NICE Single Technology Appraisal of Mifamurtide for the treatment of Osteosarcoma

Takeda UK Ltd would like to thank the National Institute for Health and Clinical Excellence (NICE) for the opportunity to submit new evidence to support the appraisal of mifamurtide (Mepact) in the treatment of osteosarcoma. We understand that this appraisal has been on hold since the 6th May 2009. At this time mifamurtide had received a centralised marketing authorisation from the EMEA for the treatment of osteosarcoma; however there was uncertainty regarding product commercialisation in the UK and as result the appraisal was placed on hold.

We understand that IDM Pharma Inc had made a submission of evidence to NICE for mifamurtide on the 13th November 2008. This was followed by two rounds of questions from the Evidence Review Group (ERG) requesting further clarity (letters sent on the 24th November and 18th December 2008 respectively).

On the 25th of June 2009 Takeda Pharmaceutical Company acquired IDM Pharma Inc and with that the rights to mifamurtide. We wish to re-engage with NICE to complete this appraisal, and to do this we need to provide the appraisal committee with further information to support the case. Our analyses of the communications between the ERG and IDM Pharma Inc would suggest a high degree of uncertainty regarding the cost effectiveness point estimate, plus several deviations from the NICE reference case. It would also suggest a cost effectiveness point estimate (approximately of £74,558 per QALY gained) that is outside of commonly understood NICE thresholds of acceptability both from the standard reference case, but also from the newly initiated considerations for end of life cancer drugs.

To gain a positive NICE recommendation, our conclusion was that these deficiencies needed to be overcome and that this would involve a reassessment of cost effectiveness for mifamurtide through a new Takeda cost effectiveness model; to define a robust point estimate whilst also satisfying requirements defined by the NICE reference case. We also believe that a patient access scheme would also be necessary to bring the cost effectiveness point estimate nearer to acceptable levels and ensure patient access to the medication.

Additionally, mifamurtide has been granted EMEA orphan status and given the eligible patient treatment population would be considered an ultra orphan drug. Whilst there has been significant debate about how these medications should be assessed (including the NICE recommendations to the Department of Health from 2006, the NICE Citizens Council report, consideration in the Kennedy review and recently the Report of the All Party Parliamentary Group on Cancer's Inquiry into Inequalities in Cancer) there is no stated procedure for differential assessment, although for such an appraisal the NICE stated "Social Value Judgements" are implicit.

The contents of this new submission of evidence are as follows:

1. A brief review of the previous IDM Pharma Inc submission.
2. Introduction of a Mifamurtide Patient access scheme.
3. Takeda mifamurtide adjustment of cost effectiveness.
4. Takeda mifamurtide adjustment of Budget Impact to the NHS.
5. Orphan drug assessment and identifying a reasonable cost effectiveness threshold.

Declaration

I confirm that all relevant data pertinent to new submission of evidence to NICE: Mifamurtide for the treatment of Osteosarcoma have been disclosed to the Institute.

Signed:	
Name:	Ross A Selby MRPharmS
Position:	National Market Access Manager Takeda UK Ltd
Date:	10th December 2009

1. A brief review of the previous IDM Pharma Inc submission.

Key points:

- The original IDM Pharma Inc cost effectiveness model was based on a Markov process with six health states. The base case of the model (first 12.25 years) are based on the INT-033 trial and subsequent extrapolations assess over 20, 40 and 60 years (the latter requested by the ERG).
- Over a 60 year time horizon, the estimated cost per QALY gained is £74,558.
- Sensitivity analysis demonstrated that cost-effectiveness results were most sensitive to the number of mifamurtide doses received and the mifamurtide acquisition cost, when considering the 12.25 year time horizon.
- Significant ERG questioning of the model would suggest that the derived cost per QALY gained point estimate was not robust and open to a high degree of uncertainty.

1.1 Key clinical and disease state information.

It is not our intention to lay out all of the mifamurtide supportive evidence, the INT-0133 clinical trial or osteosarcoma disease state information available. However it is necessary to highlight key areas which are important to both describe the previous cost effectiveness model developed by IDM Pharma Inc and provide background rationale for modification of this model.

1.2 Setting

Mifamurtide is indicated for a specific patient population within the treatment of osteosarcoma[1]:

> *Mifamurtide is indicated for use in children and adults aged between two and thirty years of age for the treatment of high grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection to remove the tumour. It is used in combination with post-operative multi-agent chemotherapy.*

To put this in the context of a patient treatment pathway, once a diagnosis of high-grade, resectable, non-metastatic osteosarcoma has been received, a patient will receive the following treatments:

1. A course of neoadjuvant chemotherapy.
2. Surgery to remove the entire primary tumour. .
3. A subsequent course of adjuvant chemotherapy being administered to target micro-metastases.

It is within this third step of treatment that mifamurtide will be used in addition to adjuvant chemotherapy. Historical overall survival rates for osteosarcoma validate the use of post operative chemotherapy. In the 1970s the standard therapy involved surgical resection of

the primary lesion and/or radiotherapy[2]. However clinical outcomes were poor, with survival rates of 15-20%[3], leading to the presumption that most patients with localised disease also have sub clinical microscopic metastases [4 5 6 7].

The proposed dose of mifamurtide for all patients is 2mg/m^2. Mifamurtide is to be administered for 36 weeks as add-on treatment to adjuvant chemotherapy following tumour resection. A total of 48 infusions are to be given; twice weekly for 12 weeks, with dosing at least 3 days apart, followed by once weekly treatment for an additional 24 weeks.

The adjuvant chemotherapy administered in combination with mifamurtide would consist of 8 doses of high dose methotrexate (with leucovorin rescue), 4 doses of doxorubicin and either:

- 4 doses with cisplatin (across neoadjuvant and adjuvant phases) or
- 4 doses with cisplatin (in the adjuvant phase) and 5 doses with ifosfamide (across neo-adjuvant and adjuvant phases)

1.3 Mifamurtide Clinical Trial design

The INT-0133 trial was a head-to-head, randomised study comparing add-on mifamurtide to 3 or 4 agent adjuvant therapy versus adjuvant chemotherapy alone. The trial was conducted in the US and included 30% of all possible osteosarcoma patients diagnosed. A full description of the key mifamurtide clinical trial can be found in the original submission of evidence from IDM Pharma Inc. This information presents clearly the integrity of the study and the generalisability of the results to patients who present with osteosarcoma in the UK.

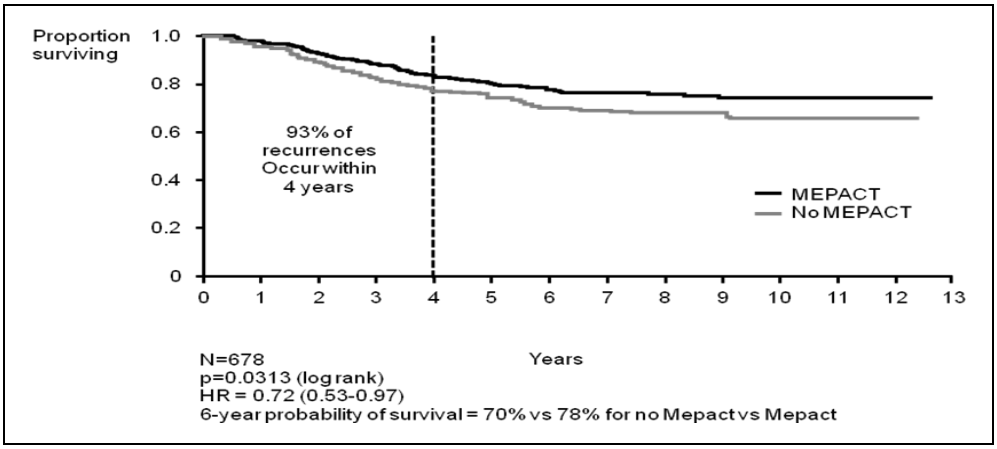
1.4 Mifamurtide Clinical trial results: Efficacy

The initial clinical study report presented data accrued to June 2003 and August 2006; an addendum subsequently provided the updated findings based on data to March 2007. Following an EMEA inspection of the Children's Oncology Group data centre in April 2008, the inspectors reported that the 2007 dataset provides the most up-to-date and comprehensive data and can be reliably used for benefit/risk assessment.

As stated in the original IDM Pharma Inc submission, the initial analysis of the 2003 data set showed that the increase in overall survival in a mifamurtide treated group was statistically significant for patients with non-metastatic resectable osteosarcoma, achieving a 6-year probability of survival of 77% (95% Confidence interval (CI): 72 to 83%) compared with 66% (95% CI: 59 to 73%) for patients receiving standard chemotherapy.

An addendum to the main clinical study report was produced in July 2008 which assessed follow-up data to March 2007. The overall survival and disease-free survival data from 2006 and 2007 demonstrated that the survival curves remained apart with extended follow-up (Figure 1.1)[1], confirming the conclusions of the 2003 data.

Figure 1.1 Overall survival in osteosarcoma patients treated with chemotherapy with and without Mifamurtide[1]



The comparability of the overall survival analysis data for the 2006 and 2007 dataset findings are summarised in Table 1.1. In the final 2007 dataset, the median survival of patients alive at last follow up was 7.9 years. The consistency of the early findings presented in Table 1.1, with those in the mature dataset, confirm that a sustainable survival benefit is associated with mifamurtide treatment.

Table 1.1 Summary of overall survival analyses for the 2006 and 2007 datasets (ITT population)[8 9]

Parameter	Patients (events)	P value	Hazard Ratio	95% CI for HR
2006 dataset				
No Mifamurtide (A-/B-)	340 (100)	---	1.00	---
Mifamurtide (A+/B+)	338 (73)	0.0352[1]	0.72	(0.53 to 0.98)
2007 dataset				
No Mifamurtide (A-/B-)	340 (100)	---	1.00	---
Mifamurtide (A+/B+)	338 (72)	0.03[1]	0.72	(0.53 to 0.97)

CI: Confidence interval, HR: hazard ratio

[1]From log-rank test stratified by ifosfamide use and randomisation strata.

All analyses show a consistent patient benefit across 2003, 2006, and 2007 INT-0133 datasets for the addition of mifamurtide to standard chemotherapy in the treatment of resectable osteosarcoma without metastases, with an approximate 30% reduction in the risk of death[10 11]. A clinically meaningful and statistically significant increase in 6-year overall survival from 70 to 78% with a p value of 0.03 and a HR of 0.71 (95% CI: 0.52 to 0.96) was demonstrated in the analysis of the final 2007 dataset[10].

Event free survival was improved with mifamurtide (p value: 0.08, HR: 0.8 [95% CI: 0.62 to 1.00], for the final 2007 data set). Various sensitivity analyses were performed to account for the impact of drop outs and missing data, including those assuming that patients with less than specified periods of follow-up after osteosarcoma recurrence had died. These sensitivity analyses demonstrated HRs consistently favouring a significant survival benefit with mifamurtide[9].

1.5 Mifamurtide Clinical trial results: Safety.

Overall, the addition of mifamurtide to three or four agent chemotherapy in study INT-0133 did not result in a detectable increase in chemotherapy side effects. The most frequent events are typically associated with intensive chemotherapy, including stomatitis, nausea and vomiting, abnormal liver enzymes, low blood counts, and infections. Mifamurtide did not appear to increase the frequency or severity of chemotherapy associated toxicities.

The addition of mifamurtide to chemotherapy appeared to increase the incidence in objective (11.5% with mifamurtide vs. 7.1% without, p=0.048) and subjective (3.6% vs. 0.6%, p=0.01) hearing loss. However the association between hearing loss and the study treatment was lost on comparison of the incidence of events in the individual mifamurtide treatment groups; specifically the incidence of auditory problems was lower in patients treated with chemotherapy plus mifamurtide than in those treated with chemotherapy alone. Ototoxicity is commonly associated with cisplatin therapy, and the frequency of hearing loss reported for patients treated with mifamurtide was within the range expected for cisplatin alone.

