Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Resubmission

mifamurtide 4mg powder for suspension for infusion (Mepact®)

SMC No. (621/10)

Takeda UK and Ireland Ltd

08 July 2011

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

mifamurtide (Mepact) is accepted for use within NHS Scotland.

Indication under review: in combination with post-operative multi-agent chemotherapy for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection, in children, adolescents and young adults. Safety and efficacy have been assessed in studies of patients 2 to 30 years of age at initial diagnosis.

Mifamurtide has been shown to increase overall survival compared with multi-agent chemotherapy alone in patients aged up to 30 years with newly-diagnosed resectable osteosarcoma.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of mifamurtide. This SMC advice is contingent upon the continuing availability of the PAS in NHS Scotland.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Mifamurtide is indicated in children, adolescents and young adults for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection. It is used in combination with post-operative multi-agent chemotherapy. Safety and efficacy have been assessed in studies of patients 2 to 30 years of age at initial diagnosis.

Dosing Information

The recommended dose of mifamurtide for all patients is 2mg/m^2 body surface area. It should be administered as adjuvant therapy following 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 infusions in 36 weeks. It is administered by intravenous infusion.

Mifamurtide treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of osteosarcoma.

Product availability date

1 February 2010

Mifamurtide was designated an orphan medicine by the European Medicines Agency (EMA) in June 2004.

Summary of evidence on comparative efficacy

Osteosarcoma is a rare bone cancer that is predominantly diagnosed in young adults, adolescents and children. Current management of osteosarcoma comprises surgical resection to remove the local tumour and chemotherapy. Mifamurtide is an immune adjuvant macrophage stimulant, in a liposomal formulation, intended for use as an additive therapy, following surgical resection, and in combination with post-operative multi-agent chemotherapy.

A phase III, open-label, randomised study recruited 678 patients ≤ 30 years with newly-diagnosed, histologically confirmed, high grade, intramedullary osteosarcoma. Patients with metastatic disease and non-resectable tumours were excluded. The primary objective of the study was to determine whether the addition of ifosfamide and/or mifamurtide to cisplatin, doxorubicin and high dose methotrexate could improve disease-free survival (defined as survival from randomisation to relapse of osteosarcoma or death) in patients with newly diagnosed osteosarcoma. Induction (neoadjuvant) chemotherapy with one of two regimens was administered during weeks 0 to 9 (regimen A including cisplatin or regimen B including ifosfamide), surgical resection was performed during weeks 10 to 11 and, if the wound had healed sufficiently, maintenance (adjuvant) chemotherapy was administered from week 12 with regimen A or B (plus cisplatin) each with or without mifamurtide. The duration of treatment was dependent on the regimen administered.

Maintenance treatment with regimen A comprised doxorubicin (four courses of 25mg/m^2/day for 3 days), cisplatin (two doses of 120mg/m^2) and high dose methotrexate (eight doses of 12g/m^2)

and was administered over 20 weeks. Maintenance treatment with regimen B comprised ifosfamide (three courses of 1.8g/m^2/day for 5 days), doxorubicin (four courses of 25mg/m^2/day for 3 days), cisplatin (four doses of 120mg/m^2) and high dose methotrexate (eight doses of 12g/m^2) and was administered over 27 weeks. Regimens A or B, plus mifamurtide (2mg/m^2, as an intravenous infusion twice weekly for twelve weeks then once weekly for an additional 24 weeks) were administered over 36 weeks. The mifamurtide dose could be escalated twice in accordance with the study protocol. The number of patients allocated to each study group was as follows: regimen A alone (n=174), regimen A plus mifamurtide (n=167), regimen B alone (n=166) and regimen B plus mifamurtide (n=171).

Analysis of overall survival was reported on an intention to treat basis (all randomised patients who did not have evidence of metastases and who had resectable tumours at the time of randomisation), estimated using the Kaplan-Meier method. With the increasing length of follow-up, the data has been analysed three times. Results from the most up to date analysis for overall survival and disease free survival for the 2007 data set, at a median follow up of 7.9 years, are reported here.

