**NICE Single Technology Appraisal - Mifamurtide for osteosarcoma**

On behalf of Takeda UK Ltd, please find our response to the NICE Appraisal Consultation Document (ACD) provided on the 2nd July 2010 with regards to the NICE Single Technology Appraisal for Mifamurtide for osteosarcoma. Takeda UK would like to offer comments under points 1, 2 and 3 of the four general headings requested:

*i) Whether you consider that all of the relevant evidence has been taken into account?*

We consider that all of the evidence submitted by Takeda UK on the 10th December 2009 and the 8th February 2010 has been taken into account. However, we do not consider the appraisal committee's interpretation of what is the appropriate comparator in the UK to be correct.

In the UK the current standard of care is entry into a randomised multicentre intergroup clinical trial (such as EURAMOS I.) 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. Hence it is important to differentiate from what is perceived to be routinely used, and what is actually used in the NHS. In the EURAMOS I trial, the adjuvant treatment regimen employed includes ifosfamide which equates to 4 agent chemotherapy. As a result it is incorrect to assume that 3 agent combination chemotherapy is the current standard of care and 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.

These considerations are further elaborated upon in section 3 of this response to ACD.

*ii) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?*

Takeda UK do not consider the summaries of clinical and cost effectiveness presented within the ACD to be generally reasonable interpretations for this appraisal for two key reasons:

1. As highlighted above, we do not consider NICE's interpretation of the standard of care to be appropriate.
2. We do not consider NICE's approach to assessing the results of the INT-0133 trial as appropriate either scientifically or philosophically. NICE have analysed the trial's 2 x 2 factorial design as four separate arms. However, the trial was not designed nor

statistically powered to be analysed in this way. The post-hoc analysis under-taken by NICE was not statistically significant in any of the arms – this is not surprising as the trial was not designed nor powered to be analysed in this way. Additionally, given the substantial time commitments in researching rare and ultra orphan diseases, the limited sample sizes and often the relative uncertainty related to such results, it seems philosophically wrong to sub divide the data of a rare disease to the point where results cannot be significant and favourable decision making is impossible. It is the opinion of Takeda UK that the INT-0133 trial should be analysed as it was statistically planned to do so in line with good clinical and statistical practice.

3. Given the considerations raised in points 1 and 2 above, we do not consider the summaries of cost effectiveness to be reasonable nor logical interpretations.

These considerations are further elaborated upon in section 1, 2, 3, 4 and 5 of this response to ACD.

*iii) Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?*

Takeda UK do not consider the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for guidance to the NHS. In particular it is not clear from the ACD how the rarity of osteosarcoma has been considered in this appraisal. Takeda UK believe it is important for NICE to be transparent in any future documentation recommending the use of mifamurtide (FAD and guidance documents) as to NICE's policy for assessing medicines for rare and ultra orphan disease and how in this case the Social Value Judgements[1] endorsed by the NICE Board have been employed for consideration for this appraisal.

Takeda UK are committed to making mifamurtide available to patients in England and Wales; however at this stage it is not clear what is required to accomplish this for an ultra orphan medication. Indeed, using the standard appraisal committee cost per QALY threshold for acceptance of under £30,000 would suggest that patients with osteosarcoma and other rare illnesses will be underserved until NICE have a transparent policy for assessment of rare illnesses to which manufacturers can work towards.

These considerations are further elaborated upon in section 5 of this response to ACD.

Given these considerations, it is the opinion of Takeda UK that the provisional recommendations of the ACD do not constitute a suitable basis for guidance to the NHS.

In addition, Takeda UK would encourage NICE to consider some of the previous thinking regarding the appraisal of ultra orphan medications for this appraisal, or alternatively, and as per stated in the Social Value Judgements, allow the other mechanisms in the NHS to assess the availability of ultra-orphan drugs, and to terminate this NICE appraisal.

Takeda UK's response to the ACD is provided in following five sections:

Section 1: We summarise the main findings from the pivotal trial INT-0133, and the quality and robustness of findings in the context of an ultra-orphan indication.

Section 2: We address concerns expressed in the ACD over specific methodology in INT-0133 relating to the analyses of A/B vs. A+/B+, and related uncertainty over the estimates of survival. We present further information pertaining to the statistical plan for INT-0133 and robustness of the trial methodology.

Section 3: We address the issue of the appropriate comparison relevant for UK practice for assessing clinical effectiveness from the INT-0133 trial.

Section 4: We address issues and concerns over the plausible ICER for mifamurtide vs. standard therapy.

Section 5: We place the clinical and cost-effectiveness results in the context of the unmet need of children, teenagers and young adults with the ultra-orphan disease osteosarcoma.

