appraisal committee may wish to discuss and

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<sup>d</sup> Partially copied from the original ERG submission

<sup>e</sup> <http://www.nice.org.uk/nicemedia/live/12023/51088/51088.pdf>



factor into their decision making that have not been evaluated. These include comparing Regimen A+ with Regimen A alone, and in assessing the impact were hearing loss deemed to be associated with mifamurtide use. These changes, amongst others, have been undertaken by the ERG and are shown to significantly increase the incremental cost effectiveness ratio (ICER).

- 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 disfavors 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 administration 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). It is probable that the limitations in trial design would be unfavourable to the clinical (and subsequent cost-) effectiveness of mifamurtide, although the magnitude of the effect is unknown.
- The clinical advice provided to the ERG indicated that it is likely that a more clinically relevant assessment for a UK population, that is treated by the NHS rather than in an RCT setting would be derived from an analyses comparing Regimen A+ with Regimen A, which constitutes standard practice in both the large, ongoing, Euramos I RCT and in

patients treated outside of this trial.<sup>f</sup> It is also noted that 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. Hence, the cost effectiveness of 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.

- The ERG note that the pre-specified and documented clinical and statistical analysis of INT-0133 was to compare overall survival (OS) and disease free survival (DFS) in a 2 x 2 factorial analysis of A/B v A+/B+ (and A/A+ v B/B+). Hence it is acknowledged that the analysis based on comparing A+ versus A, is derived from a post-hoc subgroup which may be underpowered. The appropriateness of this analysis, in terms of whether it is biologically plausible that there is an interaction between mifamurtide and chemotherapy regimen, will need to be considered by the appraisal committee
- 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

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<sup>f</sup> The manufacturer reports that 80-90% of patients diagnosed with osteosarcoma in the UK are entered into the European and US osteosarcoma trial EURAMOS I trial. Our clinical advisor believes that this figure is too high and suggests it may be in the region of 50%

events or whether these were chance events associated with cisplatin use. Mifamurtide appeared to increase the incidence of objective hearing loss (11.5% with mifamurtide versus 7.1% without,  $p=0.047$ ) and subjective hearing loss (3.6% versus 0.6%,  $p=0.007$ ).

## **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, or whether some patients are assumed to have disease progression as occurred within the pivotal trial.

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 third Patient Access Scheme (PAS). For information the technology appraisal has had four submissions

- 1) The original submission, made by IDM Pharma, (November 2008) in which the mathematical model was constructed in TreeAge (© TreeAge Software Inc). This appraisal was put on hold when the commercial rights to Mifamurtide were acquired by Takeda.
- 2) A re-submission by Takeda UK (December 2009) in which a new model was submitted coded in Microsoft Excel (© Microsoft Corp). A PAS was incorporated that allowed any doses required by a patient after the first 26 to be provided free of charge. This PAS was subsequently amended and this submission was not formally appraised
- 3) An amended PAS was agreed with the Department of Health, in which the manufacturer would provide the initial seven doses would be provided free of charge. This resulted in a new submission (February 2010) and one where a FAD was released by NICE.<sup>9</sup>
- 4) Following the negative guidance, the manufacturer has agreed a further PAS, which offers a discount of ■ on all doses.

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<sup>9</sup> <http://www.nice.org.uk/nicemedia/live/12023/51088/51088.pdf>

A report detailing the ERG critique (following a clarification process) of the third submission was submitted to NICE and used as data in determining the FAD.<sup>h</sup>

The manufacturer's re-submissions were 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 original ERG report.<sup>i</sup> 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 reviewed in this document involves a discount of [REDACTED] on all doses. This had the effect of reducing the manufacturer's base case deterministic to £60,205, with a probabilistic value of £56,667.

## **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.

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<sup>h</sup> Mifamurtide for Osteosarcoma: Addendum critiquing the revised submitted economic model incorporating a patient access scheme. Stevenson M. March 2010.  
<http://www.nice.org.uk/nicemedia/live/12023/49693/49693.pdf>

<sup>i</sup> Mifamurtide for Osteosarcoma. Pandor A, Fitzgerald P, Stevenson M, Papaioannou D.  
<http://www.nice.org.uk/nicemedia/live/12023/49692/49692.pdf>

### **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 a 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 produces 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).<sup>j</sup> 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

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<sup>j</sup> <http://www.nice.org.uk/nicemedia/live/12023/49720/49720.pdf>

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. There appears no reason not to investigate the uncertainty in hearing loss. However, the ERG does not believe that this would significantly alter the ICER when



hearing loss is included, 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 (either objective or subjective) 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 ERG note that the manufacturer has appropriately corrected mathematical errors in the model regarding the uncertainty in costs. This is welcomed. It is also noted that the costs of adjuvant chemotherapy regimen B has increased from £27,625 to £28,713 without explanation. However, the ERG note that this value does not influence the ICER.

