Issue 1 1.1 Scope of submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 5 1.1 Scope of the submission *"The manufacturer's submission (MS) generally reflects the scope of the appraisal issued by 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)."* With reference to the NICE Scope "Guidance Osteosarcoma - mifamurtide: final scope, 22nd October 2008) Guidance will only be issued in accordance with the marketing authorisation." Mifamurtide (Mepact, Takeda UK) 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. Takeda UK reiterates that the submission meets the need of scope as the marketing authorisation for Mepact does not include individuals with osteosarcoma related to Paget's disease, individuals with metastatic disease and individuals with relapsed osteosarcoma.	Takeda UK requests an update to the ERG comment on the submission meeting the population within the scope in line with the Mepact Marketing Authorisation, which states that Mepact is indicated for the treatment of 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.	The submission meets the definitions within the scope in line with the Mepact Marketing Authorisation.	The ERG is duty bound to report that the full population within the original scope were not included. The footnote at the bottom of page 5 indicates that the population in the scope not evaluated in the submission are outside of the marketing authorisation.

Issue 2 1.4 Commentary on the robustness of submitted evidence - Weaknesses

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 8 1.4 Weaknesses *"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)."* The ERG Report should be amended to confirm that the base case submitted by Takeda UK matches the base case of the NICE Appraisal Committee; it is not merely a "reflection" of the base case.	Takeda UK confirms that the model has been updated to reflect the assumptions that the NICE Appraisal Committee considered to be most plausible, as follows: • *Clinical data as per the pooled datasets of A/B versus A+/B+* • *60 year time horizon.* • *100% of the population starting in the Disease-free health state.* • *Amputation and limb salvage costs included (changed as per ACD).* • *Hearing loss adverse event not included (not changed as per ACD);* • *Mortality risk reverting to general population after a given time period (changed as per ACD);* • *Age related utility weights included (changed as per ACD);* • *Discounting rates of 3.5% for both costs and outcomes applied;* The ERG Report should be amended to confirm that the base case submitted by Takeda UK matches the base case of the NICE Appraisal Committee and referenced to the NICE Final Appraisal Determination of October 2010 Section 4.16; it is not merely a "reflection" of the base case.	The ERG Report should be amended to confirm that the base case submitted by Takeda UK matches the base case of the NICE Appraisal Committee; it is not merely a "reflection" of the base case.	The ERG is not clear that the Appraisal Committee did specify that their preferred assumption was to use the pooled datasets. Section 4.8 states that 'the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with A.' It is inferred therefore that the Committee accepted that the combined analysis of all the INT-0133 data may *not* be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with A. Section 4.16 refers to the analyses undertaken by the manufacturer which produces the £67,000 probabilistic cost per QALY. Section 4.17 comments on the analysis of unpooled data, with a probabilistic QALY in excess of £100,000 and states that there is 'substantial uncertainty around these estimates, but because the resulting ICERs were substantially higher than the 'best case' ICERs they would not change the conclusion that mifamurtide would not be a cost-effective

			use of NHS resources.' The interpretation by the ERG of these statements is that if the pooled data had been considered cost-effective by the committee then the committee would have needed to have come to a decision on their preferred method. However as neither value was considered cost-effective then this decision has not been made. It is the remit of the ERG to provide the relevant data for the Appraisal Committee to make a decision and thus both analyses will be presented.

