

National Institute for Health and Clinical Excellence

Mifamurtide for osteosarcoma

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Rarer Cancers Forum	As there has been no new therapy for osteosarcoma for 20 years it is very appropriate to refer this topic	Comment noted
	Anthony Pilcher Bone Cancer Trust	I consider it to be very appropriate	Comment noted
	Royal College of Pathologists	It is entirely appropriate	Comment noted
	Bone Cancer Research Trust	The Bone Cancer Research Trust welcome this consultation and in particular welcomes the appraisal of this agent liposomal muramyl tripeptide phosphatidyl ethanolamine	Comment noted
	Royal College of Paediatrics and Child Health	Yes. The phase III data has been in the public arena for more than a year.	Comment noted
	Sarcoma UK	This is appropriate, It is a rare cancer particularly affecting children and young people in which no improvements in survival have been identified in two decades. This agent has the promise to improve survival but it should be universally available.	Comment noted
	IDM Pharma, Inc	Osteosarcoma is a life-threatening condition. The treatment of osteosarcoma is viewed by clinical experts in the field as having a significant unmet medical need. Despite advances in therapy, it remains potentially fatal in up to a third of the children and adolescents who develop this condition. The current survival rate of osteosarcoma with surgery and multi-agent chemotherapy of 50-75% has not been improved for almost two decades as the standard of care has barely evolved during this period. Mepact will provide significant survival benefit when used in combination with multi-agent chemotherapy. We therefore believe this product should be referred for assessment so that patients can access this product in a timely manner.	Comment noted

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	CLIC Sargent	Yes, this is an appropriate appraisal. This is an important agent for NICE to appraise.	Comment noted
Wording	Rarer Cancers Forum	It would be worth stating that on the 2004 (unreferenced by yourselves) it seems there are only going to be about 150 patients with this cancer in a year and this will have little cost impact	Comment noted
	Anthony Pilcher Bone Cancer Trust	Yes	Comment noted
	Royal College of Pathologists	In outline	Comment noted
	Bone Cancer Research Trust	These appear appropriate, however our estimate is that there are slightly more patients with osteosarcoma than appear in your data. In our opinion low grade tumours appear very rare	The numbers were confirmed at the scoping workshop
	Royal College of Paediatrics and Child Health	Yes	Comment noted
	Sarcoma UK	Please add: "and in patients with metastatic or recurrent osteosarcoma."	At the scoping workshop it was agreed that these groups should be considered separately if the evidence allows and dependent on the marketing authorisation received for the technology, see other considerations section of the scope. The remit reflects this by stating that the technology will be appraised within its licensed indications.
	IDM Pharma, Inc	The wording is consistent with the proposed indication.	Comment noted

Section	Consultees	Comments	Action
Timing Issues	Rarer Cancers Forum	orphan drugs such as this are so needed by the small patient population	Comment noted
	Anthony Pilcher Bone Cancer Trust	I believe it is urgent	Comment noted
	Royal College of Pathologists	Yes	Comment noted
	Bone Cancer Research Trust	We understand that there are applications for licences pending in the US and Europe. This appraisal is timely and should be completed when the drug becomes available.	Comment noted
	Royal College of Paediatrics and Child Health	Yes.	Comment noted
	Sarcoma UK	This is urgent. If licensing is successful in 2008/9 demand for this drug to treat young people with osteosarcoma will be very difficult to resist in the absence of appraisal by NICE.	Comment noted
	IDM Pharma, Inc	The company expects to receive a final opinion from the CHMP in the third quarter of 2008 and a decision from the EMEA in the fourth quarter of 2008.	Comment noted
	CLIC Sargent	An appraisal on this technology should take place as soon as possible, within NICE's work programme. The proposal to undertake a Single Technology Appraisal will mean that guidance is rightly available to the NHS as soon as possible. The appraisal should take place alongside the market authorisation process to ensure it begins soon.	Comment noted

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Additional comments on the draft remit	Royal College of Paediatrics and Child Health	We think it is important to include consideration of the circumstance of presenting additionally with metastatic pulmonary disease in the scope.	At the scoping workshop it was agreed that these groups should be considered separately if the evidence allows and dependent on the marketing authorisation received for the technology, see other considerations section of the scope. The remit reflects this by stating that the technology will be appraised within its licensed indications.
	IDM Pharma, Inc	No additional comments.	Comment noted
	CLIC Sargent	Mepact would set a new standard of care for osteosarcoma and it is therefore vital that NICE carries out this appraisal.	Comment noted

