NICE National Institute for Health and Care Excellence

NICE guidance

Mifamurtide for the treatment of osteosarcoma

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendations

1.1 Mifamurtide in combination with postoperative multi-agent chemotherapy is recommended within its licensed indication as an option for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection in children, adolescents and young adults and when mifamurtide is made available at a reduced cost to the NHS under the patient access scheme.

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. It is not recommended for use in children below the age of 2 years.

2.2 The summary of product characteristics lists the following adverse events that may be associated with mifamurtide treatment: respiratory distress, neutropenia, pronounced 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 after 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 full details of dosage and administration, see the summary of product characteristics.

2.4 The acquisition cost of mifamurtide is £2,375 for a 4-mg vial (excluding VAT, BNF, edition 61). The manufacturer's submission states that the cost of a full treatment course of 48 doses of mifamurtide is £114,000.

2.5 The manufacturer of mifamurtide has agreed a revised patient access scheme with the Department of Health (which replaces an earlier patient access scheme, referred to as the 'original' patient access scheme in this document), in which mifamurtide for the treatment of osteosarcoma will be available at a reduced cost to the NHS. The nature of this cost reduction is confidential. 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 considered evidence submitted by the manufacturer of mifamurtide and a review of this submission by the Evidence Review Group (ERG).

3.1 In the submission, the manufacturer compared mifamurtide as an add-on treatment to postoperative multi-agent adjuvant chemotherapy (3- or 4-agent adjuvant chemotherapy using high-dose methotrexate, doxorubicin and cisplatin with or without ifosfamide) with postoperative multi-agent adjuvant chemotherapy (3- or 4-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 1 multicentre, open-label randomised controlled trial, 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 to 11, when patients were not receiving chemotherapy. Adjuvant therapy was scheduled to begin at week 12 when patients received 1 of 4 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 2 by 2 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+ compared with 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 3 datasets. The clinical study report presented data collected up to June 2003 (2003 dataset), and August 2006 (2006 dataset); an addendum provided the updated findings based on data to March 2007 (2007 dataset). Intention-to-treat (ITT) analyses were carried out on all 3 datasets. 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 (chemotherapy alone) and 78% in the mifamurtide arm (chemotherapy plus mifamurtide). For the 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 3-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 A+. For regimen B+ compared with 4-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 for regimen B+ (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 3-agent chemotherapy plus mifamurtide (regimen A+).

3.8 Additional data from phase 1 and 2 studies of over 700 patients suggested that the most common adverse events in patients and healthy volunteers treated with mifamurtide alone were fever, chills, fatigue, headache, nausea or vomiting, myalgia and tachycardia, hypotension, hypertension and dyspnoea. Chills and fever were reported as mild to moderate.

3.9 In INT-0133, the rates of discontinuation were higher in both mifamurtide groups (22% for regimen A+ and 30% for regimen B+) than in the groups not receiving mifamurtide (13% for regimen A and 17% for regimen 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 3- and 4-agent chemotherapy regimens combining cisplatin, doxorubicin and methotrexate with or without ifosfamide. The economic model had 6 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 disease-free post recurrence 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 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 seen in 1 of the mifamurtide arms was within the reported range for cisplatin-related hearing loss. An 18% decrease in utility value for hearing loss was explored in sensitivity analyses, based on data derived from 1 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 and methotrexate) with or without mifamurtide, treating 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 to 2008. 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 ERG questioned whether using all the INT-0133 data from the 3- and 4-agent chemotherapy regimens (that is regimens A+ and B+ combined and regimens A and B combined) was appropriate. The ERG noted that the absence of an interaction between ifosfamide and mifamurtide was crucial to the validity of the manufacturer's statistical approach. However, the ERG highlighted a potential interaction between ifosfamide and mifamurtide in the INT-0133 results. The ERG noted that there were potentially significant differences in clinical effectiveness among the 4 groups, as demonstrated by the analyses that compared individual mifamurtide regimens (A+ or B+) with regimens without mifamurtide (A or B). This led to a high degree of variability in the cost-effectiveness results for the groups with and without mifamurtide. The ERG stated that if it was accepted that there was no such interaction, then the results could indeed be considered to represent 2 separate trials, of mifamurtide and of ifosfamide for osteosarcoma, which would indicate a high degree of uncertainty in the true cost effectiveness of mifamurtide.