Issue 3 1.4 Commentary on the robustness of submitted evidence - Weaknesses

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 8 and 9 1.4 Weaknesses *"However, there are a number of salient uncertainties that the appraisal committee may wish to discuss and 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)."* INT0133 was a prospective, parallel group, four-arm, multi-centre, randomised and open-label design. The study posed two questions in a 2 X 2 factorial design. INT0133 was powered to assess whether addition of ifosfamide to doxorubicin, cisplatin, and HDMTX would improve event-free survival (EFS) and overall survival (OS). INT0133 was also powered to assess whether addition of mifamurtide to chemotherapy would improve EFS and OS. The INT0133 study was not designed to analyze four arms in parallel fashion with adequate power and conclusions cannot be drawn in line with good clinical trial and statistical procedure. Post-hoc analysis of Regimen A vs. Regimen A+ does not allow conclusions to be drawn from this comparison. This course of action would also necessitate consideration of Regimen B vs. Regimen B+ which significantly increases Mepact impact on overall survival from 70 to 81% over 6 years.	The INT0133 study was powered to assess in a 2 X 2 Factorial Design the addition of ifosfamide and mifamurtide to doxorubicin, cisplatin and high dose methotrexate on OS and EFS. Post hoc analysis of separate arms is not possible as the trial was not powered to detect any differences in outcomes between arms. Takeda UK asks that post-hoc analysis is removed from the ERG Report in line with good clinical trial and statistical practice.	Post hoc analysis of separate arms in a 2 X 2 Factorial design is not possible due to lack of power. Conclusions cannot and should not be drawn from this methodology in line with good clinical trial and statistical practice and should be removed from the report.	As detailed in the response for issue 2, the appraisal committee have not ruled out the use of 'unpooled' data. As such, it is the remit of the ERG to provide the committee with the relevant ICER in this scenario.

Issue 4 1.4 Commentary on the robustness of submitted evidence - Weaknesses

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 8 and 9 1.4 Weaknesses *"However, there are a number of salient uncertainties that the appraisal committee may wish to discuss and 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 addition of Mepact to chemotherapy significantly increased the incidence in objective (11.5% with Mepact 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 Mepact treatment groups; specifically the incidence of auditory problems was lower in patients treated with chemotherapy plus Mepact 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 Mepact was within the range expected for cisplatin alone.	Takeda UK asks the ERG to remove the speculation that Mepact may cause loss of hearing; this is not supported by the data or previous patient exposure in Phase II trials. This should reflect the statement referenced from the NICE Final Appraisal Determination of October 2010 Section 4.13 which states: *"The Committee accepted the views of the clinical specialists that although hearing loss was the main adverse event associated with mifamurtide treatment, the rate of hearing loss observed in INT-0133 was not unusual in cisplatin-containing regimens and its exclusion from the model could therefore be justified."*	The ERG report speculates that Mepact may cause hearing loss although the data does not support this. Ototoxicity is commonly associated with cisplatin therapy, and the frequency of hearing loss reported for patients treated with Mepact was within the range expected for cisplatin alone. This should reflect the statement referenced from the NICE Final Appraisal Determination of October 2010 Section 4.13 which states: *"The Committee accepted the views of the clinical specialists that although hearing loss was the main adverse event associated with mifamurtide treatment, the rate of hearing loss observed in INT-0133 was not unusual in cisplatin-containing regimens and its exclusion from the model could therefore be justified."*	The ERG believe that a sensitivity analysis should be conducted on hearing loss due to the statistically significant result (a p-value of 0.007 in relation to subjective hearing loss and a p-value of 0.047 in relation to objective hearing loss). As such we have undertaken this analysis. The Appraisal Committee can ignore this analysis if they wish.

Issue 5 1.4 Commentary on the robustness of submitted evidence - Weaknesses

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 9 1.4 Weaknesses *"The ERG has concern regarding the lack of face validity of the model. The modelled survival rates are greater than the observed data with increases in the range of 3-4 percentage points. It is not known whether this discrepancy favours or disfavours mifamurtide but is likely to increase the uncertainty in the results.* The 6-year Kaplan-Meier (KM) estimate of the survival rate in the mifamurtide arm is 78% and 70% in the arm without mifamurtide based on all 678 patients. It is important to note that this rate is different than the rate observed in patients who entered the adjuvant treatment phase of the INT-0133 trial. Alike to the previous Cost Effectiveness model submitted in the previous IDM Pharma Inc submission, the analyses in the Takeda cost effectiveness model is based upon an analysis of the 604 ITT patients who entered the maintenance phase. Seventy-four patients in the ITT group who did not enter the adjuvant phase were excluded from this analysis. In this patient population who received adjuvant treatment, the 6-year Kaplan-Meier estimate of the survival rate 80.4% in the mifamurtide arm and 72.9% in the arm without mifamurtide. This data has been submitted to NICE in response to Clarification questions submitted on the 14th January 2010 – Question A5.	Takeda UK requests an update to the ERG comment on the submission meeting the population within the scope in line with the Mepact Marketing Authorisation.	The submission meets the definitions within the scope in line with the Mepact Marketing Authorisation.	The ERG is unclear on the amendment being requested, and it is possible that the text from Issue 1 has not been changed to the intended text.