The most common side-effects reported in Phase I and Phase II studies are fever and chills which can be reduced by using ibuprofen pre-treatment.[10] Paracetamol and/or meperidine are additional means to reduce fever and chills in patients not responding to ibuprofen.[10]

Full information on mifamurtide tolerability can be found in the IDM Pharma Inc original submission of evidence.

1.6 Description of IDM Pharma Inc Economic Model.

The original IDM Pharma Inc Cost Effectiveness model was built in TreeAge Pro 2008 and was based on a Markov process with six health states. The Disease-Free and Disease-Progression health states were starting health states and cycle 1 in these health states represents the maintenance phase. Most patients start in the Disease-Free health state. The probability of transition between the health states for the first 12.25 years is based on data derived from the INT-0133 trial and the clinical literature. Within the trial patients could withdraw. Based on expert clinical advice, the model deals with patient withdrawals from the Disease-free state by allocating them to either the Disease-free or Recurrence state, using the probabilities from the patients that didn't withdraw. Patients who withdrew from the Recurrence state are assumed to go to the Post-Recurrence: Disease-progression state. The Markov time-cycle was 6 months except for the first cycle which is 9 months.

The first cycle is 9 months to reflect the fact that all chemotherapy and mifamurtide infusions occurred over the first 36 weeks.

The Markov process ends after 23 cycles (12.25 years). To extrapolate beyond this period, the model made assumptions about the cost and clinical outcomes of the remaining patients within each health state at the end of 12.25 years. These estimates of cost and outcomes (QALYs) beyond the 12.25 trial duration are then added to the results from the initial 12.25 years to derive an overall estimate of costs and QALYs for the mifamurtide arm and the no-mifamurtide arm.

Figure 1.2 represents a schematic of the model indicating the transition pathways between health states. Descriptions of these health states are presented in table 1.2.

Figure 1.2 Health states used for economic modelling

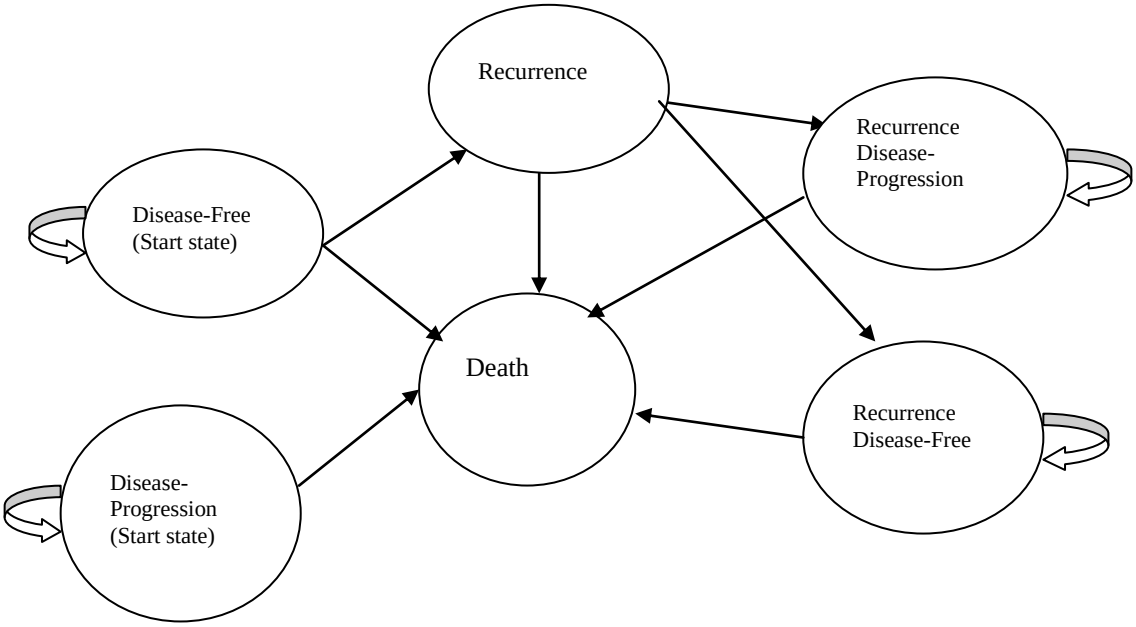


Table 1.2: Description of the health states used for modelling

State	State Description
Disease-Progression (starting state)	Cycle 1: Evidence of disease via post-surgical pathological assessment i.e. not free of gross or microscopic disease. Cycle 1 corresponds to the maintenance phase where patients receive adjuvant chemotherapy with or without mifamurtide. All other cycles: Evidence of disease via routine monitoring or when monitoring was clinically indicated.
Disease-Free (starting state)	Cycle 1: No evidence of disease via post-surgical pathological assessment i.e. free of gross or microscopic disease. Cycle 1 corresponds to the maintenance phase where patients receive adjuvant chemotherapy with or without mifamurtide. All other cycles: No evidence of disease via routine monitoring of disease status or when monitoring was clinically indicated.
Death	Death of patient.
Recurrence	A relapse of osteosarcoma, conditional on a patient having no evidence of disease prior to recurrence. Patients remain in this health state for 1-cycle.
Recurrence: Disease-Free	No evidence of disease post-recurrence. (Note, this information is based on literature estimates, as disease status post-recurrence was not collected in INT-0133) This state is set up as a tunnel state with 23 temporary states to accommodate cycle dependent monitoring costs
Recurrence: Disease-Progression	Evidence of disease post-recurrence. (Note, this information is based on literature estimates, as disease status post-recurrence was not collected in INT-0133 This state is set up as a tunnel state with three temporary states.

1.7 IDM Pharma economic model: Clinical Inputs.

The primary source of clinical information used to develop and inform the structure of the IDM Pharma Inc cost effectiveness model came from the study INT-0133. Post-recurrence estimates were derived from the literature, except in the case where death was recorded as an event post recurrence.

The base case of the IDM Pharma Inc model used a 12.25 year time horizon and costs and clinical outcomes were only allocated over this time frame (as dictated by study INT-0133). The model also assessed over 20 and 40 year time horizons. For these analyses, those patients who remain in the disease-free health-state at the end of 12.25 years were assumed to remain in that state for a further 20 or 40 years. Expert opinion advised the assumption that if patients remain disease-free after 5-6 years it is likely that they will remain disease-free for the duration of their lifetime.

Adverse events considered clinically relevant and with a higher incidence in the mifamurtide arm were included in the base case. Such events included Grade 1 and 2 infusion reactions such as fevers and chills. Clinical expert opinion considered the higher incidence of hearing loss in the mifamurtide group as a data anomaly, as hearing loss is associated with cisplatin use and the rates in the trial were consistent with those reported for cisplatin in other research. Hearing loss was included in sensitivity analyses, but not the base case. Hypotension and creatinine clearance were not included, despite a higher incidence in the INT-0133 comparator arms than the mifamurtide arms.

1.8 IDM Pharma economic model: Utility estimates.

The INT 0133 trial did not include a generic utility measure such as the EQ 5D, nor did it contain a disease specific HRQoL instrument to enable mapping to EQ 5D domains. In addition, a literature search did not identify any utility estimates specifically for osteosarcoma related health states.

The utility estimates for the IDM Pharma Inc cost effectiveness model were taken from an EQ 5D survey of UK patients with osteosarcoma and supplemented by utility estimates identified in other NICE appraisals for oncology indications. Further information from the survey and the utility estimate review can be found in the original IDM Pharma Inc submission of evidence. Disutility's associated with hearing loss were also collected. A general review of quality of life information in osteosarcoma determined that long-term quality of life is not necessarily worse for amputees compared with those receiving limb-salvage surgery, and that despite limitations, the evidence shows that patients surviving osteosarcoma can have a good long-term quality of life and do not suffer excess socioeconomic disadvantage in adult life, despite having had major limb surgery.

The EQ 5D study (based on 22 patients) resulted in a mean utility for the current disease-free health state of 0.753 (SD: 0.178) and of -0.016 (SD: 0.336) for the 6 months post-diagnosis (starting disease state). The mean utility for the disease recurrence scenario was 0.217 (SD: 0.544) (based on 4 patients). The mean utility values did not change significantly when the 4 parent/caregiver respondents were excluded: 0.748 for disease-free, 0.035 for the 6 months post-diagnosis).

Utility estimates found in other NICE appraisals for oncology indications health state utilities as follows: 0.85 for disease-free, 0.69 for disease-progression or recurrence and 0.44 for disease-progression/late phase cancer (to death). Table 1.3 below presents the utilities used in the IDM Pharma Inc cost effectiveness model.

Table 1.3: Utilities for modelling

Disease state	**Base case utility**	**Alternative value**
Initial maintenance phase (cycle 1 only for starting states)	0.0	0.20
Disease-free	0.75	-
Recurrence	0.61	0.22
Disease-progression (to death)	0.39	0.22
Recurrence/ disease-free	0.75	-
Recurrence/ disease-progression	0.39	0.22
Death	0	-

Disutility for the hearing loss adverse event was determined from a literature review where one study reported a disutility factor of -18% for hearing-loss in cancer patients[12].

Full information on utility derivation and sources can be found in Appendix 5 of the IDM Pharma Inc original submission of evidence.

1.9 IDM Pharma economic model: Resource Utilisation Inputs.

The primary cost and resource utilisation information used for the IDM Pharma Inc model were from NHS References costs 2006-07 and the British National Formulary 56, September 2006. To evaluate palliative care, resource and costing estimates were taken from the literature as they could not be quantified for this rare disease. Table 1.4 below presents the costs used in the IDM Pharma Inc cost effectiveness model. Full information on resource utilisation and costs can be found in Appendix 5 of the IDM Pharma Inc original submission of evidence.

Table 1.4: Costs of resources used in the model.

Variable Name	Description	Value (£)
C_2nd_chemo_cycle	Cost of second-line chemotherapy cycle	1636
C_AE_hearing	Cost of hearing AE (cycle 1)	50
C_AE_infus	Cost of infusion reaction AE (cycle 1)	1.91
C_catheter	Cost of central line insertion	2281
C_chemo_A	Cost of adjuvant chemotherapy regimen A	26832
C_chemo_B	Cost of adjuvant chemo regimen B	31181
C_ct_scan	Cost of CT scan	100
C_isotope_scan	Cost of bone isotope scan	183
C_mifamurtide_dose	Cost of a MIFAMURTIDE dose	2375
C_mifamurtide_outvisit	Cost of an outpatient visit for MIFAMURTIDE dosing	189
C_MRI	Cost of MRI scan	278
C_NHS_palliative_care	Cost of NHS palliative care	3403
C_other_pulm_surg	Cost of other non-pulmonary surgery only	6168
C_outpat	Cost of outpatient visit - no treatment	189
C_palliative_care	Cost of all palliative care (33% added) for hospice care provided by voluntary/charity	5105
C_pulm_surg	Cost of pulmonary surgery	5426

Patients were assumed to be 100% compliant to mifamurtide and receive a full 48 doses. This equates to a total cost of £114,000 per total treatment regimen of 48 vials at £2,375 per vial.

1.10 IDM Pharma Inc economic modelling results.

The reference case results, based on a time horizon of 12.25 years, indicate a cost/QALY of £457,624 based on an incremental effect of 0.26 QALYs and an incremental cost of £119,000. The model time horizon is a key drivers of cost-and this along with the base case are presented in Tables 1.6 below.