3.15 The ERG considered that the model lacked face validity because the modelled survival rates at 6 years (83% with mifamurtide and 77% without mifamurtide) were higher than those seen in the clinical trial (78% with mifamurtide and 70% without mifamurtide). 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 of the economic analysis, it is unclear what effect this would have on the incremental cost-effectiveness ratio (ICER) if the mortality rates seen in INT-0133 were accurately replicated in the model.

3.16 The results of the economic analysis included in the manufacturer's original submission, which incorporated the original patient access scheme, have been

replaced by updated analyses. These updated analyses incorporated a revised patient access scheme (designated as commercial-in-confidence by the manufacturer) and were submitted by the manufacturer in response to the draft final appraisal determination released in August 2010. Sections 3.17 to 3.23 give details of the original economic analyses and the related ERG critique. Sections 3.24 to 3.26 describe the updated analyses, including the revised patient access scheme, the related ERG critique and the impact of altering the yearly discount rate for outcomes while fixing the discount rate for cost at 3.5%.

3.17 The manufacturer presented the following total costs per treated patient and total quality-adjusted life years (QALYs) per patient for the base case (excluding any 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.

3.18 The manufacturer conducted a series of one-way sensitivity analyses. The results showed that the model was very sensitive to the discount rate for outcomes. The model has a time horizon of 60 years, over which the benefits associated with treatment are accumulated and discounted. The larger the discount rate used for outcomes, the smaller the difference in QALYs gained between treatment with mifamurtide and treatment without mifamurtide. It should be noted that all treatment acquisition costs for mifamurtide are incurred in the first year of the model, and are therefore not affected by discounting. The sensitivity analysis also showed that the model was sensitive to the health-related utility value used for the disease-free health state.

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

- Including amputation and limb salvage costs increased the ICER from £56,683 to £59,231 per QALY gained.
- Including adverse events related to hearing loss increased the ICER from £56,683 to £71,065 per QALY gained.
- Setting the post-recurrence mortality rate for patients who remain disease free after 5 years 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.

3.20 The manufacturer also carried out a scenario analysis that assessed applying all the assumptions described in section 3.19 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.

3.21 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 in the model (for example, whether the most appropriate comparator was used, whether the effects of hearing loss should be included, 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 and whether age-related utility values should be used). The ERG stated that, as a result, the ICER for regimen A+ and B+ combined compared with regimen A and B combined 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 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 scenario analyses; 15% for objective or subjective hearing loss for the mifamurtide regimens compared with 8% for the regimens without mifamurtide.

3.23 The ERG carried out a number of exploratory sensitivity analyses that included:

- comparing regimen A+ with regimen A rather than using all the INT-0133 data from the 3- and 4-agent chemotherapy regimens (that is, regimens A+ and B+ combined and regimens A and B combined)
- applying age-adjusted utility values
- setting post-recurrence mortality rates to those of the age-matched general population if patients were disease free for 5 years
- including amputation and limb salvage costs.

All increased the cost per QALY gained compared with the manufacturer's base case. The ERG's base-case analysis produced a deterministic ICER of £109,296 (probabilistic ICER of £103,494) per QALY gained. These analyses have been replaced by those described below.

3.24 After submission of a revised patient access scheme (see section 2.5), the manufacturer provided further updated analyses based on the Committee's preferred assumptions in the economic model (that is, applying age-adjusted utility values, setting post-recurrence mortality rates to those of the age-matched general population if patients were disease free for 5 years, including 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 £60,205 per QALY gained and the probabilistic analysis gave an ICER of £56,677 per QALY gained. The manufacturer conducted a series of one-way sensitivity analyses on its deterministic base-case results. This showed that the model was sensitive to the discount rates used for outcomes. A discount rate of 0% for outcomes (while fixing the discount rate for costs at 3.5%) reduced the ICER to £25,135 per QALY gained. A discount rate of 6% for outcomes (while fixing the discount rate for costs at 3.5%) increased the ICER to £95,097 per QALY gained.