Disease Free Survival: 2007 Dataset

	No of patients (events)	P-value*	Hazard ratio	95% CI for Hazard Ratio
No Mifamurtide	340 (133)	-	1.00	-
Mifamurtide	338 (107)	0.0586	0.78	0.61 to 1.01

Overall Survival: 2007 Dataset

	No of patients (deaths)	P-value*	Hazard ratio	95% CI for Hazard Ratio
No Mifamurtide	340 (100)	-	1.00	-
Mifamurtide	338 (73)	0.0313	0.72	0.53 to 0.97

P-value for comparing “no mifamurtide” with “mifamurtide” from log rank test stratified by ifosfamide use and randomisation strata. Median follow up for the above data was 7.9 years. CI=confidence interval

Analysis of the 2007 dataset reported an increase in 6-year event-free survival from 61% to 67% (HR 0.80 [95% CI: 0.62 - 1.0]) and an increase in 6-year overall survival from 70% to 78% (HR 0.71 [95% CI: 0.52 - 0.96]).

More patients in the groups treated with mifamurtide discontinued from the study, many of these were at the request of the patient or parent.

Summary of evidence on comparative safety

Only adverse effects that were serious or life-threatening were recorded in the pivotal study. From previous studies some of the more common adverse effects of mifamurtide include anaemia, weight loss, tachycardia, blood pressure changes and gastrointestinal symptoms.

The most frequent adverse events associated with chemotherapy were low blood counts, nausea and vomiting, stomatitis, infections, hearing loss and abnormal liver enzymes. Serious

adverse events, which may have been related to mifamurtide, included allergic reactions, pleural and pericardial effusions and neurotoxicity.

Summary of clinical effectiveness issues

Mifamurtide, an orphan medicine for this indication, increased the overall survival of patients with newly-diagnosed, resectable, high-grade osteosarcoma when used in combination with maintenance chemotherapy compared to chemotherapy alone, giving a relative reduction in the risk of death of 28% (HR = 0.72 [95% CI: 0.53 to 0.97]) at 7.9 years of follow up. However, disease free survival was not significantly improved with the addition of mifamurtide to post resection chemotherapy

Initially the European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP) raised a number of concerns with respect to the pivotal study including difficulties in interpreting efficacy and safety due to missing data and incomplete follow-up of all patients. One important issue was the absence of any interaction between mifamurtide and ifosfamide which was crucial to the analysis of the primary outcome. This was referred to the Scientific Advisory Group (SAG) who advised that a quantitative interaction with ifosfamide may exist but that was likely to be small and of slight clinical importance. They recommended more extensive follow-up and post-approval studies to address this issues and the CHMP concluded that the risk:benefit profile of mifamurtide was favourable in this indication.

This is a rare disease and the pivotal phase lll study objectives addressed a number of aspects of treatment of osteosarcoma. The benefit in the overall survival of the addition of mifamurtide to two different maintenance regimens, was only one objective of the study. This has contributed to uncertainty around the protocol specified primary outcome and the optimum combination of induction and maintenance chemotherapy to which mifamurtide may be added to provide maximal benefit.

Histological response to pre-surgical induction chemotherapy is an important prognostic factor. However, patients were randomised at the start of the study, before the histological response was known, and therefore this prognostic factor could not be stratified for in the patient randomisation. Experts consulted by SMC have suggested that the choice of maintenance therapy after surgery can be influenced by histological response.

The EMA noted that in the pivotal study the number of withdrawals during maintenance treatment by parent/patient was higher in the mifamurtide groups and may have been due to the extended treatment period for mifamurtide and the uncertainty around the benefit of this investigational agent.

From a service perspective, mifamurtide must be reconstituted, filtered and further diluted within a laminar flow cabinet prior to administration. This process takes at least 30 minutes. This may have an impact on aseptic preparation services, as initial treatment comprises twice weekly infusions for 12 weeks followed by weekly infusions for a further 24 weeks.

In addition, the Summary of Product Characteristics recommends administration by slow infusion over one hour and separate administration times for doxorubicin and mifamurtide which may prolong the time taken to administer the full chemotherapy regimen for the patient and extra nursing time may be required to administer the infusions. Due to the 36-week treatment

course, mifamurtide would be associated with additional hospital visits compared with standard chemotherapy alone.