Table 1.6: Base-case cost-effectiveness for mifamurtide

Strategy	Cost	Incremental Cost	QALY gain	Incremental effect	Cost/QALY	Incremental C/E (ICER)
Base case: 12.25 years						
No mifamurtide	£34K		6.419 years		5,237	
mifamurtide	£153K	£119K	6.679 years	0.260 years	22,855	457,624
20 year time Horizon						
No mifamurtide	£35K		13.29 years		2,609	
mifamurtide	£154K	£119K	14.31 years	1.02 years	10,749	116,879*
40 Year time Horizon						
No mifamurtide	£35K		16.79 years		2,097	
mifamurtide	£154K	£119K	18.20 years	1.41 years	8,487	84,786*

* Results as amended per answers (due to discounting error provided) to the ERG on the 8th December 2008 and not in original submission.

The IDM Pharma Inc cost effectiveness model presented sensitivity analyses but not probabilistic sensitivity analyses (PSA). Sensitivity analysis demonstrated that cost-effectiveness results were most sensitive to the number of mifamurtide doses received and the mifamurtide acquisition cost, when considering the 12.25 time horizon.

1.11 IDM Pharma Inc economic model and ERG questions.

IDM Pharma Inc received two sets of questions from the ERG with answers delivered on the 8th December 2008 and 8th January 2009. Questions answered on the 8th December 2008 raised twenty two questions on the provided economic analyses and these questions included requested analyses in the following areas:

- Rates of limb- salvage and amputation and maintenance costs in the model.
- Time horizons extended beyond 20 and 40 years to 60 years.
- Assuming 2 vials per cycle instead of 1.
- Justification for non inclusion of a half cycle correction.
- Senisitivity analyses and different scenarios of hearing loss rates.
- Justification for non adjustment of utility for age.
- Explore PSA.
- Assess ICERs comparing the individual treatment arms of the INT-0133 trial.

Full analyses requested by the ERG can be found in the answers provided to the ERG on the 8th December 2008. One of the analyses requested by the ERG was to assess the impact of mifamurtide over a 60 year time horizon which derives an incremental cost per QALY gained of £74,558 (presented in Table 1.7).

Table 1.7: Mifamurtide cost effectiveness over a 60 year time horizon.

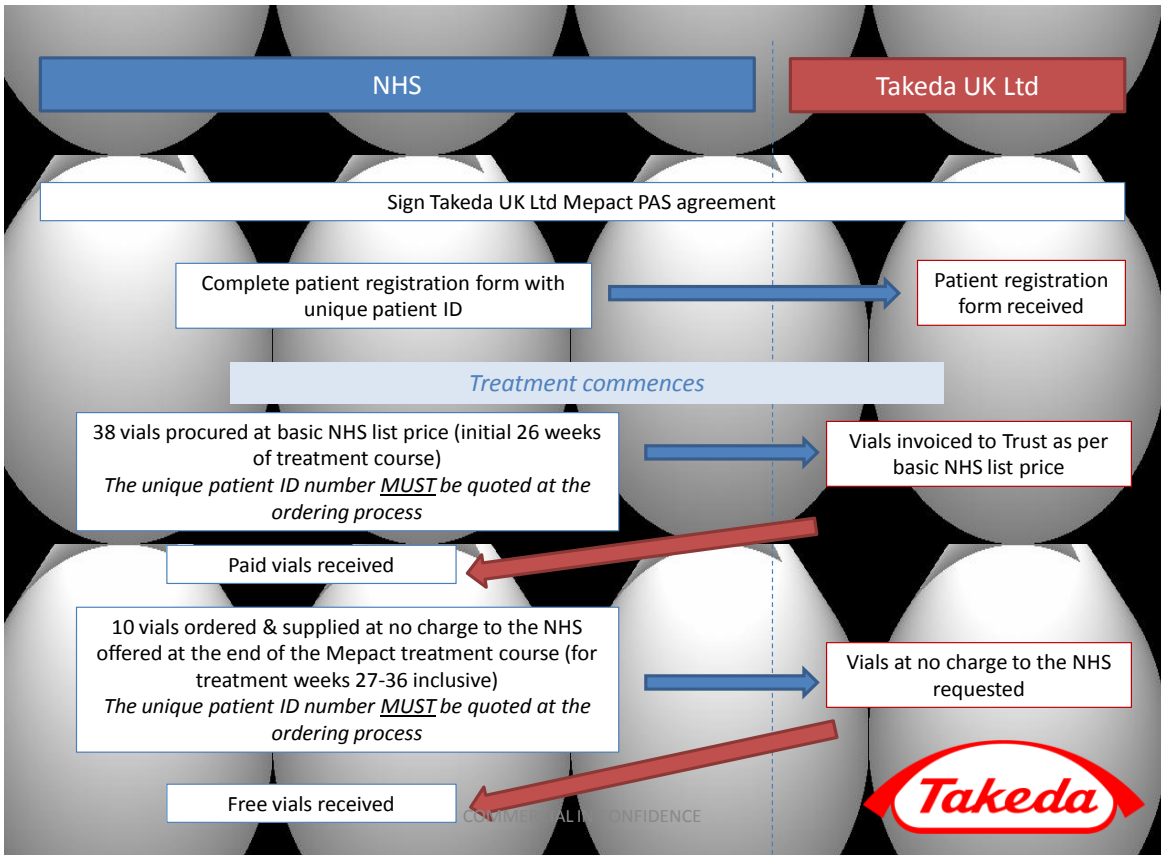
Strategy	Cost	Incremental Cost	QALYs	Incremental effect	Cost/QALY	Incremental C/E (ICER)
60 Year time Horizon						
No Mifamurtide	£35K		18.54 yrs		1,914	
Mifamurtide	£155K	£119K	20.14 yrs	1.60 years	7,683	74,558

2 Introduction of a Mifamurtide Patient access scheme.

Takeda UK Ltd propose to make mifamurtide available to the NHS through a Patient Access Scheme (PAS) and support the use of mifamurtide in the NHS in the defined licensed population. Mifamurtide is indicated in children, adolescents and young adults for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection. It is used in combination with post-operative multi-agent chemotherapy. Safety and efficacy have been assessed in studies of patients 2 to 30 years of age at initial diagnosis.

The proposed scheme would allow Takeda UK Ltd to provide mifamurtide treatment to patients, with no charge to the NHS, beyond the average treatment length (as defined by the INT-1033 trial) at no charge to the NHS, up to the defined SPC regimen amount.

Diagram 2.1 Summary of Takeda UK Mifamurtide Patient Access Scheme



3. Takeda mifamurtide adjustment of cost effectiveness.

Key Points:

- Takeda UK have rebuilt the IDM Pharma Inc cost effectiveness model in excel to minimise some of the basic errors itemised beneath and more accurately assess cost effectiveness
- The new base case ICER is £67,748. When a mifamurtide PAS is introduced the ICER is £57,408.
- The model was very sensitive to modification of the discount rate for outcomes. When this was changed to 1.5% (and 3.5% for costs) the ICER is £41,634 and £35,280 when a mifamurtide PAS is introduced.
- Even when the model is set to an extremely pessimistic scenario, the ICER is £111,814, this is dramatically reduced to £69,314 and £58,852 when the discount rate is adjusted to 1.5% for outcomes and a mifamurtide PAS is introduced.
- This analysis validates the base case ICER and demonstrates the general robustness of the base case analyses. The upside from the discount rate for outcomes ameliorates any uncertainty in the model that may come from non inclusion of other model assumptions such as limb salvage maintenance costs or adverse events associated with hearing loss.
- It is the opinion of Takeda UK that mifamurtide offers good value for money with an ICER in the region of £57,408 when a PAS for mifamurtide is introduced. On the upside the ICER may be as high as £35,280 per QALY gained when a discount rate of 1.5% and PAS are introduced.

3.1 Introduction

To gain a positive NICE recommendation, Takeda UK believe that deficiencies highlighted through ERG questioning need to be overcome to ensure a positive recommendation for mifamurtide and allow patients access to this medication on the NHS. To achieve this goal, Takeda UK conducted a reassessment of the cost effectiveness of mifamurtide to define a robust point estimate and further satisfy requirements defined by the NICE reference case.

To better understand the previous cost effectiveness assessment conducted by IDM Pharma Inc, the previous model was reconstructed in Microsoft Excel. This conversion has also included replicating the 11 scenarios which were created in different TreeAge programs. The aim of the conversion was to exactly replicate the results generated by the IDM Pharma Inc TreeAge versions including any programming errors, and this would allow correction and development. Table 3.1 below highlights the anomalies detected in the IDM Pharma Inc cost effectiveness model.

Table 3.1: Anomalies in the previous IDM Pharma Inc cost effectiveness model.

	Anomalies in the IDM Pharma Inc cost effectiveness model.	**Favours mifamurtide or not?**
	Anomaly first 12.25 years	
1	Within the model, patients who start in the Disease-progression state can only die. Inconsistencies in the starting patient population characteristics should be equalised to allow a fair assessment.	Strongly favors the No-mifamurtide arm as more patients are in the mifamurtide arm.
2	The model attributes the mortality rates (≤ 24 month recurrence, >24 month recurrence) based on the time the patient has been in the model not when the patient had the recurrence. Thus a patient who is in the Disease-free state and doesn't recur until Year 3 is attributed the higher mortality rate of a patient who has had a recurrence within ≤24 months rather than the mortality rate of a patient who had a recurrence > 24 months.	Favors the No-mifamurtide arm.
3	The model attributes the >24 month recurrence mortality rate to all Post-Recurrence: Disease-free state for the full 12.25 year duration of the Markov element of the model. It would seem more appropriate for patients who are still disease free after certain duration to revert to a mortality probability similar to the general population.	Favors no mifamurtide: reducing the mortality rate would create more QALYs in the No_ mifamurtide arm.
4	The model assumes that all patients receive 48 doses; in the INT-0133 however patients received on average 38.4 doses.	Favours No Mifamurtide as overestimates costs for mifamurtide.
	Anomaly extrapolation beyond 12.25 years	
5	All patients in the Post-Recurrence: Disease-free state after 12.25 years disappear from the model. They neither have any health benefit (additional QALYs) nor incur a monitoring cost. In the default scenario a total of 8.2% of patients in the mifamurtide arm are in the Post-Recurrence: Disease-free state after 12.25 years. For the No_ mifamurtide arm 9.4% of patients are present in the Post-Recurrence: Disease-free state after 12.25 years.	Strongly favors the No-mifamurtide arm as QALYs gained outweigh costs.
6	The calculation used in determining the additional QALY's gained and costs incurred is flawed. For the QALY's gained, the model discounts the utility of the Disease-free health (0.85) over the total duration of the model time horizon. This value is then multiplied by the remaining percentage of patients in the Disease-free health at the end of the 23 cycles (12.25 years). This results in some double counting of both cost and QALYs as cost and QALYs have already been counted during the 23 cycles of the Markov model element. Another error is the method of discounting for this post-Markov element. Currently, the model starts to discount both the QALYs and costs from year 13 as if it was year 1.	Overall this error favours mifamurtide. However in combination with anomaly 5 this strongly favors the No- mifamurtide arm as QALYs gained outweigh costs in the no Mifamurtide arm.
	Cell referencing.	
6	A review of the modelling structure and translation from TreeAge to Excel has found only two cell referencing errors/anomalies. Both of these errors relate to the routine monitoring costs.	This error currently favors mifamurtide, but the effect on the ICER is small.

3.2 Markov Model Structure Extension

The new model structure continues the 6-monthly Markov time-cycles of the initial model structure up to a total of 60 years using the following assumptions:

- Patients within the disease-free state at 12.25 years are assumed to have a mortality rate equivalent to the general population.
- Patients within the post-recurrence disease-free state are assumed to have a mortality rate dependent on the time to recurrence derived from the Ferrari et al [13]. For patients who have a recurrence within 2 years, the 6-monthly mortality rate is 14.87%. For patients who have a recurrence after 2 years, the 6-monthly mortality rate is 4.98%.

