NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Mifamurtide for the treatment of osteosarcoma

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 Mifamurtide in combination with postoperative multi-agent chemotherapy is not recommended within its licensed indication for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection in children, adolescents and young adults.

1.2 Children, adolescents and young adults currently receiving mifamurtide for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection should have the option to continue treatment until it is considered appropriate to stop. This decision should be made jointly by the clinician and the child, adolescent or young adult, and if appropriate, their parents or carers.

2 The technology

2.1 Mifamurtide (Mepact, Takeda) is an immune macrophage stimulant. It has a marketing authorisation for use in 'children, adolescents and young adults for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection'. The marketing authorisation further states that mifamurtide is used in combination with postoperative

multi-agent chemotherapy, and that safety and efficacy have been assessed in studies of patients 2 to 30 years of age at initial diagnosis.

2.2 The summary of product characteristics lists the following adverse events that may be associated with mifamurtide treatment: respiratory distress, neutropenia, inflammatory response, cardiovascular disorders, allergic reactions and gastrointestinal toxicity. The results of a clinical study also suggested that mifamurtide significantly increased the incidence of objective and subjective hearing loss. For full details of side effects and contraindications, see the summary of product characteristics.

2.3 Mifamurtide is available as a powder for suspension for intravenous infusion, with each vial containing 4 mg of mifamurtide. The recommended dose of mifamurtide for all patients is 2 mg/m^2 body surface area. Mifamurtide should be administered as adjuvant therapy following macroscopically complete resection: twice weekly at least 3 days apart for 12 weeks, followed by once-weekly treatments for an additional 24 weeks for a total of 48 doses in 36 weeks. For further details of dosage and administration, see the summary of product characteristics.

2.4 The acquisition cost of mifamurtide is £2375 for a 4 mg vial (excluding VAT, 'MIMS' August 2010 edition). The recommended dose of mifamurtide is 2 mg/m^2 body surface area. The manufacturer's submission states that the cost of a full treatment course of 48 doses of mifamurtide is £114,000. The manufacturer has agreed a patient access scheme with the Department of Health, in which mifamurtide for the treatment of osteosarcoma will be available at no charge to the NHS for the first seven doses. The Department of Health considered that this patient access scheme

does not constitute an excessive administrative burden on the NHS.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of mifamurtide and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 In the submission, the manufacturer compared mifamurtide as an add-on treatment to postoperative multi-agent adjuvant chemotherapy (three- or four-agent adjuvant chemotherapy using high-dose methotrexate, doxorubicin and cisplatin with or without ifosfamide) with postoperative multi-agent adjuvant chemotherapy (three- or four-agent) alone in patients with high-grade, resectable, non-metastatic osteosarcoma.

3.2 The evidence for the efficacy of mifamurtide in the manufacturer's submission was obtained from one multicentre, open-label randomised controlled trial (RCT), the Intergroup study 0133 (INT-0133). Most of the patients who participated in INT-0133 (n = 678) were recruited in the USA. They received 10 weeks of neoadjuvant induction therapy with either chemotherapy regimen A (methotrexate, doxorubicin and cisplatin) or chemotherapy regimen B (methotrexate, doxorubicin, cisplatin and ifosfamide) before surgical resection of their tumour. Surgical resection was performed during weeks 10–11, when patients were not receiving chemotherapy. Adjuvant therapy was scheduled to begin at week 12 when patients received one of four regimens: regimen A, regimen A+ (regimen A with the addition of mifamurtide), regimen B, or regimen B+ (regimen B with the addition of mifamurtide). Using a two by two factorial design, the study compared mifamurtide plus multi-agent chemotherapy (regimens A+ and B+)

with multi-agent chemotherapy alone (regimens A and B). Similarly the study assessed the efficacy of ifosfamide (regimens B and B+ versus A and A+). The primary endpoint was overall survival. However, the study was powered for the first planned analysis of the intermediate endpoint, which was disease-free survival (that is, time to progression or death).

3.3 The patients in the study were under 30 years of age with a new diagnosis of malignant high-grade osteosarcoma. Exclusion criteria included metastatic disease or unresectable primary disease, low-grade osteosarcoma, parosteal or periosteal sarcoma, radiation-induced sarcoma or osteosarcoma arising in premalignant bony lesions, or previous chemotherapy or radiation therapy.

3.4 The manufacturer presented analyses based on three datasets. The clinical study report presented data collected up to June 2003 (2003 dataset), and August 2006 (2006 dataset); an addendum subsequently provided the updated findings based on data to March 2007 (2007 dataset). Both the manufacturer and the ERG considered the 2007 dataset to be the most up to date and comprehensive. Therefore, only the 2007 dataset is referred to in this document. The overall survival data in INT-0133 showed that after a median follow-up of 7.9 years, adding mifamurtide to chemotherapy (regimens A+ and B+ combined) statistically significantly improved overall survival compared with chemotherapy alone (regimens A and B combined) with an overall survival of 71% in the control arm and 78% in the mifamurtide arm. For the intention-to-treat (ITT) population, the hazard ratio for death was 0.72 (95% confidence interval [CI] 0.53 to 0.97). However, adding mifamurtide to chemotherapy (regimens A+ and B+ combined) did not statistically significantly increase disease-free survival compared with chemotherapy alone (regimens A and B combined).

For the ITT population, the hazard ratio for disease-free survival was 0.78; 95% CI 0.61 to 1.01.

3.5 The manufacturer presented a number of post hoc subgroup analyses for the dataset combining regimens A and B. These analyses showed consistent increases in overall survival with mifamurtide plus chemotherapy compared with chemotherapy alone across a broad range of demographic factors (age, gender, ethnicity, study site and geographic location) and prognostic factors (tumour size, lactate dehydrogenase level, alkaline phosphatase level, cooperative study group and background chemotherapy).