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Takeda UK Ltd

30th July 2010

## Section 1: Summary of clinical effectiveness issues.

1.1 Methodology related to INT-0133

Paragraph 4.5 of the NICE ACD states:

> *"The Committee considered the evidence on the clinical effectiveness of mifamurtide as presented in the manufacturer's submission and the ERG's critique. It considered the evidence from the only relevant randomised clinical trial (INT-0133). The Committee noted that the study was relatively well conducted, but it agreed that there were substantial methodological issues identified by the ERG which led to uncertainty around the estimates of survival."*

Page 9 of the Evidence Review Group (ERG) report[2] states the following methodological issues suggested of the INT-0133 trial:

- open label design.
- delayed adminstration and failure to receive mifamurtide after randomisation.
- imbalance of histological response to neoadjuvant therapy.
- disparity of survival events in the subset of patients who did not enter the maintenance phase.
- interpretation of the statistical analyses.

Responses to these ERG concerns relating to the robustness of the data are addressed in turn through this section. Information provided is not new evidence, but has been previously submitted in response to clarification questions to IDM (December 2008), Takeda UK (January 2010) and response to the ERG Report from Takeda UK (February 2010):

### *1.1.1. "open label design"*

Blinding is not needed to assess patient survival, which was the first stated aim of study INT-0133. Blinding of treatment was not considered feasible in study INT-0133 because (i) it is not acceptable to expose children or adolescents to 48 placebo injections and (ii) the low grade side effects that usually result from initial mifamurtide doses, including fever, chills and headache, would make blinding difficult. The outcome assessments used are consistent with the European regulatory standards set out in the Note for Guidance on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95 Rev.3)[3] and the Addendum on Paediatric Oncology (CPMP/EWP/569/02)[4].

The ERG Report from 2009[2] acknowledges that:

> *"With many cytotoxic cancer drugs, the nature of the interventions precludes blinding (i.e. drug toxicities or manner of administration) for the practical and ethical reason that informed dose monitoring and adjustment is required."*

*1.1.2. "delayed adminstration and failure to receive mifamurtide after randomisation"*

The ERG refers to the delayed administration of mifamurtide within the trial due to the lack of availability of the specialist filter required for reconstitution and administration of mifamurtide (was not available from 15 June 1995 to 15 January 1996.)

During this period only 8 of the 51 patients randomised to a mifamurtide group did not receive mifamurtide therapy. These 8 patients were retained in the intention to treat analysis and therefore would have if anything, a minimal negative effect on the results against mifamurtide. Also, the expected result from such a delay would be to diminish the observed efficacy of mifamurtide, not exaggerate it.

*1.1.3. "imbalance of histological response to neoadjuvant therapy"*

The ERG refers to the imbalance in histological response to neoadjuvant therapy between treatment groups. This was particularly pronounced for those patients assigned to regimen A+, where a greater proportion of tumours showed a poor [greater than 5% remaining viable tumour] histological response.

Takeda UK agree with the appraisal committee that there is evidence of a link between poor histological response and prognosis and it is not clear the impact that this makes upon the A/A+ arms. However, this imbalance would again reduce the positive effect on patient survival from mifamurtide, not exaggerate it.

*1.1.4. "disparity of survival events in the subset of patients who did not enter the maintenance phase"*

Takeda UK refer to the response to the NICE clarification questions submitted by IDM on the 8th December 2008 and detailed below.

The requested information regarding the number of patients who did not enter maintenance (adjuvant treatment phase) in INT-0133 is included in the following table for intent-to-treat patients (Table A11a).

**Table A11a: Patient Disposition during Induction and Maintenance Phases INT-0133 (ITT Population)**

| | Regimen A | Regimen A + MEPACT | Regimen B | Regimen B + MEPACT |
|---|---|---|---|---|
| | N=174 | N=167 | N=166 | N=171 |
| **Entered Induction Phase** | 170 | 164 | 164[1] | 169 |
| **Withdrawn** | | | | |
| **Progressive Disease** | 6 | 6 | 4 | 3 |
| **Removed for Toxicity** | 0 | 0 | 2 | 1 |
| **Withdrawal by Parent or Patient** | 3 | 4 | 5 | 4 |
| **Withdrawal by Physician** | 3 | 1 | 0 | 0 |
| **Major Protocol Deviation** | 2 | 4 | 6 | 3 |
| **Death** | 2 | 0 | 0 | 0 |
| **Lost to Follow-Up** | 0 | 0 | 0 | 0 |
| **Other** | 1 | 4 | 0 | 0 |
| | | | | |
| **Entered Maintenance Phase** | 153 (88%) | 145 (87%) | 148 (89%) | 158 (92%) |
| **Withdrawn** | | | | |
| **Progressive Disease** | 9 | 8[2] | 7 | 9 |
| **Removed for Toxicity** | 1 | 1 | 4 | 2 |
| **Withdrawal by Parent or Patient** | 8 | 20 | 6 | 26 |
| **Withdrawal by Physician** | 0 | 1 | 4 | 6 |
| **Major Protocol Deviation** | 2 | 5 | 5 | 4 |
| **Death** | 1 | 1 | 0 | 1 |
| **Lost to Follow-Up** | 0 | 1 | 0 | 1 |
| **Other** | 0 | 0 | 1 | 2 |
| **Deemed Ineligible** | 2 | 0 | 1 | 1 |
| | | | | |
| **Completed Protocol Therapy** | 130 | 108 | 120 | 106 |

2. [1]One patient with prior surgery went directly to maintenance chemotherapy and did not have induction chemotherapy. This patient is not included in the total of 164.
3. [2]One patient had progressive disease documented at surgery. This patient is included among those with progressive disease.