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Rarer Cancers Forum	I wish the background information was referenced so we know from whence the information is taken	Comment noted. All evidence used in the appraisal phase is clearly referenced. The purpose of the scope is to define the questions to be asked.
	Anthony Pilcher Bone Cancer Trust	Fine	Comment noted
	Royal College of Pathologists	Outline only but accurate	Comment noted
	Bone Cancer Research Trust	See above	Comment noted
	Royal College of Paediatrics and Child Health	We feel that the document would benefit from addition of a paediatric perspective e.g. annotating specifically the number of children under 16 years diagnosed with osteosarcoma per year, and the associated mortality. Virtually all osteosarcoma in this age group is high grade. There should be an emphasis on the lack of progress in improving outcome in this disease for the last 2 decades. Death is usually the result of respiratory failure because of progressive pulmonary metastases refractory to chemotherapy.	The background section of the scope has been amended to include incidence in children and the lack of treatment development.
	Sarcoma UK	Please add: "the primary aim of surgical resection _and chemotherapy_ is patient survival."	The background section of the scope has been amended.
	IDM Pharma, Inc	The background should reflect the relative contribution of surgery and adjuvant chemotherapy to survival and the lack of treatment progress in the last 20 years.	The background section of the scope is meant to give a brief overview of the condition, a sentence has been added regarding the lack of treatment development in this area.

Section	Consultees	Comments	Action
The technology/ intervention	Rarer Cancers Forum	Yes	Comment noted
	Anthony Pilcher Bone Cancer Trust	Fine	Comment noted
	Royal College of Pathologists	Yes	Comment noted
	Royal College of Paediatrics and Child Health	The product targets lung, liver and spleen macrophages.	The technology section of the scope has been amended
	IDM Pharma, Inc	MEPACT is intended to target microscopic disease in the lungs presumed to be present in most patients at diagnosis as reflected by pulmonary relapses when surgery is the only intervention.	The technology section of the scope has been amended
Population	Rarer Cancers Forum	This is small population and usually a young population	Comment noted
	Anthony Pilcher Bone Cancer Trust	Fine	Comment noted
	Royal College of Pathologists	Yes (but note this is the question being addressed)	Comment noted
	Bone Cancer Research Trust	We understand that most patients treated with this agent in the American trial were young.	Comment noted
	Royal College of Paediatrics and Child Health	See above – with reference to the paediatric population.	Comment noted
	Sarcoma UK	Delete: "surgical resection".	Technologies are appraised in accordance with their licensed indications, current information on from clinical trials indicates that mifamurtide will only be used after surgical resection

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	IDM Pharma, Inc	The population should reflect newly diagnosed resectable high grade osteosarcoma. There are no data to support use in older patients who have osteosarcoma secondary to Paget's disease or radiation.	Comment noted.
Comparators	Rarer Cancers Forum	yes	Comment noted
	Anthony Pilcher Bone Cancer Trust	Fine	Comment noted
	Royal College of Pathologists	Yes	Comment noted
	Bone Cancer Research Trust	Standard treatment in the UK is 3 drug chemotherapy with cisplatin, doxorubicin and high dose methotrexate	It was agreed at the scoping workshop not to restrict the agents to these three, comparator section now states 'multi-agent chemotherapy alone'
	Royal College of Paediatrics and Child Health	Yes.	Comment noted
	Sarcoma UK	Standard treatment in the UK should read: doxorubicin, cisplatin and methotrexate.	It was agreed at the scoping workshop not to restrict the agents to these three, comparator section now states 'multi-agent chemotherapy alone'.
	IDM Pharma, Inc	Comparators are not alternatives. MEPACT is designed as an add-on to chemotherapy and works through a different mechanism of action (activation of macrophages).	The comparator refers to the current standard care in the UK without this intervention. At the scoping workshop it was agreed that it would be multi agent chemotherapy alone

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Outcomes	Rarer Cancers Forum	Please bear in mind the small numbers we are discussing here in terms of QULY and the fact that there has been no for treatment for many years	Comment noted
	Anthony Pilcher Bone Cancer Trust	Fine	Comment noted
	Royal College of Pathologists	Yes	Comment noted
	Bone Cancer Research Trust	The most important outcome measure is improving overall survival.	Comment noted
	Royal College of Paediatrics and Child Health	Yes.	Comment noted
	Sarcoma UK	Yes - the right outcomes.	Comment noted
	IDM Pharma, Inc	As is true for all cancers, overall survival is the most important efficacy endpoint. Clinical data published in the February 1, 2008 issue of the Journal of Clinical Oncology shows that the addition of MEPACT to adjuvant chemotherapy reduces the risk of death by approximately 30% in patients with newly diagnosed, non-metastatic resectable high-grade osteosarcoma.	Comment noted
	CLIC Sargent	Yes	Comment noted
Economic analysis	Rarer Cancers Forum	We need this quickly	Comment noted
	Anthony Pilcher Bone Cancer Trust	Fine	Comment noted
	Royal College of Pathologists	Appropriate as far as goes	Comment noted
	Bone Cancer Research Trust	We agree	Comment noted