3.6 The ERG requested additional post hoc analyses for both overall and disease-free survival comparing individual mifamurtide-containing regimens (regimen A+ or B+) with individual regimens not containing mifamurtide (regimen A or B). The analyses that compared mifamurtide plus three-agent chemotherapy (regimen A+) with the chemotherapy regimen most commonly used in UK clinical practice (regimen A) gave non-significant increases in overall survival (hazard ratio for death 0.75; 95% CI 0.49 to 1.16) and disease-free survival (hazard ratio for progression 0.96; 95% CI 0.67 to 1.38). For regimen B+ compared with four-agent chemotherapy regimen B (both including ifosfamide), there was no significant improvement in overall survival (hazard ratio 0.68; 95% CI 0.44 to 1.05) but a significant improvement in disease-free survival (hazard ratio 0.63; 95% CI 0.44 to 0.91).

3.7 In INT-0133, only severe adverse events (grade 3 or 4) were recorded. With the exception of hearing loss, the number of adverse events was similar in patients receiving mifamurtide plus multi-agent chemotherapy (regimens A+ and B+ combined) compared with multi-agent chemotherapy alone (regimens A and B

combined). Adding mifamurtide to multi-agent chemotherapy significantly increased the incidence of objective hearing loss (11.5% with mifamurtide versus 7.1% without; p = 0.047) and subjective hearing loss (3.6% with mifamurtide versus 0.6% without; p = 0.007). The post hoc subgroup analyses by treatment regimen suggested that the increased incidence of hearing problems occurred only in those treated with three-agent chemotherapy plus mifamurtide (regimen A+).

3.8 Additional data from phase I and II studies of over 700 patients suggest that the most common adverse events in patients and healthy volunteers treated with mifamurtide alone were fever, chills, fatigue, headache, nausea/vomiting, myalgia and tachycardia, hypotension, hypertension and dyspnoea. Chills, fever and pyrexia were reported as mild to moderate.

3.9 In INT-0133, the rates of discontinuation were higher in both mifamurtide groups (regimens A+ and B+) than in the groups without mifamurtide (regimens A and B). The manufacturer stated that most of the withdrawals were not caused by adverse events that required clinically significant intervention. The manufacturer also stated that the adverse events were not life threatening, and did not require mifamurtide to be stopped. The manufacturer assumed that many patients, or their parents, decided to withdraw from mifamurtide treatment because it was an investigational drug of unproven benefit and was uncomfortable or inconvenient (no further details were provided by the manufacturer) when added to existing multi-agent chemotherapy.

3.10 The manufacturer presented an economic model of the cost effectiveness of adding mifamurtide to three- and four-agent chemotherapy regimens combining cisplatin, doxorubicin and

methotrexate with or without ifosfamide. The economic model had six health states. These were: disease free (start state), disease progression (optional start state), recurrence, disease free post recurrence, disease progression post recurrence, and death. The model had a cycle length of 6 months and a time horizon of 60 years. The manufacturer assumed that patients in the disease-free health state at 12.25 years had a mortality rate equivalent to the general population. Patients in the post-recurrence disease-free state were assumed to have a mortality rate dependent on the time to recurrence, which was derived from a study by Ferrari et al. (2003). For patients who had recurrence within 2 years, the 6-monthly mortality rate was 14.87% and for those who had recurrence after 2 years, the 6-monthly mortality rate was 4.98%.

3.11 The transition probabilities used in the deterministic base case were derived from INT-0133 for 604 patients who entered the adjuvant phase, while the post-recurrence estimates were mostly derived from the literature, except when death was recorded as an event post recurrence.

3.12 The default number of mifamurtide doses to be administered to each patient was assumed to be 38.4, which was the average number of mifamurtide doses administered in INT-0133. The utility values used in the economic model were taken from a study using the EQ-5D in 22 patients from INT-0133 (for the recurrence health state), and a review by the manufacturer of utility values used in other NICE technology appraisals (for all other health states), including treatments of colon, colorectal, renal cell, and prostate cancer, myeloid leukaemia and glioma. The utility values used in the model were: 0.39 for disease progression, 0.85 for patients who remained disease free, 0.61 for recurrence, 0.85 for patients who were disease free post recurrence, 0.39 for disease progression

post recurrence, and 0.00 for death. The manufacturer's submission only included adverse events considered clinically relevant (such as those associated with infusion) in the base-case analyses. From INT-0133, hearing loss was identified as the main adverse event for mifamurtide. A decrease in utility value associated with this adverse event was not included in the model because it was considered to be an anomaly of the data; hearing loss is associated with cisplatin and the number of additional cases observed in one of the mifamurtide arms was within the reported range of cisplatin-related hearing loss. An 18% decrease in utility value for hearing loss was explored in sensitivity analyses, based on data derived from one study found in the manufacturer's Medline search on hearing loss in people with cancer

3.13 The economic model included the following costs: adjuvant chemotherapy (cisplatin, doxorubicin, ifosfamide, methotrexate) with or without mifamurtide, treatment of adverse events during the maintenance phase, routine monitoring, diagnostic tests, surgery, and second-line chemotherapy for disease progression (ifosfamide and etoposide). Costs and resource utilisation information were taken from NHS reference costs 2007/08. Information on healthcare resource use was not collected in the study and the costs of these resources were therefore estimated from information provided by clinical specialists.

3.14 The manufacturer presented the following total costs per treated patient and total quality-adjusted life years (QALYs) per patient for the base case without the patient access scheme:

- Regimen A and B combined: total costs £31,481; total QALYs 15.38.

- Regimen A+ and B+ combined: total costs £123,852; total QALYs 16.72.
- Regimen A: total costs £29,709; total QALYs 16.10.
- Regimen A+: total costs £122,604; total QALYs 16.69.
- Regimen B: total costs £33,244; total QALYs 14.66.
- Regimen B+: total costs £125,121; total QALYs 16.71.

3.15 Under the patient access scheme there would be no charge to the NHS for the first seven doses of mifamurtide. The manufacturer's analyses produced the following incremental cost-effectiveness ratios (ICERs) when the patient access scheme was included:

- Manufacturer's base case (combined data set): £56,683 per QALY gained.
- Manufacturer's base case for regimen A+ compared with A: £130,814 per QALY gained.
- Manufacturer's base case for regimen B+ compared with B: £36,913 per QALY gained.