Reasons for patients not progressing onto the maintenance phase included disease progression or protocol violation. The majority of documented protocol breaks were due to voluntary withdrawal either by the patient/parent or by the physician. Such withdrawals are fairly representative of that observed in any other oncology clinical research.[5]

The number of DFS and death events is summarised by treatment arm in the subset of patients who did not enter the maintenance phase in Table A11b.

**Table 11b: Events Reported for ITT Patients Who Did Not Reach the Maintenance Phase**

| | Treatment Assignment | | | | |
|---|---|---|---|---|---|
| | **A -** | **A +** | **B -** | **B +** | **Total** |
| **DFS Event** | | | | | |
| **No** | 6 (28.57%) | 9 (40.91%) | 6 (33.33%) | 7 (53.85%) | 28 (37.84%) |
| **Yes** | 15 (71.43%) | 13 (59.09%) | 12 (66.67%) | 6 (46.15%) | 46 (62.16%) |
| **Total** | 21 (100%) | 22 (100%) | 18 (100%) | 13 (100%) | 74 (100%) |
| **Death** | | | | | |
| **No** | 8 (38.10%) | 15 (68.18%) | 12 (66.67%) | 7 (53.85%) | 42 (56.76%) |
| **Yes** | 13 (61.90%) | 7 (31.82%) | 6 (33.33%) | 6 (46.15%) | 32 (43.24%) |
| **Total** | 21 (100%) | 22 (100%) | 18 (100%) | 13 (100%) | 74 (100%) |

Takeda UK confirm that this data is included in the intention to treat analysis as previously submitted and there is no disparity of survival events as suggested. The overall number of patient who withdrew before the maintenance (adjuvant) treatment phase (74) are very low; when subdivided per the 4 arms the numbers are too low to make any significant conclusions regarding a disparity of survival events.

It would be appreciated if the Appraisal Committee can please explain where the proposed disparity in survival events may lay.

*1.1.5 "interpretation of the statistical analyses."*

Takeda UK refer to Section 2 of this document: Summary of statistical plan and robustness of trial methodology.

## 1.2 Regulatory interrogation and approval of INT-0133

As previously noted, the licence application was based on the results of one clinical trial, and therefore the European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP) considered that the data needed to be of high quality and the results robust[6]. Initially in their assessment, the CHMP raised a number of concerns with respect to the above study[6].

The CHMP convened the scientific advisory group (SAG) for oncology to advise on these including site visits to lead investigating centres in the USA. The main findings from their review were as follows[6]:

- The CHMP Scientific Advisory Group (SAG) for oncology confirmed the data was of high quality and the results robust.
- The CHMP finally concluded that the risk benefit of mifamurtide was favourable in this indication.
- From the data presented on overall survival it was deemed possible that there exists a quantitative interaction with ifosfamide. However, the SAG agreed that this quantitative interaction was likely to be small and of little clinical importance. What was felt to be important was that the clinical data presented were reassuring about the fact that there is no important qualitative interaction.
- The SAG agreed by consensus that the benefits of mifamurtide were consistent regardless of the treatment arm used in the pivotal trial, although the treatment effect might be slightly different.
- Overall, the SAG considered that the unexplained observations and uncertainties were well within the range of what is observed with other cancer products.
- The SAG and the EMA agreed that based on the clinical efficacy data presented; treatment with mifamurtide was associated with clinically significant benefits in the proposed indication. The SAG also agreed that the observed toxicity profile raised no particular concern, given the large unmet medical need and the sufficiently convincing efficacy data.[6]

Key points concerning methods and results are as follows[7, 8]:

- 6-year survival probability was 78% in patients who received mifamurtide compared with 70% in patients who did not.
- There is an approximate 30% reduction in the risk of death with the addition of mifamurtide.
- An improvement in overall survival is the gold-standard endpoint for a new osteosarcoma drug, showing a significant clinical benefit for paediatric and young adult patients with osteosarcoma.
- The primary endpoint stated in the protocol was overall and disease-free survival for both treatment comparisons (mifamurtide maintenance and ifosfamide induction, respectively).
- Disease free and overall survivals are considered the most relevant endpoints for studies in cancer in general, and for high mortality cancers, such as osteosarcoma, in particular.
- All analyses (disease free survival and overall survival) show a consistent patient benefit across 2003, 2006, and 2007 INT-0133 datasets for the addition of mifamurtide to standard chemotherapy.
- Trend direction and magnitude are consistent across all end points with statistical analysis (identical statistical methodology) on datasets at three specified time intervals.