3.3 Update of Drug and Resource Costs

Table 3.2 shows the updated cost estimates for the resources used in the revised CE model.

Table 3.2: Resource Costs

Parameter	Value	Source
Cost of second-line chemotherapy cycle	£1,408	NICE section 10.5.4.1. Updated to BNF 58 Sept '09
Cost of hearing AE (cycle 1)	£51	NHS Ref Costs 2007-2008. DHA1 Digital Hearing Aid, AS1FA Hearing Aid Fitting, AS1FU Hearing Aid follow up.
Cost of infusion reaction AE (cycle 1)	£2	BNF 58 Sept 2009, paracetomol 500m. Net price 16 = 17p, 32 = £1.18, 100 = £1.65 (100 tablets per patient)
Cost of central line insertion	£4,288	NHS Ref cost 2007-08 (EA36B, catheter 18 years and under)
Cost of CT scan	£116	NHS Ref cost 2007-08 (RA11Z)
Cost of bone isotope scan	£164	NHS Ref cost 2007-08 (RA36Z)
Cost of an outpatient visit for MIFAMURTIDE dosing	£189	NHS Ref cost 2007-08 (O/P specialty code 370)
Cost of MRI scan	£214	NHS Ref cost 2007-08 (RA02Z)
Cost of NHS palliative care	£3,481	Average of the mean NHS cost across all cancers (2000/2001 prices) uplifted to 2007 prices (Guest et al; 2006)
Cost of other non-pulmonary surgery only	£2,194	NHS Ref Costs 2007-08. Equal to average of three elective inpatient HRGs (HD36A, HD36B, HD36C)
Cost of outpatient visit - no treatment	£189	NHS Ref cost 2007-08 (O/P specialty code 370)
Cost of pulmonary surgery (3-day inpatient stay)	£1,797	NHS Ref Costs 2007-08. Equal to average of three elective inpatient HRGs (DZ09A, DZ09B, DZ09C)
Annual cost of amputation	£5,369	Cost derived from Grimer et al., 1997, cost uplifted to 2006 via (CPI).
Annual cost of endoprosthesis assuming failure rate of 0.04	£1,091	Cost derived from Grimer et al., 1997, cost uplifted to 2006 via (CPI) - Alternative value for 0.08 failure rate £1,889.

Table 3.3 shows the updated costs estimates for the drug costs.

Table 3.3: Drug Costs

Parameter	Value	Source
Cost of adjuvant chemotherapy regimen A	£24,784	NICE Final Section 10.5.2.3, Updated to 2007 Prices
Cost of adjuvant chemotherapy regimen B	£27,625	NICE Final Section 10.5.2.3, Updated to 2007 Prices
Cost of MIFAMURTIDE dose	£2,375	

Note: Regimen A maintenance therapy consisted of four doses of doxorubicin (25mg/m2/day over 72 hours), two doses of cisplatin (120mg/m2) and eight doses of methotrexate (12g/m2).Regimen B maintenance therapy consisted of four doses of doxorubicin (25mg/m2/day over 72 hours), four doses of cisplatin (120 mg/m2), three courses of ifosfamide (1.8g/m2/day x 5 days) and eight doses of methotrexate (12g/m2).

3.4 Health-Related Quality of Life Utility Values

The default HRQoL utility values applied to each of the health states are the same as outlined in the original model and are shown in Table 3.4. It was determined that the figure of 0.75 derived from the EQ 5D survey was not realistic for the disease free patient population and the figure of 0.85 derived from the NICE utility literature review was more realistic. It must be remembered that these are patients who are of average age 14 years and currently disease free in the model. The figure of 0.75 is a figure more representative of older patients with end of life metastatic cancers as demonstrated in Table 3.5.

Table 3.4: Health State Utility Values

Health State	Value	Source
Disease Progression	0.39	NICE HTA review. The HTA review provided an estimate of 0.44 for the disease progression to death category, which was adjusted by the -12% correction factor as above.
Disease Free	0.85	It was determined that the figure of 0.75 derived from the EQ 5D survey was not realistic for this patient population and the figure of 0.85 derived from the NICE utility literature review was more realistic for patients who are of average age 14 years and currently disease free. 0.75 is a figure more representative of older patients with end of life metastatic cancers.
Recurrence	0.61	NICE HTA review. The HTA review provided an estimate of 0.69 for disease-progression/recurrence category. A correction factor of -12% was applied based on the ratio for the average utility for disease-free state in the EQ 5D survey and Alessi et al. 2007 (0.75) and the disease-free category in the NICE HTA review (0.85).
Disease Free post recurrence	0.85	Assumed to be the same as disease-free value.
Disease Progression post recurrence	0.39	Assumed to be the same as disease-progression value.
Death	0	

Table 3.5: Age-Related Utility Weights (UK Population Norms – EQ-5D)

Age (years)	Value
< 25	1.00
25 – 34	0.93
35 – 44	0.91
45 – 54	0.85
55 – 64	0.80
65 - 74	0.78
75+	0.74

3.5 Number of mifamurtide doses

The expected number of mifamurtide doses to be administrated to each patient is 48. This figure was the default assumption in the original model. However, it was clear from the original NICE submission by IDM Pharma Inc and the INT-0133 trial report that there was a large variation in the number of doses the patients received. Table 3.6 shows the patient distribution of the number of doses patients received together with the average number of mifamurtide doses the patients received. As the efficacy data is based on the number of actual mifamurtide doses administered and not the assumed 48 doses, the model default has been altered to the actual average of doses administered i.e. 38.4.

Table 3.6: Mifamurtide dosing for patients receiving adjuvant therapy.

Number of Doses	Mid-Point	Percentage of Patients
>50	53	1.7%
46-50	48	51.7%
41-45	43	10.2%
36-40	38	7.4%
31-35	33	4.0%
26-30	28	5.1%
21-25	23	6.3%
16-20	18	2.8%
11-15	13	2.9%
6-10	8	3.4%
1-5	3	4.5%
Average number of MIFAMURTIDE doses administered		**38.4**

Source: Based on Phase III actual mifamurtide dosing. Weighted average calculations exclude zero dose patients. Derived from IDM Pharma Inc response to Questions dated 8th December 2008; Table 15.

3.6 Extra outpatient Visits for mifamurtide patients

3.7.1 New Approach 1

In the original model an estimate, based on clinical advice, of the percentage of extra outpatient attendances needed in the administration of mifamurtide over and above the number of outpatient attendances associated with the maintenance chemotherapy was applied. This estimate was 30%. In other words, it was estimated that 30% of the mifamurtide doses would require the patient to make an extra outpatient attendance visit as the dosing could not be undertaken at the same time as part of the maintenance chemotherapy.

The two regimen adjuvant chemotherapies occur over a 20-26 week timeframe in which, with double dosing for the first 12 weeks, 32 doses of mifamurtide are administrated. Therefore, it was felt that extra outpatient attendances should only be applied to mifamurtide doses in excess of 32 doses. Table 3.7 shows that additional outpatient attendances needed for the number of mifamurtide doses administered together with the average number of additional mifamurtide outpatient attendances required based on the actual patient distribution of doses received shown in Table 3.6.

Table 3.7: Number of Additional Outpatient Visits for mifamurtide doses

Number of Doses	Additional Outpatient Visits
>50	17
46-50	12
41-45	7
36-40	2
31-35	0
26-30	0
21-25	0
16-20	0
11-15	0
6-10	0
1-5	0
Average number of MIFAMURTIDE Outpatient attendances	**7.4**

3.7.2 New Approach 2

A detailed analysis of the dosing timings undertaken in the trial (INT-0133) for the administration of the maintenance chemotherapy and adjuvant mifamurtide therapy shows that the additional outpatient attendances required for the administration of mifamurtide maybe in fact higher than originally thought. Appendix 1 shows the dosing regimen from Trial INT-0133 for the maintenance phase. Taking chemotherapy regimen B, we can calculate the number of times that mifamurtide was administered alone and thus conclude when an additional outpatient attendance would have been required. For example, if a patient only received the first 13 doses of mifamurtide then 7 additional outpatient attendances would be required.

Adopting this approach, Table 3.8 shows an alternative number of 22.7 additional outpatient attendances required to administrate mifamurtide doses base on the actual patient distribution of the number of mifamurtide doses patients received.

Table 3.8: Number of Additional Outpatient Visits for mifamurtide doses

Number of Doses	Additional Outpatient Visits
>50	34
46-50	29
41-45	24
36-40	21
31-35	17
26-30	15
21-25	13
16-20	11
11-15	7
6-10	5
1-5	3
Average number of MIFAMURTIDE Outpatient attendances	**22.7**

The differences in additional outpatient attendances required for the administration of mifamurtide is investigated in the sensitivity analysis.

3.8 Patient Access Scheme (PAS)

Functionality has been built into the model so that the impact of a proposed Takeda UK PAS can be assessed. The functionality takes into account the patient distribution of mifamurtide doses received.

3.9 Results and Sensitivity Analyses

3.9.1 Results

The base case result in the original IDM Pharma Inc cost effectiveness model estimated a cost per QALY gained of £74,558 over a 60 year time horizon. Using the same assumptions the Takeda excel model can derive a cost per QALY of £71,640 which is the nearest estimation to the previous IDM figures when taking into cell reference errors and the new model platform. Table 3.9 below shows the impact of correcting the major model anomalies and the impact on this figure.

Table 3.9: Impact of correcting anomalies in the previous IDM Pharma Inc cost effectiveness model.

Anomalies in the IDM Pharma Inc cost effectiveness model.	ICER Model with anomaly	ICER Model without anomaly
Anomaly first 12.25 years		
Anomaly 1: Inconsistencies in the starting patient population characteristics for Disease-progression state.	£71,640	£63,578
Anomaly 4: The model assumes that all patients receive 48 doses; in the INT-0133 however patients received on average 38.4 doses	£71,640	£57,054
Anomaly extrapolation beyond 12.25 years		
Anomaly 5 and 6: All patients in the Post-Recurrence: Disease-free state after 12.25 years disappear from the model. Double counting of cost and QALYs and discounting.	£71,640	£110,090
Combination of all anomalies and including input revisions		
Correction of Utility for disease free from 0.75 – 0.85. Correction of pharmacy costs as this item is included in other medication administration resources	£71,640	£67,748

The new base case cost per incremental QALY gained is £67,748. This is presented below in Table 3.10.

Table 3.10: Cost-effectiveness of the addition of MIFAMURTIDE to Maintenance Chemotherapy for treating high-grade non-metastatic osteosarcoma

Outcome	MIFAMURTIDE + Maintenance Chemotherapy	Maintenance Chemotherapy Alone	Difference
Total costs	£124,065	£31,717	£92,348
MIFAMURTIDE Drug costs	£91,189	–	£91,189
Adjuvant Chemotherapy costs	£26,205	£26,205	–
Resource costs	£6,672	£5,513	£1,159
QALYs	16.76	15.40	1.36
Incremental Cost-effectiveness Ratios			
Incremental cost per QALY gained	**£67,748**		

This result is based on the following assumptions:

- 60 year time horizon.
- 100% of the population starting in the Disease-free health state;
- Clinical data as previously described;
- Resource and Cost inputs as outlined in Tables x & x, patients receive on average 38.4 doses of mifamurtide;
- No Amputation or limb salvage costs;
- Hearing loss adverse event not included;
- Mortality risk reverting to general population after a given time period not included;
- Age related utility weights not included;
- Discounting rates of 3.5% for both costs and outcomes applied.

3.9.2 Sensitivity Analyses

To ascertain the robustness of the new Takeda cost effectiveness model we have undertaken a range of sensitivity analysis including one-way sensitivity analysis and probabilistic sensitivity analysis (PSA).