3.16 The manufacturer conducted a series of one-way sensitivity analyses. The results showed that the model was mainly sensitive to the discount rates used for outcomes, and the health-related utility value used for the disease-free health state.

3.17 The manufacturer's economic submission also presented a scenario analysis evaluating the effect of the following model assumptions on its base case, when including the patient access scheme and using the combined dataset:

- Incorporating amputation and limb salvage costs increased the ICER from £56,683 to £59,231 per QALY gained.
- Incorporating adverse events related to hearing loss increased the ICER from £56,683 to £71,065 per QALY gained.

- Allowing the post-recurrence mortality rate for patients who remain disease free after 5 years to equate to the general population mortality rate increased the ICER from £56,683 to £61,580 per QALY gained.
- Applying age-adjusted utility rates increased the ICER from £56,683 to £62,112 per QALY gained.

3.18 The manufacturer also carried out a scenario analysis that assessed applying all the assumptions described in section 3.17 simultaneously. This increased the base-case ICER from £56,683 to £91,442 per QALY gained. The manufacturer also carried out probabilistic sensitivity analyses, with analyses assuming a payment threshold of £50,000. The results showed that approximately 30% of the iterations were below this level.

3.19 The ERG questioned whether using all the INT-0133 data from the three- and four-agent chemotherapy regimens (that is regimens A+ and B+ combined and regimens A and B combined) was appropriate. The ERG highlighted the uncertainty about the effect of an interaction between ifosfamide and mifamurtide on the results of INT-0133. The ERG noted that there were potentially significant differences in clinical effectiveness among the four groups, as demonstrated by the analyses that compared individual mifamurtide-containing regimens (A+ or B+) with regimens not containing mifamurtide (regimen A or B). If considered in this way the analyses would indicate a high degree of uncertainty in the true cost effectiveness of mifamurtide. However, the ERG stated that if it was accepted that there was no such interaction, then the results could indeed be considered to represent two separate trials (of mifamurtide and of ifosfamide) of treatments for osteosarcoma.

3.20 The ERG was concerned that the statistically significant difference between hearing loss rates reported in INT-0133 was omitted from the base-case economic analysis. The rates were included only in the sensitivity analyses; 15% for objective or subjective hearing loss for the mifamurtide regimens compared with 8% for the non-mifamurtide regimens.

3.21 The ERG noted that the base-case assumptions used by the manufacturer were favourable to mifamurtide and had concerns about the selection of the parameters entered into the model (for example, the most appropriate comparator, whether the effects of hearing loss should be incorporated, whether a general population mortality rate should be used if there is no recurrence in 5 years, whether amputation or limb salvage costs should be used, whether age-related utility values should be used). The ERG stated that, as a result, the ICER for regimen A+ and B+ compared with regimen A and B was likely to be substantially higher than the £56,683 per QALY gained reported in the manufacturer's base-case analysis.

3.22 The ERG considered that the model lacked face validity because the modelled survival rates at 6 years (83% and 77% with and without mifamurtide respectively) were higher than the observed data in the clinical trial (80% and 73% with and without mifamurtide respectively). It was unclear what was driving this difference in estimated survival. If, for example, it was simply the length of the time cycle in the Markov model, then a more appropriate time cycle should have been chosen in the model. The ERG stated that although this lack of face validity increases the uncertainty in the results, it is unclear what effect this would have on the ICER if the mortality rates observed in INT-0133 were accurately replicated in the model.

3.23 The ERG carried out a number of exploratory sensitivity analyses, including the following: use of data from regimen A+ compared with regimen A rather than all the INT-0133 data from the three- and four-agent chemotherapy regimens (that is regimens A+ and B+ combined and regimens A and B combined), applying age-dependent utility values, mortality rates set to those of the age-matched general population if patients were disease free for 5 years, amputation and limb salvage costs. All increased the cost per QALY gained compared with the manufacturer's base case. The ERG stated that the sensitivity analyses indicated that even including the patient access scheme, it was very unlikely that the cost per QALY gained was below £50,000. The most plausible ICER, focusing on a comparison of regimens A+ with A as best reflecting UK clinical practice, would be higher than £100,000 per QALY gained. The ERG's base-case analysis produced a deterministic ICER of £109,296 (probabilistic ICER of £103,494) per QALY gained.

3.24 After consultation on the appraisal consultation document, the manufacturer provided updated analyses based on the Committee's preferred assumptions in the economic model (that is inclusion of age-dependent utility values, post-recurrence mortality rates set to those of the age-matched general population if patients were disease free for 5 years, amputation and limb salvage costs, but still excluding hearing loss as an adverse event) over a 60-year time horizon. The deterministic analysis of regimens A+ and B+ combined compared with regimens A and B combined gave an ICER of £70,062 per QALY gained (1.13 QALYs gained at an additional cost of £79,336) and the probabilistic analysis gave an ICER of £66,982 per QALY gained.

3.25 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/guidance/TAXXX

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of mifamurtide for osteosarcoma, having considered evidence on the nature of osteosarcoma and the value placed on the benefits of mifamurtide by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Management of high-grade resectable non-metastatic osteosarcoma in UK clinical practice

4.2 The Committee discussed the clinical needs of patients with high-grade resectable non-metastatic osteosarcoma. The patient experts stated that diagnosing and treating osteosarcoma has a significant impact on patients and their families and friends. This includes disruption of family life, strain on family relationships, additional stress at work and financial pressures, and the health of families, friends and carers. The Committee heard from the clinical specialists and patient experts that the main aim of treatment is to improve the cure rate (that is, the percentage of people who will subsequently have a normal lifespan, free of disease). The patient experts stated that there had been few developments that had improved optimal treatment of osteosarcoma over the past 20 years and that any improvement in overall survival from adding mifamurtide to standard chemotherapy was clinically significant and important. The clinical specialists stated that the only development in the past 10 years had been the introduction of high-dose methotrexate and better implementation of treatment regimens,

together improving survival rates by 10–20% and bringing them in line with those in Europe and the USA.