#### *Discounting*

A discount rate of 3.5% per annum was used in accordance with the NICE reference case.<sup>k</sup> 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

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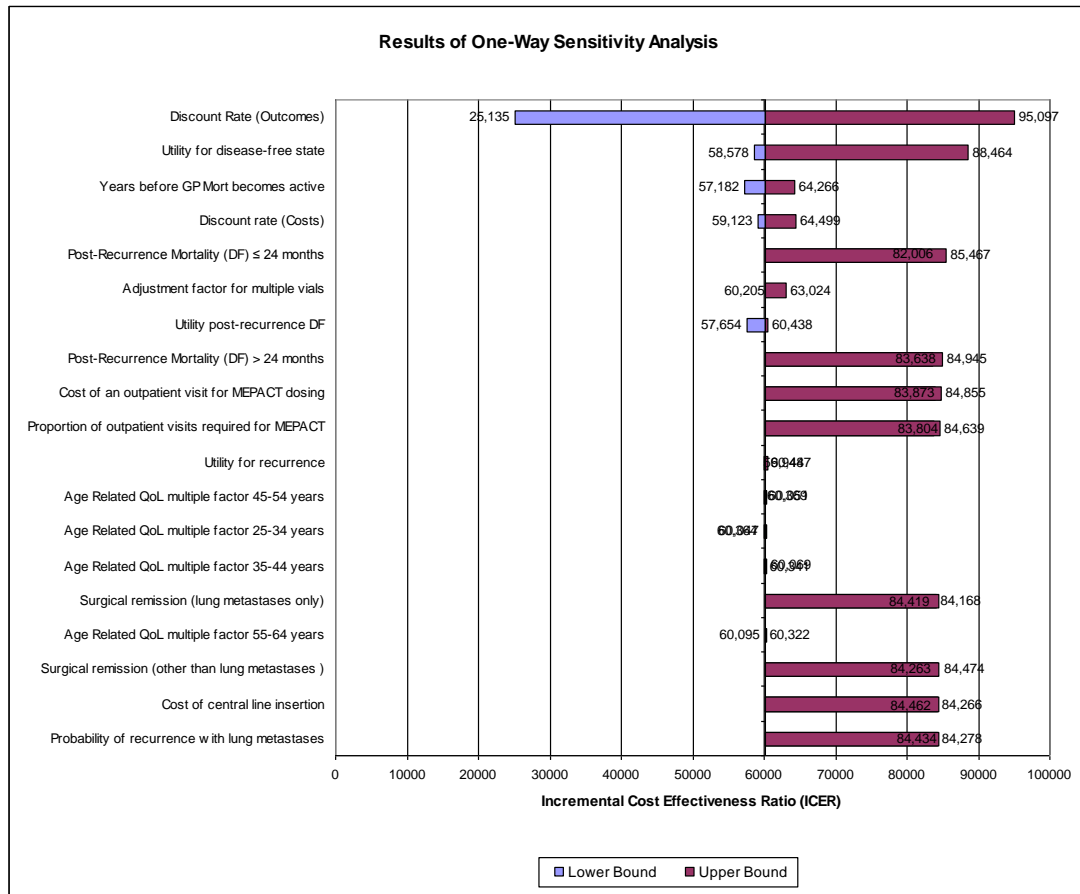
<sup>k</sup> Guide to the methods of technology appraisals. National Institute for Health and Clinical Excellence. 2008  
<http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf>

0% for utility decreased the manufacturer's base case cost per QALY to £25,135; using a discount rate 6% for utility increased the manufacturer's base case cost per QALY to £95,097.

### Sensitivity analyses

The manufacturer conducted a series of one-way sensitivity analyses on their base case results (Manufacturer's figure reproduced in Figure 1). This showed that the model was sensitive to the discount rates used for outcomes.

**Figure 1: The univariate sensitivity analyses reported by the manufacturer.**



### *Model validation*

Following the correction of inappropriately sampled costs from a Gamma distribution between the third and fourth submissions, in addition to those corrected within the previous iterations of clarifications and critiques, the ERG have found no arithmetical errors.

However, the ERG note a 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.