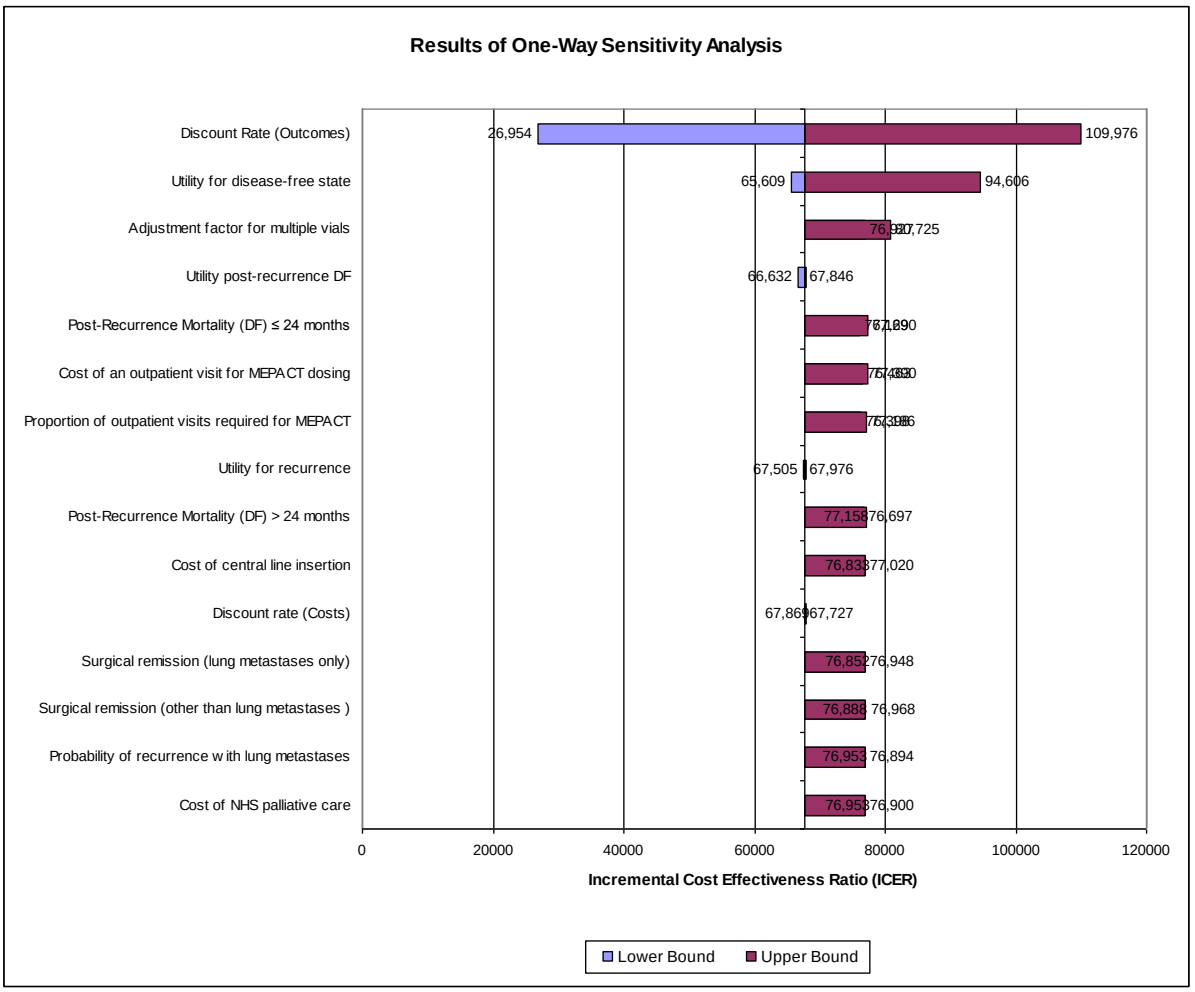
3.9.3 Standard One-way Sensitivity Analysis

The standard sensitivity analysis was based on the following model settings:

- Costs could vary by 40%, excluding drug costs, which are fixed.
- Mortality rates post recurrence and surgery and second-line chemotherapy at recurrence are assumed to vary within their 95% confidence interval.
- Recurrence rates and quality-of-life utility values varied between their 95% confidence interval derived from assuming each utility values follows a Beta statistical distribution and the total number of people used to derive the utility values are based on the number of people in the Alessi et al., 2007 study.
- Discounting varied between 0% and 6%.

Figure 3.1 shows the results of the sensitivity analysis in the form of a tornado diagram. A tornado diagram allows us simultaneously to compare one-way sensitivity analysis for many input parameters and the ICER. The length of the bar represents the sensitivity of the parameter to the ICER. Figure 3.1 shows that there are in reality only two variables that affect the ICER; the most sensitive of these is the discount rate for the outcomes which has already been discussed. If the clinical outcomes discount rate is set to its lower rate of 0% (while the discounting rate for costs remains at 3.5%) the ICER becomes £26,954 per QALY. Setting the clinical outcomes discount rate is set to its higher rate of 6% the ICER becomes £109,976 per QALY. The next most sensitive parameter is the HRQoL utility value for disease-free health state. If this value is increase from its default value of 0.85 to a higher value of 0.9 then the ICER becomes £63,933 per QALY. Conversely, decreasing this value to its lower value of 0.62 produces an ICER of £93,373 per QALY.

Figure 3.1: One Way Sensitivity Results



3.9.4 Scenario Analysis: Discount rates

The undiscounted results show that the ICER for mifamurtide + maintenance chemotherapy over maintenance chemotherapy alone is £26,954 per QALY. The primary reason that discounting (of the outcomes) has a significant effect on the ICER is that the majority of the treatment costs are incurred within the first year of the model but the clinical outcomes are obtained throughout the whole time horizon and thus discounting the outcomes (benefits) reduces the QALY difference between the treatments which adversely affects the cost-effectiveness of mifamurtide. Table 3.11 below presents the sensitivity of the ICER to varying the discount rate for outcomes whilst holding the discount rate for costs constant at 3.5%.

Table 3.11: Sensitivity of the ICER to varying the discount rate for outcomes whilst keeping the discount rate for costs at 3.5%.

Discount rate for outcomes	ICER
0%	£26,954
1%	£36,270
1.5%	£41,634
2%	£47,470
3%	£60,537
3.5%	£67,748
4%	£75,392
5%	£91,917
6%	£109,976

A discount rate for outcomes of 1.5% could be applied for this appraisal, which would be inline with the previous NICE reference case where costs and outcomes were discounted at differential rates of 6 and 1.5% respectively. In this situation the cost per incremental QALY gained would be £41,622.

With regards to the discounting rates, health economists continue to argue over the rates of discounting and whether the discounting should be uniform (same for both costs and outcomes) or differential, and whether discount rates should vary over time[14]. The current NICE report on the "Guide to the methods of technology appraisal" recommends an annual discount rate of 3.5% for both costs and outcomes, but previously had recommended differential discount rates of 6.0% for costs and 1.5% for outcomes. Opponents of using a uniform discounting approach argue that the consistency argument assumes that the relationship between life years (and hence QALY's) and costs remains independent of time; but this may not necessarily be the case. Another argument for differential discounting rates, supporting a view that health benefits should not be discounted at all, is the possibility of inadvertent double discounting of benefits [15] [16]. They argue that health related outcomes such as quality of life may already have already been incorporated into an individual's time preference, especially when utility is measured using the time trade off or standard gamble method and thus if health outcomes are also discounted in the future, the value of future benefits of an intervention will be underestimated.

The most commonly used method of discounting adopted by the reimbursement authorities, such as NICE, is uniform discounting using a constant non-zero discount rate, commonly 3% or 5%). Severens et al., 2004 [14] argues that this method leads to prioritization of immediate treatment at the expense of prevention and works against long-term public health measures including some evidence-based screening and pediatric vaccination programs. As osteosarcoma primarily affects the young this argument is also valid in the case of mifamurtide. Severens et al., 2004 goes on to state that variable discounting rates of both costs and benefits be adopted as a methodology without having to violate the theoretical principles of uniform discounting. A variable discounting approach, especially for health outcomes compared to a constant discount rate over time, would clearly support health-care programs which have costs now and health benefits in the far future.

We believe there is one clear example where a positive NICE guidance may have been reversed if a common 3.5% discount rate had been employed, and interestingly again it is for treatment in a paediatric population. For TA64 (Human growth hormone (somatropin)[17] in adults with growth hormone deficiency) the committee stated that:

> *"After reviewing the updated cost effectiveness analyses, and the data from the KIMS database on the levels of improvement (in terms of QoL-AGHDA scores) for different patient groups, the Committee considered that the subgroup of people with GH deficiency for whom treatment may be cost effective would be those who had an improvement in QoL equivalent to an absolute change in their baseline QoLAGHDA score of at least 7 points. The Committee considered that the ICER for this group of patients would be in the region of £25,000 to £45,000 per QALY".*

The underlying assessment report for this appraisal is not available so how the ICERs may be affected with a common 3.5% discount cannot be calculated. However, we estimate that the ICER may rise by 85% when 3.5% for both costs and outcomes are used rather than 6% for costs and 1.5% for outcomes: this would increase the ICERs quoted in the committee report to between £46,500 and £83,250.

This may be an example of when a lower discount rate has been utilized and been crucial in NICE decision making, albeit using the previous NICE reference case.

3.9.5 Scenario Analysis: Patient Access Scheme

Table 3.12 shows the results of introducing a PAS as described in section 2 of this document. It is clear that the introduction of a PAS brings down the ICER value to £57,408 and £35,280 with a discount rate for outcomes of 3.5% and 1.5% respectively. The true incremental cost per QALYgained for mifamurtide with a PAS lies in between these values.

Table 3.12: PAS ICER Results

	Discount rate 3.5%			Discount rate 1.5%		
Outcome	MIFAMURTIDE + Maintenance Chemo	Maintenance Chemo	Difference	MIFAMURTIDE + Maintenance Chemo	Maintenance Chemotherapy Alone	Difference
Total costs	£109,971	£31,717	£78,254	£109,971	£31,717	£78,254
MIFAMURTIDE Drug costs	£77,095	£0	£77,095	£77,095	£0	£77,095
Adjuvant Chemo costs	£26,205	£26,205	£0	£26,205	£26,205	£0
Resource costs	£6,672	£5,513	£1,159	£6,672	£5,513	£1,159
QALYs	16.76	15.40	1.36	25.03	22.81	2.22
Incremental Cost-effectiveness Ratios						
Incremental cost per QALY gained	£57,408			£35,280		

3.9.6 Scenario Analysis: Evaluating the Effect of Incorporating other Model Assumptions

The results detailed in this section relate to including other model assumptions which can be either included or excluded. In particular these include:

- Incorporating Amputation and Limb Salvage costs;
- Incorporating Hearing Loss AE's;
- Allowing the post-recurrence mortality rate to equate to the general population mortality rate for patients who remain disease-free after a given time period;
- Applying Age-related utility rates.

Table 3.13 outlines the effect of incorporating these changes and assumes the discount rate for outcomes is set to 3.5% and the mifamurtide PAS is not included. When the amputation and limb salvage costs are included into the model the ICER changes from £67,748 to £70,001. The inclusion of this variable only affects the cost element of the ICER calculation. The amputation and limb salvage costs are applied to the proportion of patients who, according to the INT-0133 trial data, entered the maintenance phase of treatment having received limb salvage or amputation during the treatment phase. The increase in the ICER is due to the increase in treatment costs being higher for the mifamurtide arm as more patients survive in the mifamurtide arm than the no mifamurtide arm.

Incorporating the hearing loss AE's assumes that 15% patients receiving mifamurtide and chemotherapy and 8% of patients receiving chemotherapy alone have hearing impairment. The hearing loss assumption affects both the costs and QALYs as a utility decrement of 18% is applied to these patients together with extra resource costs. The result is an increase of the ICER to £90,038 per incremental QALY gained.