**Section 2: Summary of statistical plan and robustness of trial methodology.**

Paragraph 4.6 of the NICE ACD states:

> *"The Committee noted that the manufacturer had presented a pooled analysis of the two mifamurtide-containing regimens (comparing chemotherapy plus mifamurtide [regimen A+ or B+] versus chemotherapy without mifamurtide [regimen A or B]) for overall survival and a number of post hoc efficacy analyses. The Committee discussed whether it was reasonable for the manufacturer to have pooled the data from the three- and four -agent chemotherapy arms (regimens A and B, and regimens A+ and B+). The Committee considered that the analysis had methodological flaws and the data should have been analysed as four separate and independent treatment regimens."*
>
> *"The Committee discussed the uncertainty around the pooled analysis and noted the ERG's concerns that although the addition of mifamurtide to multi-agent chemotherapy (regimens A+ and B+ combined) increased overall survival compared with multi-agent chemotherapy alone (regimens A and B combined), the size of the treatment effect of mifamurtide was uncertain, partly related to the disparity of survival events in the subset of patients who did not enter the maintenance phase. The Committee noted that a greater proportion of patients assigned to regimen A+ had tumours showing a poor (greater than 5% remaining viable tumour) histological response to neoadjuvant pre-operative therapy. It accepted the view of the clinical specialists that there was evidence of a link between poor histological response to neoadjuvant therapy and prognosis, but concluded that it was not possible to establish whether, or to what extent, this variation in histological response before adjuvant therapy in the different treatment groups might have affected the results".*
>
> *"The Committee also noted the ERG's concerns that there may have been interaction between treatments (that is, ifosfamide may be required to ensure activity of mifamurtide). However the Committee accepted that based on the 95% confidence intervals observed there was no strong evidence to suggest that there was interaction, and it accepted the clinical specialists' views that there was no biologically plausible reason for such an effect."*

2.1 *"The Committee considered that the analysis had methodological flaws and the data should have been analysed as four separate and independent treatment regimens."*

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.

This is detailed below from the 1992 original protocol document for INT-0133[9]:

**TEXT FROM THE ORIGINAL PROTOCOL DOCUMENT SUPPORTING THE INTENTION TO PERFORM THE MARGINAL ANALYSES**

***1.0 SPECIFIC AIMS AND HYPOTHESES***
*1.1* ***Specific Aims***
*1.11*
***To improve the survival of patients with osteogenic sarcoma.*** (This relates to the pooled analysis of the trial.)
*1.12*
*To compare the results of a prospective, randomized trial of two chemotherapeutic regimens in the treatment of osteogenic sarcoma.*
*1.121*
*To compare the results of a combined chemotherapeutic regimen (high-dose methotrexate, cisplatin, and doxorubicin) given pre-operatively and post-operatively to a similar regimen using the same drugs and adding ifosfamide.*
*1.122*
*To test whether the early introduction of ifosfamide results in a higher rate of good histological response at the time of definitive surgery.*
*1.13*
*To determine whether histological response assessed after longer pre-operative chemotherapy with more drugs predicts disease-free survival with the same power as observed in CCG-782 which used a shorter period of pre-operative chemotherapy and fewer drugs.*
*1.14*
*To determine whether liposomal muramyl tripeptide-phosphatidyl ethanolamine (MTP-PE, CGP 19835A), a stimulator of macrophage function, can improve disease-free survival for patients with osteogenic sarcoma.*
*1.15*
*To determine whether multiple drug resistance gene-encoded P-glycoprotein expression is useful for determining prognosis or assigning therapy.*

*The major questions which will determine the required accrual time and sample size are:*
*i) Do the 2 arms determined by the MTX + CDDP + DOXO ± IFOS induction randomization differ with respect to DFS and OS?*
*ii) Do the 2 arms determined by the ± MTP-PE maintenance randomization differ with respect to DFS and OS?*
*Both questions will be addressed by stratified log rank tests comparing the two levels of one factor while stratifying for the other. Since the stratification results in slightly increased power, for the purpose of sample size calculation it will be ignored. This will produce slightly conservative estimates.*

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 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.

NICE have analysed the trial's 2 x 2 factorial design as four separate arms. However, the trial was not designed nor statistically powered to be analysed in this way. The post-hoc analysis under-taken by NICE was not statistically significant in any of the arms – this is not surprising as the trial was not designed nor powered to be analysed in this way. It took 14 years to recruit sufficient patients into the INT-0133 trial to enable a valid statistical analysis of the primary end point - it would take decades to statistically power the secondary analysis of the 4 individual arms.

Hence, sub group analysis as suggested by the NICE ERG and Appraisal Committee (paragraph 4.6) has to be recognised as a post-hoc analysis that was not pre-specified and therefore is of minimal relevance when trying to determine efficacy.