4.3 The Committee heard from the clinical specialists that current UK clinical practice is neoadjuvant multi-agent chemotherapy and surgical resection, followed by postoperative adjuvant multi-agent chemotherapy. The clinical specialists stated that the standard adjuvant multi-agent chemotherapy regimen in the UK is doxorubicin, methotrexate and cisplatin and the 5-year overall survival rate is approximately 55%. The role of ifosfamide in UK clinical practice is unclear and its use is currently limited. However, the Committee heard from the clinical specialists that ifosfamide is currently being investigated in an ongoing European and US osteosarcoma trial (EURAMOS 1) as part of an adjuvant regimen (with etoposide, cisplatin, doxorubicin and methotrexate). Only patients with tumours showing a poor histological response to pre-operative chemotherapy may receive ifosfamide. The clinical specialists stated that study recruitment should be complete in 2011, with results anticipated in 2015–20, and the study may establish a role for ifosfamide in UK clinical practice. The Committee heard that a significant number of patients in the UK are taking part in EURAMOS 1 and some may therefore be taking ifosfamide in that context. Patients would not be eligible for mifamurtide while they are receiving the study drug regimens. The Committee concluded that the current standard chemotherapy regimen in England and Wales is doxorubicin, methotrexate and cisplatin, and that ifosfamide is not routinely used in UK clinical practice outside the EURAMOS 1 study.

4.4 The Committee noted evidence from the clinical specialists and patient experts that treatment with mifamurtide is safe and well tolerated. The Committee noted that standard neoadjuvant and

adjuvant chemotherapy in the UK (regimen A) is completed in approximately 30 weeks, and that an additional 18 weeks of treatment with mifamurtide would be required to be consistent with the administration schedule in INT-0133. The Committee heard from the clinical specialists that in INT-0133 a significant proportion of patients (22–30%) did not complete treatment with mifamurtide, and that, based on evidence from the EURAMOS 1 study, this may be caused by patients not wanting to extend treatment beyond the duration of standard multi-agent chemotherapy. Patient experts stated that increased overall survival is so important that patients would accept the option of prolonged treatment with mifamurtide if it was shown to improve overall survival. The Committee concluded that patients may show greater willingness to extend the treatment period if mifamurtide was shown to provide additional benefit.

Clinical effectiveness

4.5 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 generally well conducted, but it agreed that there were substantial methodological issues identified by the ERG that led to uncertainty around the estimates of disease-free interval and survival. These included delayed administration of mifamurtide (including non-administration of mifamurtide after randomisation), and imbalance in histological response to neoadjuvant therapy between treatment groups. This was particularly pronounced for patients assigned to regimen A+, where a greater proportion of tumours showed a poor (greater than 5% remaining viable tumour) histological response, which may disadvantage mifamurtide. The Committee concluded that these

aspects of the study made interpretation of the survival data more difficult, and that the effect of these factors on the results could not be reliably predicted.

4.6 The Committee noted that the manufacturer had presented an analysis of all the INT-0133 data from the three- and four-agent chemotherapy regimens (that is regimens A+ and B+ combined and regimens A and B combined) for overall survival and a number of post hoc efficacy analyses. The Committee discussed whether it was reasonable for the manufacturer to have carried out a combined analysis given the marginal evidence of interaction for disease-free survival.

4.7 The Committee was aware that the combined analysis was the primary pre-specified analysis of the trial and noted that this suggested a statistically significant improvement in overall survival from 71% in the control arm to 78% in the mifamurtide arm over a median follow-up period of 7.9 years. Although the study was powered for the intermediate endpoint of disease-free survival, it failed to show that regimens of chemotherapy plus mifamurtide (regimens A+ and B+ combined) significantly increased disease-free survival compared with chemotherapy alone (regimens A and B combined) (hazard ratio 0.78, 95% CI 0.61 to 1.01). The Committee discussed the uncertainty around the combined analysis and noted the ERG's concerns that although the addition of mifamurtide to multi-agent chemotherapy increased overall survival compared with multi-agent chemotherapy alone (hazard ratio 0.72, 95% CI 0.53 to 0.97), the size of the treatment effect attributable to mifamurtide alone was uncertain. 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 this variation in histological response before adjuvant therapy in the different treatment groups might have affected the results, or by how much. The Committee also noted the ERG's concerns that it remained possible that there may have been interaction between treatments (that is, there may be synergy between ifosfamide and mifamurtide), given that the test for statistical interaction for disease-free survival was very close to the prespecified threshold for interaction of 0.10 ($p = 0.102$). The Committee heard from the clinical specialists that factorial trials are designed on the assumption that there is no interaction between the study drugs, and that power to detect plausible interactions requires greatly increased sample sizes. However, the Committee accepted that the statistical test for interaction showed that there was no strong evidence to suggest that there was interaction between the drugs in the analysis of overall survival. Furthermore, it accepted the clinical specialists' views that there was no biologically plausible reason for such an effect.

4.8 The Committee then discussed the post hoc analyses requested by the ERG that compared regimen A+ with A, and regimen B+ with B. It was aware that this was an alternative approach to the analysis and that INT-0133 was not designed for these comparisons or powered for this analysis. The Committee noted that for regimen A+ compared with A, there was a non-significant improvement in overall survival (hazard ratio 0.75; 95% CI 0.49 to 1.16). For regimen B+ compared with B, there was a non-significant improvement in overall survival (hazard ratio 0.68; 95% CI 0.44 to 1.05). Both comparisons were consistent with the overall estimate but the confidence intervals were wider, possibly because of

smaller patient numbers in the subgroups than in the whole trial. The Committee then discussed the analyses in the context of UK clinical practice. It noted that currently ifosfamide is usually only administered in a clinical trial setting in the UK. The comparison that best reflected current UK clinical practice was therefore agreed to be the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.7, 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.