Summary form

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	Royal College of Paediatrics and Child Health	It is important to consider the implication of including a paediatric population in the analysis.	It was agreed at the scoping workshop not to consider them separately
	IDM Pharma, Inc	Since osteosarcoma is primarily a disease of adolescents, the life-time perspective of clinical benefit is appropriate.	Comment noted
Equality	Anthony Pilcher Bone Cancer Trust	Fine	Comment noted
	Rarer Cancers Forum	It is important to note that those with orphan diseases need the same fair and equal treatment as those with the more common diseases and drugs should be sympathetically be considered as there are so few of them	The Department of Health has not indicated that the Institute use different methods in appraising orphan diseases.
	Royal College of Pathologists	Not an issue	Comment noted
	Bone Cancer Research Trust	If shown to be effective this drug must be available for all. Osteosarcoma is a rare disease that occurs mainly in children and young people	NICE will appraise the clinical and cost effectiveness of the technology.
	Royal College of Paediatrics and Child Health	Health related analyses would also need to be validated in the paediatric population.	Comment noted.
	IDM Pharma, Inc	MEPACT will be distributed under restricted medical prescription. Initial dose(s) should be administered under the care of a pediatric oncologist (or comparable medical practitioner). Subsequent doses can be administered locally on an out-patient basis under appropriate supervision which may make MEPACT more accessible.	Comment noted
	CLIC Sargent	This appraisal is essential to ensuring equality of access to this important technology for young people with curable cancer.	Comment noted
Other considerations	Rarer Cancers Forum	None	Comment noted

Summary form

Section	Consultees	Comments	Action
	Anthony Pilcher Bone Cancer Trust	Fine	Comment noted
	Royal College of Pathologists	None	Comment noted
	Royal College of Paediatrics and Child Health	Is there scope for consideration of the product, adjuvant to chemotherapy, in presentations with pulmonary metastatic disease?	At the scoping workshop it was agreed that these groups should be considered separately if the evidence allows and dependent on the marketing authorisation received for the technology, see other considerations section of the scope. Remit has been changed to "To appraise the clinical and cost effectiveness of mifamurtide within its licensed indications as an adjunct to multi-agent chemotherapy for the treatment of osteosarcoma". If the evidence allows and dependent on the marketing authorisation for the technology, other groups will be considered, see other considerations section of the scope.
	IDM Pharma, Inc	No additional comment	Comment noted
Questions for consultation	Rarer Cancers Forum	None	Comment noted

Section	Consultees	Comments	Action
	Anthony Pilcher Bone Cancer Trust	Fine	Comment noted
	Royal College of Pathologists	This is	Comment noted
	IDM Pharma, Inc	No additional comment	Comment noted
Additional comments on the draft scope.	Rarer Cancers Forum	None	Comment noted
	Royal College of Pathologists	Histopathologists are key to identifying the effectiveness of therapy in terms of tumour cell "kill", and are pivotally involved in diagnosis, grading and staging. The input of histopathologists directly into the question being asked is limited but it is important they should be involved because, in their role in diagnosis, prognosis and staging histopathologists play a key role in every step of patient management, including assessing the success of treatment	Comment noted
	Bone Cancer Research Trust	The appraisal should consider: a) those with metastatic disease as well - but separately b) those who have relapsed and not received this drug	At the scoping workshop it was agreed that these groups should be considered separately if the evidence allows and dependent on the marketing authorisation received for the technology, see other considerations section of the scope.
	IDM Pharma, Inc	There is a typographical error in the 4th paragraph of background. Should read "osteosarcoma can be divided...". On page 2 of 3, the last paragraph in the background section. Sentence should read "Most standard regimens include doxorubicin and cisplatin, with or without methotrexate and with or without ifosfamide." In the technology section, MEPACT is the EU designated trade name, mifamurtide is the generic name, and L-MTP-PE is the chemical name. The drug has also been referred to as MTP or MTP-PE in publications.	The background and technology sections of the scope have been amended accordingly.

Comment 4: Regulatory issues

Section	Consultees	Comments	Action
Remit	IDM Pharma, Inc	Yes	Comment noted
Current or proposed marketing authorisation	IDM Pharma, Inc	<p>None</p> <p>MEPACT is indicated in children and adults for the treatment of high-grade resectable non-metastatic osteosarcoma (bone cancer) after macroscopically complete surgical resection to remove the tumour. It is used in combination with post-operative multi-agent chemotherapy.</p> <p>MAA was submitted in November 2006</p> <p>European Centralized Procedure</p> <p>Q3 2008</p> <p>The expectation of a final CHMP opinion in Q3 is public information</p>	Comment noted

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

ASGBI
 Department of health
 Marie Curie Cancer Care
 NHS Quality improvement Scotland

NPHS Wales
 Wyeth Pharmaceuticals