Furthermore, it is noted that the number of vials used has been grouped in ranges of five (i.e. 1-5, 6-10 etc) rather than using the raw data. It is unclear how this affects the ICER, but previous analyses indicated that increasing all midpoint values by 1 produced a cost per QALY that was only £4,000 higher than if all midpoints had been reduced by 1, so this was considered not to greatly influence the ICER.

## **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.
- The base case assumptions selected by the manufacturer are reported to be those preferred by the appraisal committee. However, there are a number of structural assumptions that are not evaluated that may wish

to be considered by the committee; all of which increase the ICER. These have been undertaken by the ERG

### **5.3 Results included in manufacturer's submission**

The manufacturer's report a deterministic ICER of £60,205 and a probabilistic ICER of £56,677. Additionally cost-effectiveness planes and a cost-effectiveness acceptability curve is presented. The latter indicates that mifarmurtide has an approximate 40% chance of being cost-effective at a threshold of £50,000 given the assumptions used in the base case. No further results are presented.

For clarity, the assumptions used to populate the manufacturer's base case are listed: where these differ from previous submission the bullet point has been italicised.

- Efficacy taken from Regimens A+/B+ combined compared with Regimens A/B combined
- All patients starting in the 'disease free' state
- *Amputation or limb salvage costs included*
- Hearing loss adverse events excluded
- *Mortality risk reverting to that of the general population after a determined time in the 'disease free' state included*
- *Age related utility weights included*
- Discount Rates of 3.5% per annum for both costs and outcomes
- PAS employed
- 60-year time horizon

Parameters within the manufacturer's base case for which the ERG believe further analyses are warranted are summarised in Table 1. This table indicates the sensitivity analyses undertaken by the ERG and a set of parameters that the ERG would consider to be a plausible base case.

**Table 1 Describing the manufacturer’s base case, the sensitivity analyses undertaken by the ERG and the ERG base case**

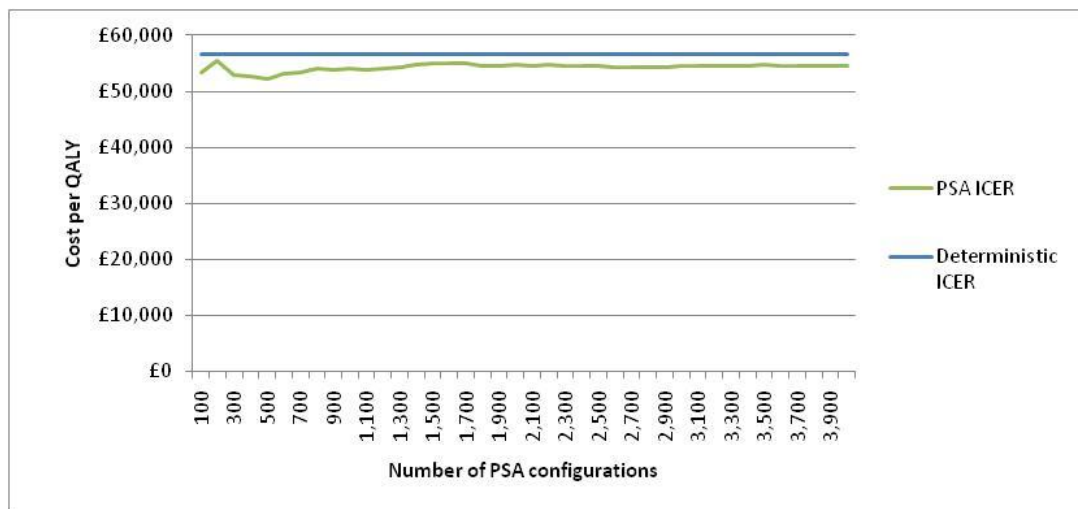
Manufacturers base case	Sensitivity analyses performed by the ERG (using the functionality of the supplied model unless stated)	ERG base case	Reason for difference, where appropriate, between the two base cases.
Efficacy data assumed to be that from Regimens (A+/B+) compared with Regimens (A/B)	Efficacy 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 pivotal 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 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 <sup>2</sup> which would require a second vial.

## 6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

### 6.1 Additional sensitivity analyses

For a previous critique the ERG had 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 2.

**Figure 2 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 3-10 minutes dependent on the processing speed of the computer used. In the manufacturer's submission 10,000 parameter configurations were used for their base case analyses.