4.9 The Committee discussed the adverse effects of mifamurtide plus multi-agent chemotherapy and noted that the combined analysis of all the INT-0133 data from the three- and four-agent chemotherapy regimens showed a significant increase in subjective and objective hearing loss in patients receiving mifamurtide regimens. The Committee was aware that in the post hoc subgroup analyses an increased incidence of hearing loss occurred only in patients treated with regimen A+. It noted that there was uncertainty about which agent in the regimen could be associated with hearing loss. The Committee accepted the clinical specialists' views that cisplatin was used in all arms of the study and there is a known risk of hearing loss associated with its use (usually in the range 5–15%). Accordingly, the rate of hearing loss observed in INT-0133 was not unusual and could be an effect of cisplatin rather than mifamurtide. The Committee also accepted the clinical specialists' view that objective hearing loss after treatment may not be clinically important or necessarily require the use of hearing aids, and that this risk should be considered in the context of a possible higher cure rate for osteosarcoma.

4.10 The Committee concluded that based on the primary combined analysis of all the INT-0133 data from the three- and four-agent chemotherapy regimens carried out by the manufacturer, mifamurtide plus postoperative multi-agent chemotherapy may be more clinically effective than postoperative multi-agent chemotherapy alone. However, there was substantial uncertainty around the size of this effect, particularly in the context of the standard treatment regimen used in the NHS.

Cost effectiveness

4.11 The Committee considered the manufacturer's economic model and the critique and exploratory sensitivity analyses performed by the ERG. The Committee noted that the efficacy data for the manufacturer's base-case analyses were taken from INT-0133 for regimens A+ and B+ combined compared with regimens A and B combined, but that on the request of the ERG the manufacturer had also presented cost-effectiveness estimates for the post hoc analyses for regimen A+ compared with regimen A and regimen B+ compared with regimen B. The Committee noted that the manufacturer's additional analyses incorporated a patient access scheme agreed by the Department of Health (section 2.4) and that the ICERs were markedly higher than the range normally considered to be a cost effective use of NHS resources. The Committee discussed the following parameters in the manufacturer's economic model, which were explored in a number of sensitivity analyses:

- Incorporating amputation and limb salvage costs.
- Incorporating the hearing loss adverse events.
- Returning post-recurrence mortality to the general population rate after 5 years' disease-free survival.
- Applying age-adjusted utility values.

- Varying the discount rates for outcomes.

4.12 The Committee considered the assumptions used in the manufacturer's base case analysis and agreed that some of the assumptions examined in the sensitivity analyses were more appropriate. The Committee considered incorporating the costs associated with amputation and limb salvage. It noted that these costs were omitted from the base-case analysis and agreed with the ERG that it was appropriate to include amputation and limb salvage costs in the model. The Committee noted that when these costs were included, the manufacturer's original base-case ICER increased marginally from £56,700 to £59,200 per QALY gained.

4.13 The Committee noted that adverse events, other than those associated with infusion, were not included in the manufacturer's original base-case analysis. When hearing loss was included in the model the ICER increased substantially from £56,700 to £71,000 per QALY gained. However, the Committee accepted the views of the clinical specialists that although hearing loss was the main adverse event occuring more frequently with mifamurtide treatment in the clinical study, 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.

4.14 The Committee considered the mortality rates used by the manufacturer in its original base-case analysis, in which patients in the post-recurrence disease-free state were assumed to have a mortality rate dependent on the time to recurrence. Mortality rates were derived from a study by Ferrari et al. (2003). The Committee heard from the clinical specialists that 25% of patients with recurrent disease may be cured and that the prognosis after recurrence was dependent on time to recurrence (that is, patients

with a longer time to recurrence have a better prognosis). The Committee agreed that after 5 years free of disease, it was reasonable to use the mortality rates of the general population.

4.15 The Committee considered the utility values used in the model and that the manufacturer's model contained utility values from two different sources: a review of NICE technology appraisals for cancer treatments and a small study using the EQ-5D in patients from INT-0133. The Committee noted that the technology appraisals included in the review were from very different populations and did not generally use NICE's preferred method to derive the utility values. The Committee also noted that although the sample size for the study using the EQ-5D was small, it included the population of interest (that is, only people with osteosarcoma) and used a method to derive the utility values that met NICE's reference case. The Committee was aware that a utility value of 0.85, derived from the manufacturer's review of NICE technology appraisals, had been applied to the disease-free state in the model and that this utility value was subsequently maintained throughout the length of the model. The Committee agreed that in the general population, utility value declines with age, and therefore age-adjusted utility values should be used in the model. It noted that the ICER increased when age-adjusted utility values were used. After consultation on the appraisal consultation document, the Committee reconsidered the use of the EQ-5D in the INT-0133 trial population. It heard from the patient experts that young people with osteosarcoma are able to live full lives and they have a similar quality of life to their peers, with many adapting well to having a disability, and in some cases being empowered by their experience. The Committee noted that the age-adjusted utility values used in the manufacturer's updated analysis were

appropriate and reflected the quality of life of children, adolescents and young people as reported by the patient experts.

4.16 The Committee agreed that it was appropriate to include the following assumptions in the cost-effectiveness analysis: age-dependent utility values, post-recurrence mortality rates set to those of the age-matched general population if patients were disease free for 5 years, and amputation and limb salvage costs. The Committee considered the additional analyses carried out by the manufacturer after consultation on the appraisal consultation document, incorporating the Committee's preferred assumptions (see above) and results for regimens A+ and B+ combined compared with regimens A and B combined (that is, independent of the use of ifosfamide) over a 60-year time horizon. The manufacturer's additional analyses reported 'best-case' ICERs of £70,100 per QALY gained (deterministic analysis) and £67,000 per QALY gained (probabilistic analysis), both including the patient access scheme. The Committee concluded that the best-case ICERs were substantially higher than those normally considered to be an acceptable use of NHS resources. The Committee accepted that there may be a case for accepting a higher ICER for a patient population of children, adolescents and young people, but it was unable to reach a positive decision given the very high ICERs presented.

4.17 The Committee was aware that the above analysis (section 4.16) used data from a comparison of combined three- and four-agent chemotherapy regimens, and that an alternative cost-effectiveness analysis was available using data from the post hoc analysis comparing the individual mifamurtide containing regimen (A+) with a regimen reflecting UK clinical practice (regimen A). The Committee noted that the cost-effectiveness estimates based on

this analysis gave substantially higher ICERs (greater than £100,000 per QALY gained) than the best-case ICER described above (section 4.16). The Committee concluded that there was 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.