If the assumption regarding the mortality risk for post-recurrence disease-free patients returning to the equivalent value for the general population after 5 years is introduced, this

increases the ICER to £82,697 per QALY gained. The inclusion of this assumption has the effect of increasing the ICER as it reduces the mortality of patients in the post-recurrence disease-free health states. These health states contain a higher proportion of patients in the no mifamurtide arm than in the mifamurtide arm due to the patients in the no mifamurtide arm having a higher recurrence rate. Altering the time point where patients revert to the general population mortality rates effects the ICER also. Increasing the time point at which the mortality rates change lessens the effect on the ICER while decreasing the time point increases the effect on the ICER. For example, increasing the time point to 10 years results in the ICER increasing to £68,850 per QALY. Decreasing the time point to 2 years results in the ICER being £82,697 per QALY gained (results not shown in table 3.13 below).

Applying the age-related utility rates has the effect of decreasing the QALY's gained as it reduces the HRQoL utility values for older patients. This variable only affects the QALY element of the ICER and increases it to £74,191 per QALY gained as it reduces the QALY's gain in the mifamurtide arm more due to its higher survival rate.

Table 3.13: Sensitivity Analysis: Inclusion of other Model Assumptions

Parameter	mifamurtide + Maintenance Chemotherapy	Maintenance Chemotherapy Alone	Difference
Default	£124,065	£31,717	£92,348
	16.76	15.40	1.36
			£67,748
Incorporate Amputation and Limb Salvage costs	£164,512	£69,093	£95,420
	16.76	15.40	1.36
			£70,001
Incorporate Hearing Loss AE's	£124,228	£31,862	£92,366
	16.23	15.21	1.03
			£90,038
Post-recurrence mortality rate equal Gen pop rate after 5 years DF	£123,977	£31,618	£92,359
	18.64	17.52	1.12
			£82,697
Apply Age-related utility rates	£124,065	£31,717	£92,348
	15.64	14.40	1.24
			£74,191

3.9.7 Scenario analyses: most pessimistic scenario and the impact of the discount rate.

In these analyses we wanted to set the model to include all of the other model assumptions as in section 3.9.6 at the same time. These results are presented below in table 3.14.

Table 3.14: Most pessimistic scenario.

Parameter	mifamurtide + Maintenance Chemotherapy	Maintenance Chemotherapy Alone	Difference
Default (without mifamurtide PAS)	£124,065	£31,717	£92,348
	16.76	15.40	1.36
			£67,748
• Amputation and Limb Salvage costs, • Hearing Loss AE's, • Post-recurrence mortality rate equal Gen pop rate after 5 years DF, • Apply Age-related utility rates	£164,895	£71,517	£93,378
	15.89	15.05	0.83
			£111,814
Use discount rate of 1.5% for outcomes and 3.5% for costs	£164,895	£71,517	£93,378
	23.42	22.07	1.35
			69,314
Introduce mifamurtide PAS	£150,801	£71,517	£79,284
	23.42	22.07	1.35
			£58,852

Table 3.14 above shows that when all of the other model assumptions as assessed in section 3.9.6 are applied together then the ICER is £111,814. This is dramatically reduced to £69,314 and £58,852 when the discount rate is adjusted to 1.5% for outcomes and the mifamurtide PAS is introduced. This analysis validates the base case ICER and demonstrates the general robustness of the base case analyses.

3.9.8 Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis was run for 10,000 model iterations using the default scenario with both discounting rates for both cost and outcomes set to 3.5%. In each probabilistic sensitivity analysis iteration, the model simultaneously sampled parameter values from assumed statistical distributions.

The results of the probabilistic sensitivity analysis are shown in Figure 3.2. Analyses have assumed a willingness to pay (WTP) threshold of £50,000. Analyses also reflect the affect of having the treatment cost primarily in the early years (mainly year 1) by the flatness of the cost-effectiveness scatter plot.

Figure 3.3 shows the Cost-effectiveness Acceptability Curve.

Figure 3.2: PSA Cost-effectiveness Plot

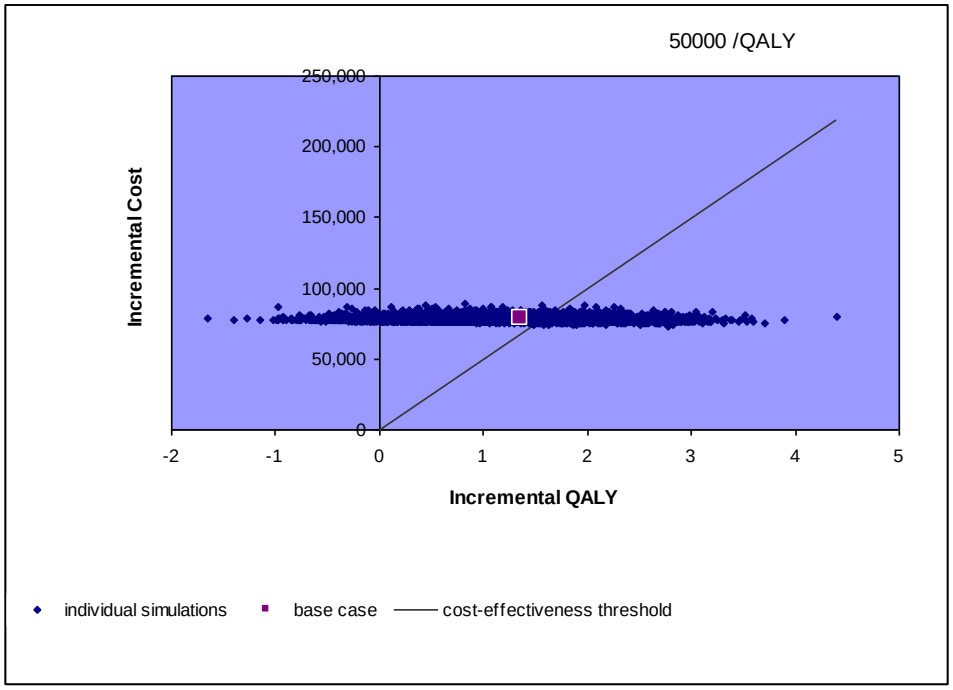
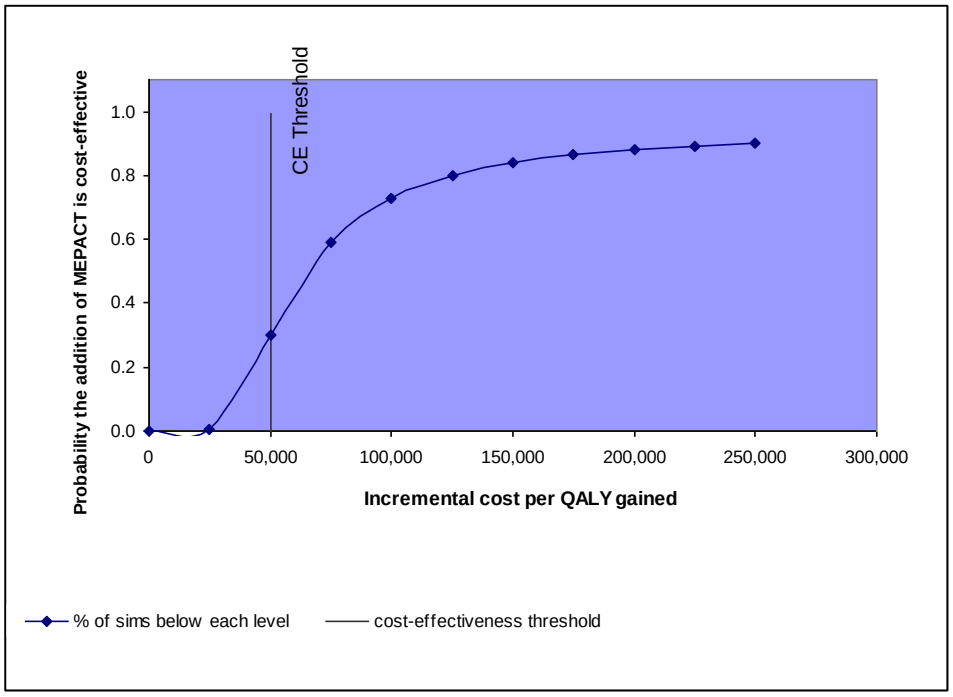


Figure 3.3: Cost-effectiveness Acceptability Curve:



The discounted results show that at a WTP threshold of £50,000 approximately 30% of the iterations were below this limit. Assuming a WTP of £70,000 for an ultra orphan medication, then almost 60% of the iterations are below this limit.

3.9.9 Conclusion

The Takeda cost effectiveness model shows that the deterministic ICER is between £67,748 and £41,634 per QALY gained (no mifamurtide PAS), and between £57,408 and £35,280 per QALY gained for discount rates of 3.5% and 1.5% for cost and outcomes respectively when a PAS for mifamurtide is introduced.

The difference in results due to discounting the outcomes shows that this is the most sensitive variable on the results. The results from sensitivity analyses also showed that the utility value for the disease-free health states of 0.85 is another important parameter.

Even when the model is set to include all of the other model assumptions as assessed in section 3.9.6 and then applied together for a super pessimistic scenario, and the ICER is £111,814, this is dramatically reduced to £69,314 and £58,852 when the discount rate is adjusted to 1.5% for outcomes and the mifamurtide PAS is introduced. This analysis validates the base case ICER and demonstrates the general robustness of the base case analyses.

In this case, the sensitivity of the discount rate and impact that can be made through modifying the discount rate for outcomes to 1.5% ameliorates any uncertainty in the model that may come from non inclusion of other model assumptions such as limb salvage maintenance costs or adverse events associated with hearing loss.

It is the opinion of Takeda UK Ltd that mifamurtide offers good value for money with an ICER in the region of £57,408 when a PAS for mifamurtide is introduced. On the upside the ICER may be as high as £35,280 per QALY gained when a discount rate of 1.5% and PAS are introduced.

4. Takeda Mifamurtide adjustment of Budget Impact to the NHS.

- The original budget impact model submitted by IDM Pharma Inc has been updated to incorporate two important elements: to use unadjusted population rates to model a more accurate description of the patient population; to assess the societal impact of the introduction of mifamurtide.
- The overall budget impact to the NHS from the introduction of mifamurtide in 2010 is estimated to be £2,684,988 (£2,496,432 with the introduction of a mifamurtide PAS) to £5,876,926 in 2015 (£5,200,458 with PAS).
- From a societal perspective, the breakeven point related to treatment cost of mifamurtide and positive contribution to society through tax contributions and benefits to national income is 37 years of age. Over a lifetime the discounted lifetime net tax contribution is £122,812 and undiscounted is £409,871 per average patient treated with mifamurtide.

Table 4.1 shows the number of patients assumed to use mifamurtide based on reported UK incidence rates for osteosarcoma in children, adolescents, and young adults of approximately 0.3/million, 0.7/million and 0.3/million of the population, respectively and the overall budget impact to the NHS. Figures for the children age group (aged 0-14 years) has been amended based upon data from the Automated Childhood Information System.

The annual budget impact for the NHS in England and Wales is estimated to be a £2,684,988 in 2010 rising to £5,876,926 in 2014. These figures are reduced to £2,496,432 and £5,200,458 in 2010 and 2014 respectively with the introduction of mifamurtide PAS.