3.25 The ERG carried out a number of exploratory sensitivity analyses on the manufacturer's updated analyses that included:

- comparing regimen A+ with regimen A rather than using all the INT-0133 data from the 3- and 4-agent chemotherapy regimens (that is, regimens A+ and B+ combined and regimens A and B combined)

- assuming that people receiving mifamurtide experienced hearing loss, as seen in the trial
- assuming that a small proportion of patients enter the model in the disease progression health state
- assuming that 8% of patients would require 2 vials of mifamurtide per dose.

All these increased the cost per QALY gained compared with the manufacturer's base case. The ERG stated that the sensitivity analyses showed that even with the revised patient access scheme, it was unlikely that the cost per QALY gained was below £60,000. The ERG reported that if clinically meaningful hearing loss can be attributed to mifamurtide, the cost per QALY gained could plausibly be much higher.

3.26 The ERG also undertook an analysis to assess the impact of altering the yearly discount rate used for outcomes (while fixing the discount rate for costs at 3.5%) on the manufacturer's and ERG's probabilistic ICERs:

- A discount rate of 0% for outcomes reduced the manufacturer's probabilistic ICER to £23,831 per QALY gained and the ERG's probabilistic ICER to £36,893 per QALY gained.
- A discount rate of 1.5% for outcomes reduced the manufacturer's probabilistic ICER to £36,076 per QALY gained and the ERG's probabilistic ICER to £54,334 per QALY gained.
- A discount rate of 6% increased the manufacturer's probabilistic ICER to £89,810 per QALY gained and the ERG's probabilistic ICER to £141,766 per QALY gained.

3.27 Full details of all the evidence are in the manufacturer's submission and the ERG report.

4 Consideration of the evidence

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

4.1 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 a negative effect on 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 cure the patient. The patient experts and clinical specialists stated that there had been few developments that had improved treatment outcomes for 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 to add high-dose methotrexate to the treatment regimen for osteosarcoma, but that there is currently limited evidence available about whether overall survival rates in the UK have improved in the last decade. 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 Committee noted that this survival rate is for all patients, including some with more advanced disease for whom mifamurtide would not be indicated. The Committee heard from the clinical specialists that ifosfamide is currently being investigated in an ongoing European and US osteosarcoma study

(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 can receive ifosfamide. The clinical specialists stated that study recruitment should be complete in 2011, with results anticipated in 2015 to 20, and the study may establish a role for ifosfamide in UK clinical practice. They explained that meaningful research in osteosarcoma is difficult to carry out because of the small number of patients and the long follow-up required. The Committee heard that a significant number of patients in the UK are taking part in EURAMOS 1, and some may be taking ifosfamide in that context. Patients would not be eligible for mifamurtide while they are receiving the study drug regimens. It also heard that a follow-up trial to EURAMOS 1 is in development. It is expected that the EURAMOS 2 trial will commence in 2012 to 2013. The Committee welcomed continued research into the best regimen for this condition. The Committee concluded that the current established chemotherapy regimen in England and Wales is doxorubicin, methotrexate and cisplatin, and that the extent of ifosfamide use in UK clinical practice outside the EURAMOS 1 study had not been quantified.

4.2 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% to 30%) did not complete treatment with mifamurtide, and based on evidence from the ongoing EURAMOS 1 study, this may have been because patients did not want to extend treatment beyond the duration of standard multi-agent chemotherapy in a trial setting. 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 agreed that patients would be more willing to extend treatment in clinical practice if mifamurtide provided them with a higher chance of cure.