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. Recent examples include NICE technology appraisal guidance 160 and 161 assessing technologies in the treatment of primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women. In both of these cases NICE criticised the manufacturer for reliance on post-hoc subgroup analyses. In particular NICE state in TA 161:

- *"The Committee noted that strontium ranelate was effective in preventing vertebral and non-vertebral fractures, and the drug resulted in a non-significant 15% reduction in hip-fracture risk. The Committee was also aware of the result of a post-hoc subgroup analysis showing a statistically significant reduction in the incidence of hip fractures in women over the age of 74 years who had a T-score of –2.4 SD or below".*
- *"The Committee did not accept the estimate of efficacy for strontium ranelate in preventing hip fracture from the post-hoc subgroup analysis, but it accepted the statistically non-significant RR of 0.85 for hip fracture to acknowledge an effect on this important type of fracture".*

Consequently, the most robust evidence base for assessment of the disease free survival and overall survival benefit associated with mifamurtide is to use the whole patient population in INT-0133 where A+/B+ is compared to an A/B regimen.

2.2 *"the size of the treatment effect of mifamurtide was uncertain, partly related to the disparity of survival events in the subset of patients who did not enter the maintenance phase".*

Takeda UK refer to the response previously provided in section 1.14 of this document.

Takeda UK confirm that this data is included in the intention to treat analysis as previously submitted and there is no disparity of survival events as suggested. Takeda UK confirm that this data is included in the intention to treat analysis as previously submitted and there is no disparity of survival events as suggested. There are also no significant differences in the

percentage of patients in each group who progressed to the maintenance phase. Reasons for patients not progressing onto the maintenance phase included disease progression or protocol violation. The majority of documented protocol breaks were due to voluntary withdrawal either by the patient/parent or by the physician. Given the small numbers of patients involved in each sample and the randomised nature of the study, any disparities are likely the result of chance.

2.3 *"It (the appraisal committee) accepted the view of the clinical specialists that there was evidence of a link between poor histological response to neo-adjuvant therapy and prognosis, but concluded that it was not possible to establish whether, or to what extent, this variation in histological response before adjuvant therapy in the different treatment groups might have affected the results".*

Takeda UK agree with the appraisal committee that there is evidence of a link between poor histological response and prognosis and it is not clear the impact that this makes upon the A/A+ arms. Indeed information presented at the request of the EMA clearly show the imbalance of patients with tumours grades I/II (unfavourable) and grades III/IV (favourable) between the A and A+ arms (presented below in Table 2.2.1 and Table 2.2.2). There was no imbalance present in the B/B+ arms of the study or in those patients less than 16 years old; these may be more accurate reflection of mifamurtide efficacy.

Table 2.2.1 Neoadjuvant Histological Response: Patients < 16 years

**Neoadjuvant Histologic Response**
**Patients < 16 Years***

| Viable Tumor / Regimen | Grades I/II Unfavorable | Grades III/IV Favorable | Not reported** | Total |
|---|---|---|---|---|
| MEPACT | 109 (45%) | 101 (42%) | 31 (13%) | 241 |
| No MEPACT | 116 (45%) | 107 (42%) | 32 (13%) | 255 |
| Total | 225 | 208 | 63 | 496 |

*p=0.9421
** Includes patients who progressed before surgery or for whom data not available

Table 2.2.2 Neoadjuvant Histological Response: Patients > 16 years

**Neoadjuvant Histologic Response**
**Patients > 16 Years***

| Viable Tumor / Regimen | Grades I/II Unfavorable | Grades III/IV Favorable | Not reported** | Total |
|---|---|---|---|---|
| MEPACT | 57 (59%) | 23 (24%) | 17 (17%) | 97 |
| No MEPACT | 40 (47%) | 32 (38%) | 13 (15%) | 85 |
| Total | 97 | 55 | 30 | 182 |

*p=0.0626
** Includes patients who progressed before surgery or for whom data not available

Given it is not clear the quantitative impact of poor histological response and prognosis upon the A/A+ arms then it would seem most appropriate to either assume efficacy as reported in the B/B+ arms (where there was no imbalance in histological response) or as Takeda UK suggest, to use the overall A/B vs. A+/ B+ analysis to assume efficacy data of which the INT-0133 trial was statistically powered.

2.4 *"The Committee also noted the ERG's concerns that there may have been interaction between treatments (that is, ifosfamide may be required to ensure activity of mifamurtide). However the Committee accepted that based on the 95% confidence intervals observed there was no strong evidence to suggest that there was interaction, and it accepted the clinical specialists' views that there was no biologically plausible reason for such an effect".*

Takeda UK agree with the appraisal committee that there is no strong evidence to suggest there was interaction, and that there was no biological plausible reason for such an effect. To analyze the study in accordance with the initial factorial design, there had to be no interaction between the two study questions.

For event free survival the proportional hazards regression analysis P value associated with the test of the hypothesis of no interaction between the chemotherapy intervention and the MTP intervention was 0.102, which does not meet the conventional level of significance of less than 0.1 (Table 2.4.1).