Table 4.1: Budget Impact Estimates

POPULATION DATA		**2010**	**2011**	**2012**	**2013**	**2014**
Total UK population (millions)		61.5	62	63	63.0	64
England and Wales population	0.89	54.7	55.2	55.6	56.1	56.5
Incidence in children (0-14 years)	3.0	29	29	29	29	30
Incidence in adolescents (15-19 yrs)	7.3	26	26	25	24	24
Incidence in young adults (>20 yrs)	3.3	13	13	13	13	13
% of patients with non-metastatic	80%	67	67	67	66	67
POTENTIAL PATIENT POPULATION		**54**	**54**	**53**	**53**	**53**
Uptake rate		25.0%	60.0%	70.0%	80.0%	90.0%
TREATED PATIENTS		**13**	**32**	**37**	**42**	**48**
MIFAMURTIDE	**/dose**	**Cost/cycle of 48 doses**				
	£2375	£114,000				
BUDGET IMPACT (including VAT @17.5%)		**£2,684,988**	**£4,414,642**	**£4,901,490**	**£5,360,205**	**£5,876,926**
BUDGET IMPACT ASSUMING INTRODUCTION OF PAS		**£2,496,432**	**£3,962,108**	**£4,374,323**	**£4,761,607**	**£5,200,458**

4.1 The eligible treatment population.

Table 4.2 shows the number of patients assumed to use mifamurtide based on reported UK incidence rates for osteosarcoma in children, adolescents, and young adults of approximately 0.3/million, 0.7/million and 0.3/million of the population. These figures vary from the originally defined eligible patient population submitted by IDM Pharma Inc in which adjusted incidence rates per million of the population were employed rather than unadjusted rates. The original model used an incidence rate of 0.7 for the "children" group aged 0-14 years. The model has been updated to utilise information from the Automated Childhood Information System and the children group has been adjusted.

Table 4.2: Estimate eligible number of patients

POPULATION DATA		2010	2011	2012	2013	2014
Total UK population (millions)		61.5	62	63	63.0	64
England and Wales population	0.89	54.7	55.2	55.6	56.1	56.5
Incidence in children (0-14 yrs)	3.0	29	29	29	29	30
Incidence in adolescents (15-19 yrs)	7.3	26	26	25	24	24
Incidence in young adults (>20 yrs)	3.3	13	13	13	13	13
% of patients with non-metastatic	80%	67	67	67	66	67
POTENTIAL PATIENT POPULATION		**54**	**54**	**53**	**53**	**53**

These figures make the following assumptions:

- 80% of all osteosarcomas would be newly diagnosed, non-metastatic and resectable.
- Patients receive the average number of mifamurtide doses that are administered in the INT-0133 study, i.e. 38.4 doses. Budget impact figures are also provided with the assumption that mifamurtide is available to the NHS through a PAS in the UK.
- 89% of the total UK population is located in England and Wales.

4.2 Estimated uptake of mifamurtide?

Table 4.3 below presents the estimated uptake of mifamurtide through 2010 to 2015.

Table 4.3: Market share and patient uptake

POPULATION DATA	2010	2011	2012	2013	2014
POTENTIAL PATIENT POPULATION	54	54	53	53	53
UPTAKE RATE	25.0%	60.0%	70.0%	80.0%	90.0%
TREATED PATIENTS	**13**	**32**	**37**	**42**	**48**

It was assumed that market share would be 25% in 2010 increasing to 60, 70, 80 and 90% in 2011 through to 2015. These figures are derived from taking into account two important factors; firstly in 2010, NICE guidance would dictate mandatory NHS funding from September 2010; secondly, the current standard of care for patients with high grade resectable osteosarcoma is to enter patients into a clinical trial and currently the EURAMOS

I study, which does not include mifamurtide. This clinical trial culture is expected to continue and limit mifamurtide market share in the future.

4.3 Consideration of other significant costs associated with treatment.

All other significant costs associated with mifamurtide treatment have been considered and are aligned with resources assessed in the cost effectiveness model in section 3. Table 4.4 below shows the other total other costs related to mifamurtide treatment.

Table 4.4: Other significant costs associated with treatment.

Parameter	2010	2011	2012	2013	2014
Mifamurtide Treated Pts	13	32	37	42	48
No mifamurtide Treated Pts	40	21	16	11	5
Mifmaurtide only Related Costs (No PAS)	£1,238,522	£2,972,454	£3,462,678	£3,931,869	£4,443,349
1st line Chemotherapy Costs	£1,402,255	£1,402,255	£1,400,159	£1,391,144	£1,397,434
AE - Hearing Loss	£0	£0	£0	£0	£0
AE -Infusion Reaction	£22	£52	£60	£69	£78
Recurrence Related Costs					
Cost of Recurrence	£43,963	£39,663	£38,376	£36,910	£35,853
Cost of Palliative Care	£225	£219	£217	£213	£212
Total Costs	**£2,684,988**	**£4,414,642**	**£4,901,490**	**£5,360,205**	**£5,876,926**
Total Cost (inc mifamurtide PAS)	**£2,496,432**	**£3,962,108**	**£4,374,323**	**£4,761,607**	**£5,200,458**

The proposed dose of mifamurtide for all patients is 2mg/m^2 body surface area. In most cases one vial is sufficient per patient/ dose.

4.4 Estimated resource savings; societal impact.

There are no potential resource savings through the introduction of mifamurtide. However, given the young age at which the average patient may be treated for high grade resectable osteosarcoma, the societal impact may be significant. The original budget impact model submitted to NICE as part of the original submission of evidence has been amended to take into account societal aspects, and in particular to understand when, on average, a patient will repay society for treatment with mifamurtide through taxation and benefits to society. Table 4.5 presents the societal aspects and their unit cost/benefit applied.

Table 4.5: Societal Impact unit costs and benefits.

Cost		Unit costs	Source
Age at start of treatment		14	
Education		£4,830	DCFS, 2008
Healthcare	0-4 yrs	£550	p.46, http://www.archive.official-documents.co.uk/document/cm51/5103/5103.pdf
	5-15 yrs	£115	
	16-44 yrs	£270	
	45-64 yrs	£450	
	65-74 yrs	£750	
	75-84 yrs	£1,500	
Child Tax Credits		£539	Effects of taxes and benefits in the UK (2008)
State Pension		£8,580	Pensioners Income Series 2007/2008
Private Pension		£11,648	Pensioners Income Series 2007/2009
Tax (non-retired households)		35%	Effects of taxes and benefits in the UK (2008)
Tax (retired households)		30%	Effects of taxes and benefits in the UK (2008)
Mifamurtide Costs		£77,095	
Labour Productivity Growth		1.90%	OECD
Healthcare Expenditure Growth		3.00%	Connelly et al;Human Reproduction, Vol.1, No.1, pp.1-7,2009
Discount Rate		3.50%	HM Treasury
Age Child Tax Credits stop		18	Connelly et al;Human Reproduction, Vol.1, No.1, pp.1-7,2009
Age Education stops		19	Connelly et al;Human Reproduction, Vol.1, No.1, pp.1-7,2009
Age Retirement Begins		68	Connelly et al;Human Reproduction, Vol.1, No.1, pp.1-7,2009

The budget impact model is aligned with mortality in the cost effectiveness model. Table 4.6 below presents the different rates for probability of death, recurrence of disease and death post recurrence.

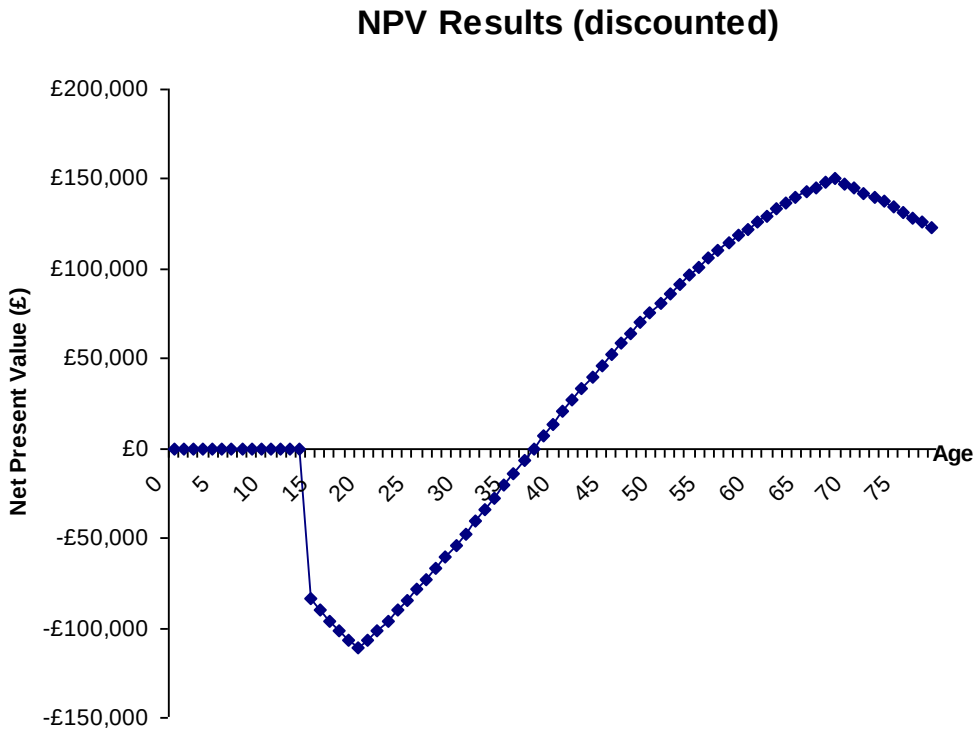
Table 4.6: Budget impact model Mortality rates

	Probability of Death (pre-recurrence)	Probability of Recurrence	Probability of Death Post- Recurrence
Yr 1	0.85%	3.41%	0.00%
Yr 2	0.19%	4.81%	16.13%
Yr 3	0.43%	2.56%	6.25%
Yr 4	0.24%	2.14%	0.00%
Yr 5	0.27%	0.00%	0.00%

Figure 4.1 below presents the results of the societal impact analyses. The starting age is 14 years, and the breakeven point is 37 years of age. Over a lifetime the discounted lifetime net tax contribution is £122,812 and undiscounted is £409,871.

This would suggest that on average, a patient who receives mifamurtide has repaid all costs of treatment by the age of 37 years and then go on to make significant positive contributions to society.

Figure 4.1: Societal Impact Analyses



5 Orphan drug environment in the UK and identifying a reasonable cost effectiveness threshold.

5.1 Background

It has been recognised for many years that, because of the costs associated with development, special incentives are required if pharmaceutical manufacturers are to be encouraged to develop and market treatments for rare diseases (orphan indications). In both the US, and the EU, legislation has been put in place to promote the development of treatments for rare diseases.

Orphan product definition

The European Medicines Agency (EMEA) defines orphan medicinal products as those which are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions that affect no more than five in 10,000 people in the European Union, or are medicines which, for economic reasons, would be unlikely to be developed without incentives[18]. In some cases the eligible patient population is very small and these diseases are termed ultra orphan.

The National Institute for Health and Clinical Excellence (NICE) defines a disease as ultra orphan if it has a UK prevalence of less than one in 50,000 people and if there are less than 1,000 cases per year[19.]

Osteosarcoma is the most common primary bone cancer in children, adolescents and young adults but remains a rare, ultra orphan disease with an estimated incidence of 3 cases per million population per year[5]. **This approximates to less than 100 new patients annually across the United Kingdom and meets NICEs criteria for ultra orphan designation[18].**

5.2 Mifamurtide - Comprehensive Orphan Drug Database

Over the last 20 years, almost 400 young patients with osteosarcoma have received Mifamurtide, **which is a significant development database for a rare disease.** The efficacy and safety of mifamurtide have been established in the INT-0133 Phase III randomised clinical trial which included the use of mifamurtide as an add-on to multi-agent chemotherapy in children, adolescents and young adults with osteosarcoma[10,11]. INT-0133 was designed and conducted independently by a leading paediatric cooperative study group and is the largest study completed in osteosarcoma to date. INT-0133 demonstrated that:

The addition of mifamurtide to standard chemotherapy significantly increased overall survival in patients with non-metastatic resectable osteosarcoma, and achieved an increase in 6 year overall survival from 70% to 78% with a p value of 0.0313 and an HR of 0.71 (95% CI: 0.52 to 0.96)[10] .Survival curves plateau above 60% and remain divergent at 12 years, long after the risk of recurrence is past, suggestive of an increased cure rate, with a 30% reduction in the risk of death[10].