Issue 6 1.4 Commentary on the robustness of submitted evidence – Areas of uncertainty

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 9 1.4 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)…"* Takeda UK refer to Takeda UK response to the NICE Appraisal Consultation Document Section 1 30th July 2010 for detail. As INT-0133 was analysed on an intention to treat basis, the impact of the stated parameters (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) would have if anything, a minimal negative effect on the results against mifamurtide. The expected result from these suggested uncertainties would be to diminish the observed efficacy of mifamurtide, not exaggerate it.	Takeda UK request that the ERG acknowledge that the potential impact of these parameters would diminish the observed efficacy of mifamurtide. Hence the Mepact CE model produces cost effectiveness estimates which could be termed as conservative.	The ERG Report suggests that the magnitude of the improvement in overall survival is uncertain due to the stated parameters. Takeda UK request that the ERG acknowledge that the potential impact of these parameters would diminish the observed efficacy of mifamurtide, not enhance it. Hence the Mepact CE model produces cost effectiveness estimates which could be termed as conservative.	Text has been inserted to state that "It is probable that the limitations in trial design would be unfavourable to the cost-effectiveness of mifamurtide, although the magnitude of the effect is unknown."

Issue 7 1.4 Commentary on the robustness of submitted evidence - Areas of uncertainty

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 9 1.4 Areas of uncertainty *"…and the interpretation of the statistical analyses (wide confidence intervals (CI) with similar point estimates for efficacy)."* Takeda UK refer to Takeda UK response to the NICE Appraisal Consultation Document Section 2 30th July 2010 for detail. Takeda UK confirm 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+). This was done to answer two separate clinical questions using the same limited data set, a particularly appropriate method given the ultra-orphan and serious nature of this disease. This is unquestionably a more statistically robust analysis than splitting the trial post-hoc to perform separate sub-group analyses for comparisons which it was not powered for. To try and argue otherwise is both statistically inaccurate & manifestly perverse. Statistical analysis was pre-specified in the INT-0133 trial protocol and performed as planned to ensure credibility in line with good clinical trial practice. Hence, the approach to analyse the INT-0133 trial as planned is in line with good clinical trial practice and statistical methodology from the ICH-GCP, the Declaration of Helsinki, the EU Clinical Trials	Takeda UK request that the ERG acknowledge that the pre-specified statistical analysis must be used in line with good clinical and statistical practice and to assess the evidence base for assessment of the disease free survival and overall survival benefit associated with mifamurtide using the whole patient population in INT-0133 where A+/B+ is compared to an A/B regimen.	NICE Appraisal Committees in the past have sited statistical analysis issues with primary and sub group analysis and suggested it as poor clinical trial practice, refuting to accept the clinical case on this basis. Takeda UK request that the ERG acknowledge that the pre-specified statistical analysis must be used in line with good clinical and statistical practice.	Additional text has been added. "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 mifarmutide and chemotherapy regimen, will need to be considered by the appraisal committee" However, as detailed in the response for issue 2, the appraisal committee have not ruled out the use of 'unpooled' data. As such, it is the remit of the ERG to provide the committee with the relevant ICER in this scenario.

Directive (EUCTD) and the FDA Regulations Relating to Good Clinical Practice and Clinical Trials; it is inappropriate to carry out sub group analysis if not pre-specified in the statistical protocol. Moreover, sub group or secondary outcome analysis is only considered valid for hypothesis generation if the primary outcome measure meets significance and the original hypothesis proven and accepted.			