For overall survival, the proportional hazards regression analysis P value associated with the test of the hypothesis of no interaction between the chemotherapy intervention and the MTP intervention was .60, which definitely does not meet a conventional level of significance (Table 2.4.1).

The stratified analysis was performed as prospectively defined. There is no evidence of an interaction. Given the committee's conclusion, it is only appropriate to then interpret the results of INT-0133 using the pre-specified factorial analyses of A/B vs. A+/B+ rather than doing a post-hoc subset analysis of the 4 separate arms.

Table 2.4.1 Analysis of Interaction of mifamurtide in INT-0133

**Table 2.** Analysis of Interaction of MTP

| | Hazard Ratio | 95% CI |
|---|---|---|
| Event-free survival* | | |
| Regimen A | 0.99 | 0.69 to 1.4 |
| Regimen B | 0.65 | 0.45 to 0.93 |
| All patients | 0.80 | 0.62 to 1.0 |
| Overall survival† | | |
| Regimen A | 0.76 | 0.49 to 1.2 |
| Regimen B | 0.66 | 0.43 to 1.0 |
| All patients | 0.71 | 0.52 to 0.96 |

Abbreviation: MTP, muramyl tripeptide.
*Test of the hypothesis of no interaction, $P = .102$.
†Test of the hypothesis of no interaction, $P = .60$.

## Section 3: Confirmation of appropriate comparison relevant for UK practice for assessing clinical effectiveness from the INT-0133 trial.

Paragraph 4.7 of the NICE ACD states:

> *"The NICE Committee concluded that the most appropriate analysis compared the individual mifamurtide-containing regimen (A+) with a regimen reflecting UK clinical practice (regimen A). The Committee also concluded that given that ifosfamide is only administered in a clinical trial setting in the UK, the analysis of B+ versus B and the pooled analysis including A+ and B+ combined versus A and B combined were not considered to represent UK clinical practice."*

In Section 2 we have confirmed that the most appropriate comparison for adjuvant mifamurtide is versus regimen A/B on the basis of the pre-specified statistical plan and the original trial design. It is also 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 which reflects the trial design of INT-0133.

The clinical standard of care for osteosarcoma patients within the UK is in line with national and international recommendations. The European Society for Medical Oncology (ESMO) Osteosarcoma Guidelines: ESMO Clinical Recommendations for diagnosis, treatment and follow-up[10] state:

> *"Patients with osteosarcoma should be treated in reference centres able to provide access to the full spectrum of care or shared with such centres within reference networks. There, therapy is usually given within the framework of prospective, often collaborative, clinical studies, or established treatment protocols."*

British Sarcoma Group Guidelines on the treatment of osteosarcoma[11] state:

> *"Curative treatment for high-grade osteosarcoma consists of surgery and chemotherapy. All patients should be considered for inclusion into National or International clinical trials."*

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 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.

**Section 4: Summary of comparative health economic evidence.**

Information provided in sections 1-3 of this response document have reiterated the rigour of the INT-0133 trial, and the relevant comparisons appropriate for analysis. It is important to bring these factors to account for health economic modelling and determining a reliable base case cost effectiveness relevant for publication in future NICE documentation (FAD and guidance documents).

In consideration of the evidence on cost-effectiveness for this comparison the Appraisal Committee considered that it was appropriate to include the following parameters in the cost-effectiveness analysis: age dependent utility values, post recurrence mortality rates set to those of the age-matched population if patients were disease free for 5 years, and amputation and limb salvage costs (section 4.16 of the ACD). It was stated that this increased the ICER from £56,700 to £91,400 (with PAS), although this also included the cost of treating hearing loss adverse events. The committee did not consider it was necessary to include hearing loss attributed to mifamurtide but an ICER without hearing loss in the revised base case was not available or presented in the ACD.

Takeda UK have re-run the model based on the following assumptions:

- *Clinical data as per the pooled datasets of A/B versus A+/B+*
- *Comparator in the UK is 3 agent and 4 agent chemotherapy.*
- *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 included (changed as per ACD);*
- *Age related utility weights included (as per ACD);*
- *Discounting rates of 3.5% for both costs and outcomes applied;*
- *PASLU approved PAS.*

When we re-run the model with the revised base case but without the hearing loss AE, this produces an ICER of **£70,062** (deterministic analysis) or £66,982 (probabilistic analysis) (see Table 4.1), with a 54% probability of cost-effectiveness at a willingness to pay threshold of £70K (or 25% at £50K). We believe it is appropriate that this figure is cited in the ACD rather than the current statement that the “most plausible ICER would be less than £91,400” (section 4.16) which is somewhat vague and misrepresentative.