Clinical effectiveness

4.3 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 about the estimates of disease-free survival and overall survival. These included delayed or non-administration of mifamurtide and an imbalance in histological response to neoadjuvant therapy between treatment groups. The imbalance was particularly pronounced for patients assigned to regimen A+, who had a greater proportion of tumours showing a poor (greater than 5% remaining viable tumour) histological response, which may have disadvantaged 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.

4.4 The Committee noted that the manufacturer had presented an analysis of all the INT-0133 data from the 3- and 4-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 was aware that the combined analysis was the primary prespecified 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 (hazard ratio 0.72, 95% CI 0.53 to 0.97). Although the study was powered for the intermediate endpoint of disease-free survival, it did not show a statistically significant increase in disease-free survival for regimens of chemotherapy plus mifamurtide (regimens A+ and B+ combined) compared with chemotherapy alone (regimens A and B combined; hazard ratio 0.78, 95% CI 0.61 to 1.01). 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 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. The Committee accepted that the statistical test for interaction did not suggest a strong interaction between the drugs in the analysis of overall survival. It also accepted the clinical specialists' views that there was no biologically plausible reason for such an effect.

4.5 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-statistically significant improvement in overall survival (hazard ratio 0.75; 95% CI 0.49 to 1.16). For regimen B+ compared with B, there was also a non-statistically 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. The Committee understood that in trials for the treatment of rare diseases such as this, recruiting the numbers of patients needed to adequately power the trial is difficult, and even more so to allow subgroup analyses of this nature. 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 most relevant to UK clinical practice was therefore agreed to be the mifamurtide regimen (A+) compared with the regimen reflecting current UK clinical practice (A). However, for the reasons above, the Committee accepted that the combined analysis of all the INT-0133 data was 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.

4.6 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 3- and 4-agent chemotherapy regimens showed a statistically

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% to 15%). Accordingly, the rate of hearing loss seen in INT-0133 was not unusual and could be an effect of cisplatin rather than mifamurtide. The Committee also accepted the clinical specialists' views 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.

Cost effectiveness

4.7 The Committee considered the manufacturer's economic analyses and the respective critiques and exploratory sensitivity analyses performed by the ERG. The Committee noted that the efficacy data for the manufacturer's 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 most recent additional analyses incorporated a revised patient access scheme agreed by the Department of Health (see section 2.5). The Committee discussed the following assumptions in the analyses:

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

4.8 The Committee considered including the costs associated with amputation and limb salvage. It noted from the scenario analyses carried out by the manufacturer (see section 3.19) that there was a marginal increase in the ICER when these costs were included. The Committee agreed with the ERG that it was appropriate to include amputation and limb salvage costs in the model.

4.9 The Committee noted that hearing loss adverse events were not included in the manufacturer's economic analyses. However, the Committee accepted the views of the clinical specialists that although hearing loss was the main adverse event, occurring more frequently with mifamurtide treatment in the clinical study, the rate of hearing loss seen in INT-0133 was not unusual in cisplatin-containing regimens and its exclusion from the model could be justified.

4.10 The Committee considered the mortality rates used by the manufacturer in its economic analyses. The Committee heard from the clinical specialists that 25% of patients with recurrent disease may be cured and that the prognosis after recurrence depends 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.

4.11 The Committee considered the utility values used in the model. It noted that the manufacturer's model contained utility values from 2 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 patients 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. The Committee discussed whether this utility value should be maintained throughout the length of the model. It noted that the ICER increased when age-adjusted utility values were used. The Committee 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 any remaining disability, and in some cases being empowered by their experience. The Committee agreed that in the general population utility declines with age, and therefore age-adjusted utility values should be used in the model.

4.12 The Committee considered the most recent additional analyses carried out by the manufacturer (see section 3.24), including the Committee's preferred assumptions (see sections 4.8 to 4.11), the results for regimens A+ and B+ combined compared with regimens A and B combined (that is, independent of ifosfamide) over a 60-year time horizon and the revised patient access scheme. The Committee noted that the ERG had carried out exploratory sensitivity analyses (see section 3.25) on the manufacturer's most recent additional analyses using data from regimen A+ compared with regimen A rather than all the INT-0133 data from the 3- and 4-agent chemotherapy regimen. The Committee agreed that it was appropriate for the discussion to focus on the manufacturer's most recent additional analyses rather than the ERG's exploratory sensitivity analyses. The most recent analyses by the manufacturer (regimens A+ and B+ combined compared with regimens A and B combined) reported 'best-case' ICERs of £60,200 per QALY gained (deterministic analysis) and £56,700 per QALY gained (probabilistic analysis).