The tolerability profile for the mifamurtide treatment arm in INT-0133 is consistent with that expected for standard multi-agent chemotherapy and the most frequent reported adverse events included stomatitis and nausea.

Mifamurtide may be used concurrently with other chemotherapy agents without increased toxicity[10].

The addition of mifamurtide to standard chemotherapy significantly increased overall survival in patients with non-metastatic resectable osteosarcoma, and achieved an increase in 6 year overall survival from 70% to 78% with a p value of 0.03 and an HR of 0.71 (95% CI: 0.52 to 0.96)[10]. Mifamurtide may be used concurrently with other chemotherapy agents without increased toxicity[10].

In comparison to the dataset that may be available for appraising other ultra orphan medications, it is clear that mifamurtide is not only well studied, but also demonstrable results.

5.3 Mifamurtide – Orphan Cost Comparison

Mifamurtide is cost effective in comparison to other funded ultra orphan drugs.

The cost-effectiveness of mifamurtide for the treatment of osteosarcoma was evaluated in a Markov analysis in the mifamurtide NICE submission based on INT-0133 trial data[10].

The Takeda cost effectiveness model shows that the deterministic ICER is between £67,748 and £41,634 per QALY gained (no mifamurtide PAS), and between £57,408 and £35,280 per QALY gained for discount rates of 3.5% and 1.5% for cost and outcomes respectively when a PAS for mifamurtide is introduced.

Mifamurtide is cost effective in comparison to other orphan, ultra orphan and orphan oncology indications: a review of other orphan indications suggests that a cost per QALY of this range can be considered good value for money.

5.4 Report on NICE Recommendations for Appraisal of Orphan Products to the Department of Health, 2006

NICE submitted a proposal for appraising orphan and ultra-orphan drugs to the Department of Health in 2006: this was in response to a ministerial request on how such drugs might be appraised. (Available at www.nice.org.uk/niceMedia/pdf/smt/120705item4.pdf). To date NICE have not been asked to implement this proposal, and currently drugs with orphan status or considered ultra-orphan in the UK are considered under the existing appraisal process.

NICE's conclusions and recommendations in the proposal are as follows:

- A number of drugs which can be categorised as "orphan drugs" have been referred to NICE and appraised successfully suggesting that for these drugs it was possible to apply NICE methodology [section 4.1.1 of the NICE report]. Therefore no changes to its processes are needed for the appraisal of conventional orphan drugs [4.1.3]. However, NICE considers that there would be problems in the appraisal of "ultra-orphan drugs" largely because of their high acquisition costs [4.2].
- The Institute is confident that it is able to provide the NHS with robust and reliable advice on the clinical effectiveness of ultra-orphan drugs [4.4].
- NICE has considered whether the QALYs achieved with ultra-orphan drugs could be "weighted" so as to produce a final cost per QALY aligned to the Institute's current approach to cost effectiveness. As a matter of general policy NICE neither recommends,

accepts, nor uses equity weighting in its current technical appraisal processes and it does not recommend this approach for the future [4.7].

- Separate decision rules (i.e. the range of ICERs considered "cost effective") will need to be developed and adopted for ultra-orphan drugs if the Institute is prepared to accept substantially higher ICERs than those currently considered to be cost effective [4.9].
- The Institute proposes that these ultra-orphan drug decision rules are based on the ICERs of those ultra-orphan drugs currently on the UK market (our italics). NICE states that this will provide an implicit benchmark against which new ultra-orphan products can be evaluated. NICE emphasises that a final position on cost effective ICERs will need to be confirmed through wider consultation. At current prices [2005 in the report] indicative ICERs for ultra-orphan products are in the range of £200,000 to £300,000 per QALY (i.e. a ten-fold increase on the decision rules currently applied in conventional appraisals) [4.9].
- It is possible that even with these new decision rules NICE will consider that some products to be cost ineffective. Under these circumstances, and on the recommendation of the Institute, it is proposed that the Department be given the opportunity to enter negotiations with manufacturers to investigate the possibility of a price reduction that would bring the ICER into line with NICE's ultra-orphan decision rules. If some price reduction were to be negotiated, the Department would then re-refer the product to the Institute [4.10].
- The Institute recommends that a new programme is developed which would draw a distinction between standard appraisals and ultra-orphan appraisals and their different decision rules. Features of this new programme would be that i) it should not be described as an "appraisal"; ii) a separate and distinct process would be developed and applied; iii) advice should be developed by a new committee under a chair who is not involved with the appraisal programme [4.11].

Appendix 1 in the proposal shows conditions for which orphan drug designation has been granted and for which NICE appraisals have been completed. The ICERs that NICE deem to be cost ineffective are: metastatic colorectal adenocarcinoma – Irinotecan/oxaliplatin (second line) at £29,000/LYG; Crohn's disease – eternacept (fistulising) at £100,000/QALY; multiple sclerosis – beta interferons (20 year and 5 year perspectives) at £69,000/QALY and £580,000/QALY respectively. Note that these are all "per QALY gained" apart from metastatic colorectal adenocarcinoma ("per life year gained).

Appendix 2 shows some ultra-orphan drugs in current use. The preliminary estimated ICERs range from £23,324/QALY (Iloprost for primary pulmonary hypertension) through to £391,244/QALY (Imiglucerase for Gaucher's types I and III).

The (crucial) proposal that ultra-orphan drug decision rules are based on the ICERs of those ultra-orphan drugs currently on the UK market has no basis in welfare economics, nor, specifically, allocative or distributive efficiency: it is a 'stop-gap' position that provides a crude benchmark.

NICE has paid some heed to the input from the Citizens Council Report on Ultra Orphan drugs from a session held in November 2004. The main conclusions and finding from that meeting were as follows:

- Of the 27 participants 16 thought that, with certain conditions, the NHS should consider paying premium prices for drugs to treat patients with very rare diseases: 4 people thought that the NHS should pay whatever premium price is required for drugs to treat patients with very rare diseases; 7 people thought that the NHS should not consider paying premium prices for drugs to treat patients with very rare diseases, but should decide whether or not to provide ultra-orphan drugs using the same clinical and cost effectiveness appraisals as any other treatment;
- The criteria the NHS should take into account when deciding to pay premium prices for ultra-orphan drugs are, in descending order of importance: i) the degree of severity of the disease; ii) if the treatment will provide health gain, rather than just stabilisation of the condition; iii) if the disease or condition is life-threatening.

This balance of opinion and the criteria are reflected in the NICE proposal.

In addition to the November 2004 Citizens Council Report NICE has also consulted, in November 2008, the Citizens Council on the question "In what circumstances should NICE recommend interventions where the cost per QALY is above the threshold range of £20-30,000?"

Two of the 29 Council members attending the meeting took the view that there were no circumstances in which NICE appraisal committees should depart from the established threshold. Of the remaining 27 Council members, the numbers who favoured taking account of each of a list of various possible circumstances were - in order of support - as follows:

1 the treatment in question is life-saving (n=24)

2 the illness is a result of NHS negligence (23)

3 the intervention would prevent more harm in the future (23)

4 the patients are children (22)

5 the intervention will have a major impact on the patient's family (22)

6 the illness under consideration is extremely severe (21)

7 the intervention will encourage more scientific and technical innovation (21)

8 the illness is rare (20)

9 there are no alternative therapies available (19)

10 the intervention will have a major impact on society at large (16)

11 the patients concerned are socially disadvantaged (13)

12 the treatment is life extending (10)

13 the condition being tackled is time-limited (9)

14 the illness is a result of corporate negligence (2)

Mifamurtide for the treatment of osteosarcoma would appear to fulfill the criteria for items 1, 4, 5, 6, 8, 9 and 12.

The overall position of NICE is, therefore, that if they were asked to consider ultra orphan as a separate category then the 'rules' applied may be different from that used in standard appraisals and the threshold may be amended (perhaps substantially). This appears partly to be in response to the findings from the Citizens Councils meetings where social value judgments have been expressed.

5.5 Report of the All Party Parliamentary Group on Cancer's (APPGC) Inquiry into Inequalities in Cancer, December 2009 Westminster London

In April 2009 the APPGC launched an Inquiry into inequalities in cancer reviewing evidence from cancer patients, charities, cancer service providers and policy makers. Eight priorities for action were identified including recommendations on rarer cancers. Specifically the APPGC called for:

- The Department of Health should continue to encourage NICE take a more flexible approach to the appraisal of orphan drugs
- The commissioning of ultra orphan drugs should be undertaken by the National Specialised Commissioning Group (NSCG).
- The APPGC used the example of "primary bone cancer" of which osteosarcoma is the most frequent diagnosis as a service that should be under the remit of the NSCG.

5.6 Conclusion

In summary, there is no clear procedure for how ultra orphan medications should be assessed differentially from non orphan indications, although the NICE Social Value Judgments may imply some allowance, and it is clear there is a political will to modify how these medications should be assessed; for example the newly devised "Innovation Pass". Perversely, mifamurtide is not eligible for such an accolade because the dataset is complete and the results are demonstrable, and these awards are reserved for medications whereby there is a degree of uncertainty regarding efficacy of treatment.

However, it is clear that an ICER threshold of £20,000 to £30,000 is not appropriate for ultra orphan medications and a threshold of £50,000 to £60,000 as accepted for, "end of life medications". For example, sunitinib for renal cell carcinoma was approved with an incremental cost per QALY gained of approximately £55,000. Its hard to believe that ultra orphan medications are not worthy of a similar cost effectiveness threshold.

Appendix 1:

Figure 1: Trial INT-0133 dosing schema

	Week of maintenance phase treatment																										
	12	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39-47**
A	C, 3D			MX	MX	C, 3D			MX	MX	3D			MX	MX	3D			MX	MX								
A+	C, 3D, 2M	2M	2M	MX, 2M	MX, 2M	C, 3D, 2M	2M	2M	MX, 2M	MX, 2M	3D, 2M	2M	M	MX, M	MX, M	3D, M	M	M	MX, M	MX, M	M	M	M	M	M	M	M	M
B	C, 3D			MX	MX	5I, 3D			MX	MX	C, 3D			MX	MX	5I, 3D			MX	MX	C			5I			C	
B+	C, 3D, 2M	2M	2M	MX, 2M	MX, 2M	5I, 3D, 2M	2M	2M	MX, 2M	MX, 2M	C, 3D, 2M	2M	M	MX, M	MX, M	5I, 3D, M	M	M	MX, M	MX, M	C, M	M	M	5I, M	M	M	C, M	M

MX – single dose methotrexate, 3D – 3 days dosing with doxorubicin (given over 72 hours), C – single dose cisplatin, 2M – 2 days dosing with MIFAMURTIDE at least 3 days apart, M – 1 day dosing with MIFAMURTIDE, 5I – 5 days dosing with ifosfamide

The assumption that 7 additional outpatient attendances are required for a patient receiving only 13 mifamurtide doses on Regimen B is based on the following calculations:

Week 12: No additional outpatient attendance as mifamurtide could be administered same day as doxorubicin.

Week 13 & Week 14: Two additional outpatient attendances required for both weeks = total 4 outpatient attendances.

Week 15 & Week 16: One additional outpatient attendances required for both weeks as 1 could be administered the same day as the methotrexate was given = total 6 outpatient attendances.

Week 17: No additional outpatient attendance as mifamurtide could be administered same day as doxorubicin.

Week 18: One additional outpatient attendance required to total 13 mifamurtide doses. Total = 7 outpatient attendances.

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