**Table 4.1: Base case using Appraisal Committee preferred parameters (with PAS)**

| | Mifamurtide + standard 3-4 agent maintenance therapy (A+/B+) | Standard 3-4 agent maintenance therapy alone (A/B) |
|---|---|---|
| **Total costs £** | 151,431 | 72,095 |
| **Difference in total costs £** | £79,336 | |
| QALYs | 14.81 | 13.68 |
| **QALYs difference** | 1.13 | |
| **Incremental cost per QALY gained** £ - deterministic** | **£70,062** | |
| **Incremental cost per QALY gained** £ - probabilistic** | **£66,982** | |

*Drug costs are adjusted to take account of actual doses administered from INT-0133 (mean of 38.4).
** Results are generated from the model so there are some rounding adjustments in the table.

As the committee is concerned over the uncertainty associated with the survival benefit it is also appropriate to consider the sensitivity of the ICER to more pessimistic survival outcomes. One way this can be handled simply in the economic model is to adjust the time horizon. The base case time horizon is 60 years, which has been considered appropriate by the ERG. However, applying a shorter time horizon reduces the mean survival benefit estimated by the model.

Hence, using our original base case the survival estimate with a 60 year time horizon is a mean of 4.02 life year (undiscounted) or 1.57 discounted, whereas with a 50 year time horizon the estimated undiscounted survival benefit is a mean of 3.39 life years (a 16% LYG reduction from the base case), the 40 year time horizon the estimated survival benefit from the model is 2.68 years on average (a 33% reduction in survival benefit from the base case). The mean life years gained are slightly lower in the NICE appraisal committee base case. The impact these sizeable hypothetical reductions in survival benefit have is to increase the deterministic ICER to up to £67,000 per QALY gained using our original base case or £80,000 using the appraisal committee preferred base case (Table 4.2) and a 40 year time horizon. As the 60 year time horizon has been accepted as an appropriate base case the calculations in Table 4.2 are hypothetical illustrations to show the relatively limited sensitivity of survival benefit on the ICER.

**Table 4.2: Impact on the ICER of more pessimistic time horizon/survival benefit estimates (PAS) – deterministic analysis**

| | Regimen A+/B+ vs A/B Mean life years gained (discounted). Original manufacturer base case applied | Regimen A+/B+ vs A/B Cost/QALY Original manufacturer base case applied (£) | Regimen A+/B+ vs A/B Mean life years gained (discounted) NICE Appraisal Committee base case applied | Regimen A+/B+ vs A/B Cost/QALY NICE Appraisal Committee base case applied (£) |
|---|---|---|---|---|
| **Time horizon of 60 years (base case)** | 1.57 | £56,683 | 1.32 | £70,062 |
| **Time horizon of 50 years** | 1.48 | £60,275 | 1.26 | £73,480 |
| **Time horizon of 40 years** | 1.33 | £66,976 | 1.15 | £79,850 |

The cost-effectiveness results are particularly sensitive to the choice of discount rate for benefits (QALYs). Applying a 1.5% discount rate to future QALYs the ICER based on the NICE preferred base case decreases from £70,062 to £44,222 (and from £67,982 to £42,599 in probabilistic analysis) whilst 0% discounting of QALYs and costs produces an ICER of £31,043 per QALY gained (£27,823 in probabilistic analysis).

In section 4.15 of the ACD it is stated that for consistency across all technology appraisals a 3.5% discount rate should be applied. It is, however, legitimate to vary the discount rate in sensitivity analysis. Despite the sensitivity of the ICER for mifamurtide to the discount rates selected for QALYs (more so than survival), there is no mention in the ACD of the actual impact varying the discount rate has on the ICER (only brief mentions in section 3.16 and 4.15). Therefore, we strongly feel more attention should be given in the ACD to the impact varying the QALY discount rate has on the ICER.

In conclusion, whilst the base case ICER is above £30,000/QALY and we agree with the appraisal committee that it is also likely to be at least £50,000/QALY assuming a base case discount rate of 3.5%. We have provided an estimate of £70,000 per QALY (£66,982 probabilistic analysis) gained using the parameters in the NICE appraisal committee base case. Certainly, we feel that the ICER is not likely to exceed £100,000 per QALY gained (section 4.19 of the ACD). This is based on a comparison with regimen A/B which we have argued is the most appropriate comparison consistent with actual best clinical practice for the treatment of osteosarcoma in the UK.

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

Takeda UK do not consider the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for guidance to the NHS. In particular it is not clear from the ACD how the rarity of osteosarcoma has been considered in this appraisal. Takeda UK believe it is important for NICE to be transparent in any future documentation recommending the use of mifamurtide (FAD and guidance documents) as to NICE's policy for assessing rarity and ultra orphans indications and how in this case the social value judgements have been employed for consideration in this appraisal.

In particular, Takeda UK are concerned regarding the appraisal committees preference to consider post hoc sub group analyses to inform decision making for treatments of rare diseases. Given the substantial time commitments in researching rare diseases and the limited sample size's produced, it seems philosophically wrong to sub divide the data of a rare disease to the point where results cannot be significant and favourable decision making is impossible. There is already relative uncertainty related to the clinical trial results of a rare disease without further subdividing the available information. It is the opinion of Takeda UK that the INT-0133 trial should be analysed as it was statistically planned to do so.