4.13 The Committee discussed the sensitivity of the manufacturer's 'best-case' ICER to the discount rate applied (see section 3.26). The Committee noted the exploratory sensitivity analysis carried out by the manufacturer which showed that applying a discount rate of 0% on QALYs gained (but keeping the discount rate on costs at 3.5%) decreased the manufacturer's deterministic ICER from £60,200 to £25,100 per QALY gained and a discount rate of 6% increased the manufacturer's deterministic ICER to £95,100 per QALY gained. It also noted the wide range in these figures. The Committee noted the clarification to the 'Guide to the methods of technology appraisal' issued by the Board of NICE, which states that 'where the Appraisal Committee has considered it appropriate to undertake sensitivity analysis on the effects of discounting because treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years), the Committee should apply a rate of 1.5% for health effects and 3.5% for costs'. The Committee discussed whether these criteria were met in the case of mifamurtide. It noted that mifamurtide is a treatment with curative intent that increased the overall survival from 71% to 78%

compared with chemotherapy alone in the whole trial (regimens A+ and B+ combined versus regimens A and B combined). It also noted that patients who are cured are expected to have a long and sustained benefit and regain normal life expectancy. The Committee concluded that both criteria were met and a discount rate of 1.5% should be used for health effects. This resulted in a manufacturer's best-case probabilistic ICER of £36,000 per QALY gained (see section 3.26).

4.14 The Committee noted that the ICER of £36,000 per QALY gained is higher than what is normally considered an effective use of NHS resources and that the NICE 'Guide to the methods of technology appraisal' states that a strong case should be identified for an ICER that is higher than £30,000 per QALY gained. The Committee noted that, in these circumstances, the NICE 'Guide to methods of technology appraisal' states that judgements about the acceptability of the technology, as an effective use of NHS resources, will specifically take account of any strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured or whether the innovative nature of the technology may not have been adequately captured in the QALY measure. The Committee discussed whether the assessment of the change in health-related quality of life had been inadequately captured in the economic analysis. It heard from patient experts that successfully treated patients could lead an active and fulfilling life and were able to contribute to society. The Committee also heard from the patient experts that supporting a young person with osteosarcoma has a profound impact on the health-related quality of life of the family and friends of the person affected, particularly when 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 very important issues affecting the health-related quality of life of those close to the person with osteosarcoma which should be taken into account but on this occasion had not been adequately captured in the economic analysis.

4.15 Furthermore, the Committee accepted that mifamurtide plus adjuvant chemotherapy may represent a potentially valuable new therapy and that the mechanism of action was novel. It acknowledged that few advances had been made in the treatment of osteosarcoma in recent years and mifamurtide could be considered a significant innovation for a rare disease. The Committee concluded that the combined value of these factors, in addition to the potential uncaptured

QALY benefits, meant that mifamurtide could be considered a cost-effective use of NHS resources.

4.16 The Committee considered whether there were issues relating to equality to be taken into account in light of its duties under the equalities legislation. The Committee discussed comments made at the scoping stage. These included the observation that osteosarcoma mainly affects children, teenagers and young adults, and that osteosarcoma is a rare disease. The Committee considered that no different recommendations were made for the patient population within the licensed indication, that is, the recommendations are not based on age and do not vary according to the age of the patient. The Committee was therefore satisfied that there were no equalities issues relating to age in this appraisal and that the recommendations were consistent with NICE's obligations under the equalities legislation and the requirement for fairness.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

5.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has osteosarcoma and the healthcare professional responsible for their care thinks that mifamurtide is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Recommendations for further research

6.1 Further studies on the clinical effectiveness of mifamurtide when combined with the chemotherapy typical of UK clinical practice would be useful to determine the size of the effect of mifamurtide.