4.18 The Committee considered whether there were any health-related quality of life benefits that may not have been adequately captured in the estimated gains used in the QALY calculation. The Committee heard from the patient experts that supporting a young person with osteosarcoma has a substantial impact on the health-related quality of life of the family and friends of the person affected, particularly where treatment is not successful. For example, parents and siblings may develop mental health problems and family relationships may be strained. The Committee concluded that these are important issues affecting the health-related quality of life of those close to the person with osteosarcoma, but noted that these issues are not unique to the condition. On balance, however, the Committee was not persuaded that across the treated population and their relatives, incorporating these potential quality of life benefits would lower the ICER for mifamurtide compared with adjuvant multi-agent chemotherapy to the extent necessary for it to be considered a cost-effective use of NHS resources.

4.19 The Committee discussed the sensitivity of the manufacturer's original base-case ICER to the discount rate applied to outcomes, and how this would affect the ICERs estimated in the manufacturer's additional analyses. The Committee noted that no formal case had been made for varying the discount rate. The

Committee was aware of the policy relating to the NICE reference case and section 5.6.2 of the 'Guide to the methods of technology appraisal', which specifies that a discount rate of 3.5% should be used for both costs and outcomes. The Committee was aware that it also states that consideration should be given to sensitivity analyses that use different rates for costs and outcomes and/or that vary the rate between 0% and 6%. The Committee considered that in some situations discounting may have a large effect on ICERs, but it concluded that the discount rates recommended for the reference case were the most appropriate to use in this appraisal.

4.20 The Committee then considered that mifamurtide is indicated for a small patient population with a rare disease, and noted that NICE had not received direction from the Department of Health that treatments for rare conditions ('orphan' or 'ultra-orphan') should be appraised differently from any other treatments. The Committee discussed the innovative nature of the technology and that the clinical trial was conducted in the 1990s. Based on the magnitude of the additional benefit and associated uncertainty, it was not persuaded that adjuvant chemotherapy with mifamurtide significantly and substantially changes the way that the current need is met (see section 4.3), or that it has been shown to have an appropriate level of effectiveness, given the wide confidence intervals of the hazard ratios (see section 4.7).

4.21 The Committee considered whether there were issues related to equality to be taken into account in its considerations in light of its current and future duties under the equalities legislation. The Committee discussed comments made at the scoping stage. These included the observation that osteosarcoma predominantly affects children, teenagers and young adults, and that osteosarcoma is a rare disease. The Committee further noted that when an appraisal

affects a particular age group it does not mean that a negative recommendation in that appraisal constitutes discrimination on the grounds of age. The Committee noted that no different recommendations were made for the patient population for which mifamurtide is licensed, that is, the recommendation is not based on and does not vary according to the age of the patient. There was no evidence heard or submitted to suggest that different recommendations on the basis of age would be necessary to meet patient needs or that a different recommendation for one or more patient groups within the overall patient population would be clinically and cost effective. The Committee was therefore satisfied that there were no equalities issues in relation to age in this appraisal and that the recommendations were consistent with NICE's obligations under the equalities legislation and the requirement for fairness.

4.22 The Committee concluded that mifamurtide plus postoperative multi-agent chemotherapy for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection might represent a potentially valuable new therapy, but the size of the treatment effect relative to standard UK clinical practice was uncertain. Furthermore, the Committee agreed that the best-case ICER based on the evidence available was £70,100 per QALY gained. Although the Committee accepted that there may be a case for accepting a higher ICER for a patient population of children, adolescents and young people, this ICER was too high to allow the Committee to recommend mifamurtide, even when taking into account a number of other considerations such as other aspects of health-related quality of life not adequately captured in the QALY, the innovative nature of the drug, the rarity of the condition, and possible discount rates. The Committee

therefore concluded that mifamurtide could not be recommended as a cost-effective use of NHS resources.

Summary of the Appraisal Committee's key conclusions relevant to the draft recommendation

TAXXX (STA)	**Appraisal title: Mifamurtide for the treatment of osteosarcoma**	**FAD section**
Key conclusion		
Mifamurtide in combination with postoperative multi-agent chemotherapy is not recommended within its licensed indication for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection in children, adolescents and young adults. The main reasons for this decision were that the size of the treatment effect relative to standard UK clinical practice was uncertain and that the ICERs based on the evidence available were too high.		
Current practice		
Clinical need of patients, including availability of alternative treatments	The main aim of treatment is to improve the cure rate (that is, the percentage of people who will subsequently have a normal lifespan, free of disease). The current standard adjuvant multi-agent chemotherapy regimen in the UK is doxorubicin, methotrexate and cisplatin, and the 5-year overall survival rate is approximately 55%. The patient experts stated that there had been few developments that had improved optimal treatment of osteosarcoma over the past 20 years. The Committee noted that the clinical specialists stated that the only development in the past 10 years had been the introduction of high-dose methotrexate and better implementation of treatment regimens, which had together improved survival rates by 10–20%, bringing them in line with those in Europe and the USA. A significant number of patients in the UK are taking part in the EURAMOS 1 study. Ifosfamide is not routinely used in UK	4.2 4.2, 4.3 4.3