Issue 8 1.4 Commentary on the robustness of submitted evidence - Areas of uncertainty

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 9 1.4 Areas of uncertainty *"The clinical advice provided to the ERG indicated that it is likely that a more clinically relevant assessment for a UK population would be derived from an analyses comparing Regimen A+ with Regimen A. The mathematical model submitted by the manufacturer also estimates that, on average, a patient being treated with Regimen A would accrue more QALYs at a lower cost than a patient receiving Regimen B."* *"Importantly, the addition of mifamurtide to multi-agent chemotherapy may be substantially reduced if it is assumed that Regimen A represents current UK practice hold, rather than a combination of Regimen A and Regimen B."* Takeda UK refer to Takeda UK response to the NICE Appraisal Consultation Document Section 3 30th July 2010 for detail. Takeda UK confirms that the clinical standard of care for osteosarcoma patients within the UK is entry into a randomised multicenter intergroup clinical trial (such as EURAMOS I) and this is suggested by NICE within the ACD. Currently it is estimated that 80-90% of patients diagnosed with osteosarcoma in the UK are entered into the European and US osteosarcoma trial EURAMOS I trial as part of an adjuvant regimen (with ifosfamide, etoposide, cisplatin, doxorubicin and methotrexate) for patients with tumours showing a poor histological response to pre-operative chemotherapy. Therefore, key points to note of relevance for the comparisons	Takeda UK request the ERG Report is updated to acknowledge that the majority of patients receive care through an RCT such as EURAMOS I and this treatment includes ifosfamide and is more akin to treatment arms B/B+ in the INT-0133 trial. Hence, it is the opinion of Takeda UK that the appraisal committee should consider both 3-agent and 4-agent combination chemotherapy treatment as the standard of care in England and Wales.	Takeda UK request the ERG Report is updated to acknowledge that the majority of patients receive care through an RCT such as EURAMOS I and this treatment includes ifosfamide and is more akin to treatment arms B/B+ in the INT-0133 trial.	Additional text has been added to state that a relatively large proportion of patients are treated within RCTs. The clinical advisor to the ERG has indicated that chemotherapy without ifosfamide is the standard treatment in both the large, ongoing, Euramos I RCT and in patients treated outside of this trial.

as discussed in the ACD are as follows: • Regimens with and without ifosfamide represent the current and future standard of care for the treatment of osteosarcoma in England and Wales. Even though many patients are currently treated within the context of a clinical trial, given the rarity of the condition the treatment provided within clinical trials (i.e. the EURAMOS I trial) represents the standard of care across treatment centres in the UK. • The most robust evidence base for assessment of the disease free survival and overall survival benefit associated with mifamurtide is that using the whole patient population in INT-0133 where A+/B+ is compared to an A/B regimen. • The survival benefit associated with A/B v A+/B+ provides a more realistic proxy for the clinical benefits associated with A+ v A, and B+ v B than splitting the trial to perform separate sub-group analyses for these comparisons. For reasons explained above (Sections 2), we do not feel a reliable assessment of cost-effectiveness can be performed for A+ vs. A, or B+ vs. B. Hence it is important to differentiate from what is perceived to be routinely used, and what is actually used in the NHS. It is incorrect to assume that 3-agent chemotherapy is the current standard of care when only a minority of patients receive non protocol, non RCT (EURAMOS I) care. The majority of patients receive care through an RCT and this treatment includes ifosfamide and is more akin to treatment arms B/B+ in the INT-0133 trial. Hence, it is the opinion of Takeda UK that the appraisal committee should consider both 3-agent and 4-agent combination chemotherapy treatment as the standard of care in England and Wales.			

Issue 9 1.4 Commentary on the robustness of submitted evidence - Areas of uncertainty

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 10 1.4 Areas of uncertainty *"It is unclear whether the loss of hearing observed when mifamurtide was added to chemotherapy regimens is representative of actual events or whether these were chance events associated with cisplatin use. 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)".* Please see the response to Issue 4.	Please see the response to Issue 4.	Please see the response to Issue 4.	Please see the response to Issue 4.