Summary of comparative health economic evidence

The submitting company presented a cost-utility model comparing the addition of mifamurtide to standard maintenance chemotherapy to standard chemotherapy alone. Standard maintenance chemotherapy was with doxorubicin, cisplatin, methotrexate or doxorubicin, cisplatin, methotrexate and ifosfamide. The population of interest was patients under the age of 30 with high-grade osteosarcoma after macroscopically complete resection. A lifetime horizon was taken which equated to a 60 year time period.

Information from the clinical trial was used to estimate the outcomes in the model in terms of disease recurrence and death for the first 12 years of the model for which follow-up data existed from the study. This was supplemented with data from other published studies in order to estimate outcomes for patients in terms of disease progression and survival post- recurrence. It was assumed that patients who were still disease-free at 12 years reverted to having a mortality rate equivalent to the general population.

The company stated that there was a lack of utility values for osteosarcoma patients and thus used an average set of values derived from recent NICE health technology appraisals for a range of other cancers. A sensitivity analysis was conducted using some utility values collected from a small sample of UK osteosarcoma patients. No disutilities for side effects were included in the base case analysis.

Resource use costed in the model related to the drug costs associated with treatment and administration and costs associated with disease progression, such as subsequent chemotherapy, surgery or palliative care costs. A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the list price of mifamurtide.

The results of the model gave an incremental cost-effectiveness ratio (ICER) of £48,579 per quality adjusted life year (QALY) with the PAS **(**incremental cost £65,014 Incremental QALYs 1.34).

Sensitivity analysis indicated that the results were sensitive to the following:

- The impact of assuming a lower or zero discount rate on health benefits. This resulted in an ICER of £19,016 (0% discount rate) or £29,550 (1.5% discount rate) in the with-PAS scenario. This is because the costs of mifamurtide are accrued in the first few years of the model but the benefits arise over a long period of time in a relatively young population.
- Use of utility values adapted from the EQ-5D survey undertaken by company increased the ICER to £54,943 with the PAS. This indicated that the results were sensitive to the utility values used in the analysis, which should be noted given that the base case values were taken from patient populations without osteosarcoma.

SMC considered the likely range of cost-effectiveness ratios and the uncertainties above. Although there were some limitations in the economic analysis, the economic case was considered demonstrated when SMC modifiers, in particular those relating to the improvement in life expectancy were applied.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Sarcoma UK
- Campaigning and Advocacy Bone Cancer Research Trust

Additional information: guidelines and protocols

The Scottish Sarcoma Network Treatment Algorithm advises that patients under 40 years of age are treated according to the EURAMOS I clinical study. This is an on-going study looking at combination chemotherapy followed by surgery and two different combination chemotherapy regimens, with and without PEG-interferon -2b

Additional information: comparators

Mifamurtide is proposed as add-on therapy, thus there are no active comparators.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Mifamurtide	2mg/m^2 twice weekly for 12 weeks then once weekly for 24 weeks by intravenous infusion	114,000

Doses are for general comparison and do not imply therapeutic equivalence. Dosing is based on average body surface area of 1.8m^2 and assumes no vial sharing. Costs from eVadis on 9 May 2011.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 5 patients, to which an assumption was made regarding market share for mifamurtide. The impact on the medicines budget was estimated at £128K in year 1 and £255K in year 5 with the PAS. No net drug budget impact was presented as mifamurtide is an additional treatment. However, the manufacturer estimated that after accounting for additional outpatient visits to administer mifamurtide, the overall NHS budget impact would be £130K and £261K respectively with the PAS.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission.

The European Medicines Agency (EMA) European Public Assessment Report. Mifamurtide (Mepact®). EMEA H-C-000802. http://www.ema.europa.eu

Meyers PA, Schwartz CL, Krailo M et al. Osteosarcoma: A Randomized, Prospective Trial of the Addition of Ifosfamide and/or Muramyl Tripeptide to Cisplatin, Doxorubicin and High-Dose Methotrexate. Journal of Clinical Oncology 2005; 23(9): 2004-11.

Meyers PA, Schwartz CL, Krailo M et al. Osteosarcoma: The Addition of Muramyl Tripeptide to Chemotherapy Improves Overall Survival – A Report from the Children's Oncology Group. Journal of Clinical Oncology 2008; 26(4): 633-8.

This assessment is based on data submitted by the applicant company up to and including 01 July 2011.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override

the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.