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 such as osteosarcoma.

In the UK there have been initiatives without tangible development as to how orphan drugs may be assessed. Nonetheless NICE, despite stating clearly in section 4.4 (page 20) of their, "Social Value Judgements Principles for the development of NICE guidance" [2], under rare conditions:

> *"NICE considers that it should evaluate drugs to treat rare conditions, known as 'orphan drugs', in the same way as any other treatment (see Glossary).*
>
> *NICE does not expect to receive referrals from the Secretary of State for Health to evaluate 'ultra-orphan drugs' (drugs used to treat very rare diseases or conditions). This is because the Department of Health currently has other mechanisms to assess the availability of ultra-orphan drugs in the NHS".*

<u>On this premise Takeda UK would question why NICE are assessing mifamurtide.</u>

In addition, NICE have developed two key initiatives in how orphan drugs may be assessed.

- NICE Recommendations for Appraisal of Orphan Products to the Department of Health, 2006. "Appraising Orphan Drugs" [12]
- NICE Citizens Council report on departing from the threshold November 2008 "Departing from the threshold." [13]

In the 2006 report on NICE Recommendations for Appraisal of Orphan Products to the Department of Health[12], NICE submitted a proposal for appraising orphan and ultra-orphan drugs. Whilst the proposals in this report were not implemented, NICE's conclusions and recommendations in the proposal are of interest for this appraisal:

- *"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]. <u>However, NICE considers that there would be problems in the appraisal of "ultra-orphan drugs" largely because of their high acquisition costs [4.2]".</u>*
- *"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. 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]".*

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?" [13] 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)*

Of these criterion, mifamurtide would qualify for 8/14 of these criteria (numbers 1,3,4,5,6,8,9,12) which if implemented may suggest an alternative approach to this appraisal.

Takeda UK are committed to making mifamurtide available to patients in England and Wales; however at this stage it is not clear what is required to accomplish NICE approval for an ultra orphan medication. Indeed, using the standard appraisal committee cost per QALY threshold for acceptance of under £30,000 would suggest that patients with osteosarcoma and other rare illnesses will be underserved until NICE have a transparent policy for assessment of rare illnesses to which manufacturers can work towards. If NICE had adopted criteria as per the aforementioned 2006 report, then mifamurtide would easily prove a cost effective treatment. Likewise if NICE had adopted modification criteria as proposed by the citizen's council report then undoubtedly mifamurtide would have proven cost effective.

Takeda UK would encourage NICE to consider some of the previous thinking regarding the appraisal of ultra orphan medications for this appraisal, or alternatively, and as per stated in the Social value Judgements, allow the other mechanisms in the NHS to assess the availability of ultra-orphan drugs, and to terminate this NICE appraisal.

## Summary

In summary, Takeda UK Ltd believe that the NICE Appraisal Consultation Document should change to recognise the points in this response and support the use of mifamurtide in the care of appropriate patients with osteosarcoma in NHS England and Wales.

In particular, it is important to recognise:

- The robustness of the data which has been scrutinised in detail by the CHMP,
- The lack of progress and unmet need of young patients with osteosarcoma,
- Potential lifetime survival benefit for the additional responders to mifamurtide.

The overall conclusion of the EMA in respect of the clinical efficacy of mifamurtide was very clear and this is reflected in the EPAR where it states that "Mepact significantly increased the overall survival of patients with newly-diagnosed resectable high-grade osteosarcoma when used in conjunction with combination chemotherapy when compared to chemotherapy alone". Takeda UK Ltd believes it is totally unacceptable to use post-hoc sub-analyses to question the clinical effectiveness of mifamurtide in relation to the data scrutinised by the Regulatory Authority the EMA resulting in our product licence.

Whilst the base case ICER is above £30,000/QALY, we agree with the Appraisal Committee that it is also likely to be at least £50,000/QALY assuming a base case discount rate of 3.5%. We have provided an estimate of £70,000 per QALY gained using the parameters in the NICE appraisal committee base case. Certainly, we feel that the ICER is not likely to exceed £100,000 per QALY gained (section 4.19 of the ACD). This is based on a comparison with A/B which we maintain is the only appropriate comparison consistent with actual best clinical practice for the treatment of osteosarcoma in the UK.

We believe the economic case represented in the submission and the updates in the model have enabled us to increase our confidence in the boundary of the plausible impact of uncertainty in key variables on the mifamurtide cost-effectiveness ratios.

If NICE had adopted criteria as per the aforementioned 2006 report, then mifamurtide would easily prove a cost effective treatment. Likewise if NICE had adopted modification criteria as proposed by the citizen's council report then undoubtedly mifamurtide would have proven cost effective. Takeda UK would encourage NICE to consider some of the previous thinking regarding the appraisal of ultra orphan medications for this appraisal, or alternatively, and as per stated in the Social Value Judgements, allow the other mechanisms in the NHS to assess the availability of ultra-orphan drugs, and to terminate this NICE appraisal.

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