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

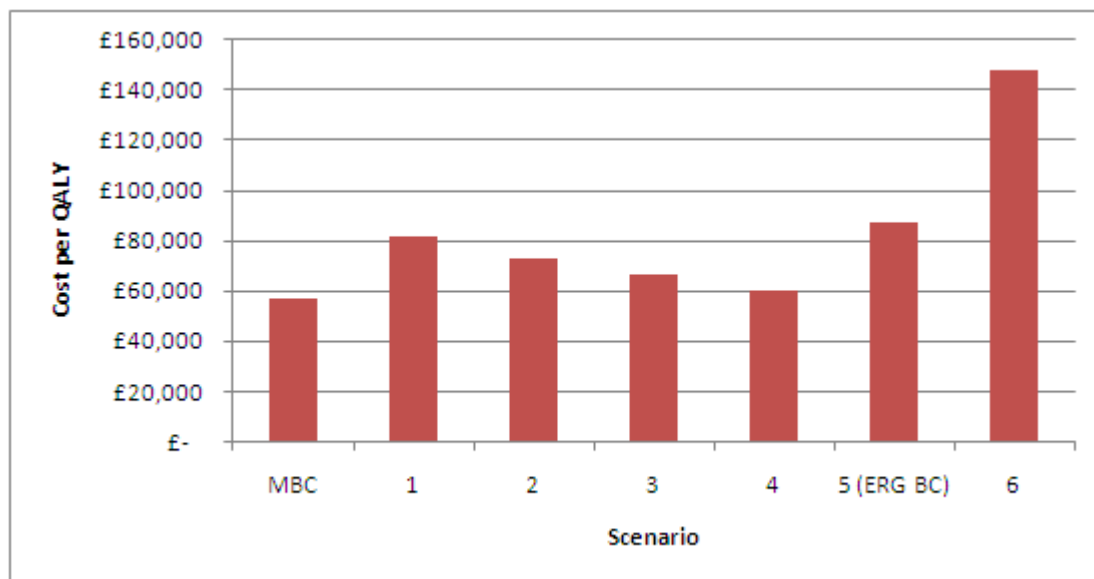
**Table 2 The results from the ERG’s sensitivity analyses**

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)	60,205	56,763*	0%	39%	82%
1	MBC, but efficacy data used only from Regimen A+ compared with Regimen A.	87,179	81,604	1%	25%	58%
2	MBC, but effects of observed hearing loss rates included	78,590	73,001	0%	21%	67%
3	MBC, but 0.66% of patients start in the progressed disease state	70,505	66,433	0%	26%	73%
4	MBC, but an assumption that 8% of patients would require 2 vials	64,715	60,409	0%	32%	80%
5	ERG base case (MBC with the addition of 1 & 4)	93,760	87,401	1%	22%	55%
6	ERG base case with the addition of 2 & 3	195,999	147,494	0%	9%	34%

\* Slightly differs from manufacturer’s reported probabilistic estimate due to Monte Carlo sampling error.



**Figure 3 The cost per QALY values calculated by the ERG in sensitivity analyses**



The scenarios are fully described in Table 3. All sensitivity analyses increase the cost per QALY compared with the manufacturer's base case.

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, nor for using the midpoints of the banded number of doses.

Following a request by the appraisal committee a further analysis was undertaken to assess the impact of altering the discount rate per annum used for outcomes on the ICER. A range of 0% to 6% was explored using intervals of 0.5% with the analyses undertaken for both the probabilistic MBC and the probabilistic ERG base case. The results are provided in Table 3. In all analyses the discount rate for costs were held constant at 3.5% per annum

Table 3: The effect of the discount rate for outcomes on the ICER

Discount Rate per annum	Probabilistic MBC ICER (£)	Probabilistic ERG Base Case ICER (£)
0.0%	23,831	36,893
0.5%	27,560	42,223
1.0%	31,417	48,099
1.5%	36,076	54,334
2.0%	41,055	64,526
2.5%	45,354	70,647
3.0%	51,256	80,319
3.5%	56,763*	87,401
4.0%	62,595	97,057
4.5%	68,366	109,715
5.0%	76,420	118,923
5.5%	83,685	128,634
6.0%	89,810	141,766

\* Slightly differs from manufacturer's reported probabilistic estimate due to Monte Carlo sampling error.

## 7 DISCUSSION

### 7.1 Summary of clinical effectiveness issues<sup>1</sup>

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

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<sup>1</sup> 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, using the discount rates recommended by NICE, the cost per QALY is below £60,000 and the ERG believes that the value could plausibly be much higher. 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 over £100,000.
- Further research is needed in other patient groups, namely in individuals with metastatic disease, recurrent disease, older patients and other osteosarcomas.