	clinical practice outside the EURAMOS 1 study.	
The technology		
Proposed benefits of the technology. How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The patient experts stated that any improvement in overall survival from adding mifamurtide to standard chemotherapy was clinically significant and important.	4.2
What is the position of the treatment in the pathway of care for the condition?	Mifamurtide is intended to be used after macroscopically complete surgical resection in combination with postoperative multi-agent chemotherapy consisting of methotrexate, doxorubicin and cisplatin.	2.1, 4.3, 4.8
Adverse effects	INT-0133 showed that with the exception of hearing loss, the number of adverse events was similar for patients receiving mifamurtide plus multi-agent chemotherapy compared with multi-agent chemotherapy alone. However, hearing loss was considered usual for treatments containing cisplatin, and could therefore be an effect of cisplatin rather than mifamurtide. The Committee accepted the clinical specialists' view that objective hearing loss after treatment may not be clinically important or necessarily require the use of hearing aids and that this risk should be considered in the context of a possible higher cure rate for osteosarcoma.	3.7, 4.9
Evidence for clinical effectiveness		
Availability and nature of evidence	The Committee noted that INT-0133 was generally well conducted, but it agreed that there were substantial methodological issues identified by the ERG.	3.6, 4.5
Quality of the evidence	The Committee noted that the study was generally well conducted, but there were substantial methodological issues such as an imbalance in histological response to	4.5, 4.7

	neoadjuvant therapy between treatment groups. Furthermore, although the study was powered for the intermediate endpoint of disease-free survival, a statistically significant reduction for this was not shown (hazard ratio 0.78, 95% CI 0.61 to 1.01). The Committee concluded that these aspects of the study made interpretation more difficult, and that the effect of these factors on the results could not be reliably predicted.	
Relevance to general clinical practice in the NHS	The Committee then discussed the analyses in the context of UK clinical practice. It noted that currently ifosfamide is only administered in a clinical trial setting in the UK. The comparison that best reflected current UK clinical practice was therefore agreed to be the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.7, the Committee accepted that the combined analysis of all the INT-0133 data may more appropriate in determining the effect of adding mifamurtide to the standard UK regimen rather than the post hoc analysis directly comparing regimen A+ with regimen A.	4.8
Uncertainties generated by the evidence	The ERG was concerned that there may have been interaction between ifosfamide and mifamurtide, but there was no strong evidence to suggest that there was interaction between the drugs in the analysis of overall survival, and the Committee accepted the clinical specialists' views that there was no biologically plausible reason for such an effect. A greater proportion of patients assigned to regimen A+ had tumours showing a poor histological response to neoadjuvant pre-operative therapy. The Committee accepted the view of the clinical specialists that there was evidence of a link between	4.7

	poor histological response to neoadjuvant therapy and prognosis, but concluded that it was not possible to establish whether this variation in histological response before adjuvant therapy in the different treatment groups might have affected the results, or by how much.	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee discussed the uncertainty around the combined analysis and noted the ERG's concerns that although the addition of mifamurtide to multi-agent chemotherapy increased overall survival compared with multi-agent chemotherapy alone (hazard ratio 0.72, 95% CI 0.53 to 0.97), the size of the treatment effect attributable to mifamurtide alone was uncertain. Based on the magnitude of the additional benefit, the Committee was not persuaded that adjuvant chemotherapy with mifamurtide significantly and substantially changes the way that the current need is met, or that it has been shown to have an appropriate level of effectiveness, given the wide confidence intervals of the hazard ratios. The Committee concluded that although mifamurtide plus multi-agent chemotherapy for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection might represent a potentially valuable new therapy, the evidence of its benefit relative to standard UK clinical practice was not conclusive.	4.7, 4.20, 4.22
Are there any clinically relevant subgroups in whom there is evidence that effectiveness is different?	Apart from analyses by treatment regimen, no other subgroups were considered.	-
Evidence for cost effectiveness		
Availability and nature of evidence	The manufacturer presented an economic model of the cost effectiveness of adding mifamurtide to three- and four-agent chemotherapy regimens combining	3.10, 4.11

	cisplatin, doxorubicin and methotrexate with or without ifosfamide. The Committee noted that efficacy data for the manufacturer's base-case analyses were taken from INT-0133 (for regimens A+ and B+ combined compared with regimens A and B combined) and that post hoc analyses for regimen A+ compared with regimen A and regimen B+ compared with regimen B had been requested by the ERG.	
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee agreed that the following assumptions explored in the manufacturer's sensitivity analyses were appropriate: • Incorporating amputation and limb salvage costs. • Returning post-recurrence mortality to the general population rate after 5 years' disease-free survival. • Applying age-adjusted utility rates. • Using the discount rates in the current methods guide. 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 Committee considered that in some situations discounting may have a large effect on ICERs but concluded that discount rates recommended for the reference case were the most appropriate to use in this appraisal.	4.16 4.13 4.19
Incorporation of health-related quality of life benefits and utility values	The Committee considered that the manufacturer's model contain utility values from two different sources: a review of NICE technology appraisals for cancer treatments and a small study using the EQ-5D in patients from INT-0133. The latter was considered to include the	4.15

Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	population of interest. The Committee agreed that age-adjusted utility values should be used in the model. It noted that the ICER increased when age-adjusted utility values were used. The Committee considered whether there were any health-related quality of life benefits that may not have been adequately captured in the estimated gains used in the QALY calculation. The Committee heard from the patient experts that supporting a young person with osteosarcoma has a substantial impact on the health-related quality of life of the family and friends of the person affected, particularly where treatment is not successful. For example, parents and siblings may develop mental health problems and family relationships may be strained. The Committee concluded that these are important issues affecting the health-related quality of life of those close to the person with osteosarcoma, but noted that these issues are not unique to the condition. On balance, however, the Committee was not persuaded that across the treated population and their relatives, incorporating these potential quality of life benefits would lower the ICER for mifamurtide compared with adjuvant multi-agent chemotherapy to the extent necessary for it to be considered a cost-effective use of NHS resources.	4.18
Are there specific groups of people for whom the technology is particularly cost effective?	Apart from analyses by treatment regimen as described above, no other subgroups were considered.	-
What are the key drivers of cost effectiveness?	The Committee was aware that the analysis in section 4.16 used data from a comparison of three- and four-agent chemotherapy regimens combined, and that an alternative cost-effectiveness analysis was available using data from the post hoc analysis comparing the individual	4.17