6.2 Further collection of quality-of-life data from people who are cured and who have experience of amputation and chemotherapy are also needed. Additional data on the health effects on parents, siblings and others with life-threatening illness would also be of value.

7 Appraisal Committee members and NICE project team

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 4 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), member until May 2011
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, member until November 2010
Lay member

Professor Karl Claxton, member until February 2010
Professor of Health Economics, University of York

Dr Fiona Duncan
Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Christopher Earl
Surgical Care Practitioner, Renal Transplant Unit, Manchester Royal Infirmary

Dr Paul Ewings, member until November 2010
Statistician, Taunton and Somerset NHS Trust, Taunton

John Goulston, member until May 2011
Chief Executive, Barking, Havering and Redbridge Hospitals NHS Trust

Adrian Griffin
VP Strategic Affairs, LifeScan, Johnson & Johnson

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

Dr Peter Heywood
Consultant Neurologist, Frenchay Hospital

Dr Sharon Saint Lamont
Head of Quality and Innovation, North East Strategic Health Authority

Dr Ian Lewin
Consultant Endocrinologist, North Devon District Hospital

Dr Louise Longworth
Reader in Health Economics, HERG, Brunel University

Dr Alec Miners
Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Dr James Moon, member until July 2011
Consultant Cardiologist and Senior Lecturer, University College London Hospital (UCLH) and UCL

Dr David Newsham
Lecturer (Orthoptics), University of Liverpool

Ms Pamela Rees
Lay member

Dr Ann Richardson
Lay member

Dr Paul Robinson
Medical Director, Merck Sharp & Dohme

Angela Schofield
Chairman, Bournemouth and Poole Teaching PCT

Mr Stephen Sharp
Senior Statistician, MRC Epidemiology Unit

Dr Eldon Spackman
Research Fellow, Centre for Health Economics, University of York

Mr Mike Spencer
Assistant Director Patient Experience, Cardiff and Vale University Health Board

Professor Iain Squire
Consultant Physician, University Hospitals of Leicester

David Thomson
Lay member

William Turner
Consultant Urologist, Addenbrooke's Hospital

Dr Luke Twelves
General Practitioner, Ramsey Health Centre, Cambridgeshire

Dr John Watkins
Clinical Senior Lecturer, Consultant in Public Health Medicine, Cardiff University and

National Public Health Service Wales

Dr Anthony S Wierzbicki
Consultant in Metabolic Medicine, Chemical Pathology, Guy's and St Thomas' Hospitals NHS Trust

Dr Olivia Wu
Reader in Health Economics, University of Glasgow

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Pall Jonsson, Fay McCracken and Whitney Miller
Technical Leads

Nicola Hay and Helen Knight
Technical Advisers

Bijal Joshi
Project Manager

8 Sources of evidence considered by the Committee

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

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). Manufacturers or sponsors were also invited to make written submissions. Professional or specialist, patient or carer groups, and other consultees, had the opportunity to give their expert views. Manufacturers or sponsors, professional or specialist, patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- Takeda UK (mifamurtide)

Professional or specialist, and patient or 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

Other consultees:

- Department of Health
- Welsh Government

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)
- Healthcare Improvement Scotland
- School of Health and Related Research (ScHARR), The University of Sheffield

The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer or sponsor consultees and commentators. They gave their expert personal view on mifamurtide by attending the Committee discussions 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
- Professor Andrew Bassim Hassan, Professor of Medical Oncology and Consultant Medical Oncologist, nominated by Bone Cancer Research Trust– clinical specialist
- Dr Bruce Morland, Consultant Paediatric Oncologist, nominated by Royal College of

Paediatrics and Child Health. Supported by Children's Cancer and Leukaemia Group– 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

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

- Takeda UK

Update information

February 2014: Implementation section updated to clarify that mifamurtide is recommended as an option for treating osteosarcoma.

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