	mifamurtide containing regimen (A+) with a regimen reflecting UK clinical practice (regimen A). The Committee noted that the cost-effectiveness estimates based on this analysis gave substantially higher ICERs (greater than £100,000 per QALY gained) than the best-case ICER described in section 4.16. The Committee concluded that there was 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.	
Most likely cost-effectiveness estimate (given as an ICER)	The manufacturer's additional analyses were based on regimens A+ and B+ combined compared with regimens A and B combined. These analyses reported 'best-case' ICERs of £70,100 per QALY gained (deterministic analysis) and £67,000 per QALY gained (probabilistic analysis), both including the patient access scheme. The Committee concluded that the best-case ICERs were substantially higher than those normally considered to be an acceptable use of NHS resources. The Committee accepted that there may be a case for accepting a higher ICER for a patient population of children, adolescents and young people, but it was unable to reach a positive decision given the very high ICERs presented.	4.16
Additional factors taken into account		
Patient access schemes	The Committee noted that the manufacturer's additional analyses incorporated a patient access scheme agreed by the Department of Health (in which there is no charge to the NHS for the first seven doses of mifamurtide).	4.11
End-of-life considerations	Not applicable because the treatment is indicated for patients with a life expectancy of more than 24 months.	-
Equalities considerations, social	Comments made at the scoping stage relating to equalities issues included the	4.21

value judgement	observation that osteosarcoma predominantly affects children, teenagers and young adults, and that osteosarcoma is a rare disease. The latter point was not related to obligations under the equality legislation. The recommendation for mifamurtide is not based on age and does not vary according to the age of the patient. The Committee was therefore satisfied that there were no equalities issues in relation to age in this appraisal.	

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing report and costing template to estimate the savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.

- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 The Committee agreed that further studies on the clinical effectiveness of mifamurtide when combined with three-agent chemotherapy typical of the UK context would be useful to determine the size of the effect of mifamurtide. Further collection of quality of life data from apparently cured people with a previous amputation and experience of chemotherapy is also needed. Data on the health effects on parents, siblings and others with life threatening illness would be of value.

7 Related NICE guidance

Published

Improving outcomes for people with sarcoma. NICE cancer service guidance (2006). Available from www.nice.org.uk/guidance/CSGSarcoma

8 Review of guidance

8.1 The guidance on this technology will be considered for review in November 2013. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Philip Home

Vice Chair, Appraisal Committee

October 2010

Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)

Department of Diagnostic Radiology, St George's Hospital

Professor Philip Home (Vice Chair)

Professor of Diabetes Medicine, Newcastle University

Professor A E Ades

Professor of Public Health Science, Department of Community Based Medicine, University of Bristol

Elizabeth Brain

Lay Member

Dr Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Dr Paul Ewings

Statistician, Taunton and Somerset NHS Trust, Taunton

John Goulston

Chief Executive, Barking, Havering and Redbridge Hospitals NHS Trust

Adrian Griffin

VP Strategic Affairs, LifeScan, Johnson & Johnson

Dr Ann Richardson

Lay Member

Angela Schofield

Chairman, Bournemouth and Poole Teaching PCT

Mr Mike Spencer

Assistant Director Patient Experience, Cardiff and Vale University Health Board

David Thomson

Lay Member

William Turner

Consultant Urologist, Addenbrooke's Hospital

Professor Karl Claxton

Professor of Health Economics, University of York

Dr David Newsham

Lecturer (Orthoptics), University of Liverpool

Professor Iain Squire

Consultant Physician, University Hospitals of Leicester

Dr James Moon

Consultant Cardiologist and Senior Lecturer, University College London Hospital (UCLH) and UCL

Dr Peter Heywood

Consultant Neurologist, Frenchay Hospital

Dr Ian Lewin

Consultant Endocrinologist, North Devon District Hospital

Dr Louise Longworth

Reader in Health Economics, HERG, Brunel University

Christopher Earl

Surgical Care Practitioner, Renal Transplant Unit, Manchester Royal Infirmary

Dr Anthony S Wierzbicki

Consultant in Metabolic Medicine/Chemical Pathology, Guy's and St Thomas' Hospitals NHS Trust

Professor Jonathan Grigg

Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London

Dr John Watkins

Clinical Senior Lecturer/Consultant in Public Health Medicine, Cardiff University and National Public Health Service Wales

Dr Olivia Wu

Reader in Health Economics, University of Glasgow

Dr Paul Robinson

Medical Director, Merck Sharp & Dohme

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Fay McCracken

Technical Lead

Nicola Hay

Technical Adviser (until August 2010)

Helen Knight

Technical Adviser (from August 2010)

Bijal Joshi

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by the School of Health and Related Research (ScHARR), University of Sheffield:

- Pandor A et al. Mifamurtide for Osteosarcoma, January 2009
- Stevenson M, Mifamurtide for osteosarcoma: addendum critiquing the revised submitted economic model incorporating a patient access scheme, February 2010

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Takeda UK (mifamurtide)

II Professional/specialist and patient/carer groups:

- Adam Dealey Foundation for Ewing Sarcoma
- Bone Cancer Research Trust
- Rarer Cancers Forum
- Royal College of Nursing
- Royal College of Paediatric and Child Health
- Royal College of Pathologists
- Royal College of Physicians, Medical Oncology Joint Special Committee
- Royal College of Radiologists
- Sarcoma UK

III Other consultees:

- Department of Health
- Welsh Assembly Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- National Collaborating Centre for Cancer
- National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme)
- NHS Quality Improvement Scotland
- School of Health and Related Research (ScHARR), The University of Sheffield

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on mifamurtide by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Tim Eden, Professor of Teenage and Young Adult Cancer, nominated by the Bone Cancer Research Trust – clinical specialist
- Professor Anthony Freemont, Professor of Bone and Joint Pathology, nominated by the Royal College of Pathologists – clinical specialist
- Dr Maria Michelagnoli, Consultant paediatric and adolescent oncologist, nominated by the Bone Cancer Research Trust – clinical specialist
- Ms Sally Hurst, nominated by the Bone Cancer Research Trust – patient expert
- Mr Michael Francis, nominated by the Bone Cancer Research Trust – patient expert
- Ms Hannah Millington, nominated by the Bone Cancer Research Trust – patient expert
- Master Callum Flynn, nominated by the Bone Cancer Research Trust – patient expert

D Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Takeda UK