HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

17 November 2010

MEPACT 4 mg, powder for suspension for infusion
B/1 (CIP code: 398331 6)

Applicant : IDM PHARMA S.A.S

mifamurtide
ATC code: L03AX15

List I
Medicine for hospital prescription only. Prescription restricted to oncology or haematology specialists or doctors with cancer training. Medicine requiring special monitoring during treatment.

Orphan drug status (21 June 2004)

Date of Marketing Authorisation (centralised European procedure): 6 March 2009

Reason for request: Inclusion on the list of medicines approved for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

mifamurtide

1.2. Background

Mifamurtide (muramyl tripeptide phosphatidyl ethanolamine, MTP-PE) is a synthetic derivative of muramyl dipeptide (MDP), the smallest natural immunostimulatory component of the cell walls of Mycobacterium sp. Its immunostimulatory action is similar to that of natural MDP with a longer plasma half-life.

1.3. Indication

”MEPACT is indicated in children, adolescents and young adults for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically-complete surgicalresection. 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.”

1.4. Dosage

“The recommended dose of mifamurtide for all patients is 2 mg/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.”

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

L : Antineoplastic and immunomodulating agents
L03 : Immunostimulants
L03A : Immunostimulants
L03AX : Other immunostimulants
L03AX15 : mifamurtide

2.2. Medicines in the same therapeutic category

Comparator medicines
None

2.3. Medicines with a similar therapeutic aim

- ADRIBLASTINA (doxorubicin) and its generics
- HOLOXAN (ifosfamide)
- CISPLATYL (cisplatin) and its generics
- METHOTREXATE BELLON (methotrexate) and its generics
- ENDOXAN (cyclophosphamide)

3. ANALYSIS OF AVAILABLE DATA

The file submitted includes one pivotal study INT-0133, the results of which are analysed below.

Background to the pivotal study:
The study, which was started in 1993 by Ciba-Geigy, was conducted by the Children's Oncology Group (COG) under the guidance of the National Cancer Institute (NCI) in the United States. In the late 90s, the COG lost interest in this product, the development of which was suspended by Ciba-Geigy following its merger with Sandoz, then the cessation of operations by Jenner Biotherapies which had acquired rights to it. When IDM Pharma took over Jenner Biotherapies in 2003 it analysed data forwarded by the COG and decided to invest in the completion of this study. The data held on the database held by the COG were analysed on three dates: 2003, 2006 and 2007.

3.1. Efficacy

Study INT-0133[1, 2]
A randomised open-label study to compare the association of MEPACT with chemotherapy with doxorubicin, cisplatin and methotrexate, with or without ifosfamide, to the same chemotherapy administered alone, in patients with an osteogenic sarcoma following surgical excision.

The study involved three phases:
- an induction phase (neo-adjuvant therapy[3]) lasting 10 weeks,
- a surgical treatment phase lasting 2 weeks,
- a maintenance phase (adjuvant therapy) lasting between 20 and 36 weeks, depending on the treatments given.

Neo-adjuvant therapy comprised:
Protocol A: doxorubicin, cisplatin and methotrexate
Protocol B: doxorubicin, ifosfamide and methotrexate

Surgical treatment was then carried out over the following 2 weeks (W10 to W11), during which time patients did not receive any medicinal treatment.

Following surgical excision of the tumour, patients in each group were randomised into two groups each (with or without MEPACT) for adjuvant therapy for 20 to 36 weeks depending on the treatments given (maintenance phase):

Protocol A: (doxorubicin, cisplatin and methotrexate) + MEPACT
Protocol A: (doxorubicin, cisplatin and methotrexate)
Protocol B: (doxorubicin, ifosfamide and methotrexate) + cisplatin + MEPACT
Protocol B: (doxorubicin, ifosfamide and methotrexate) + cisplatin

During this maintenance phase, MEPACT was administered at a dosage of 2 mg/m², (which could be increased up to 4 mg/m²) as an infusion twice a week for 12 weeks then once a week for a further 24 weeks, making a total of 48 infusions over 36 weeks.

[1] Meyers et al. Osteosarcoma: a randomized, prospective trial of the addition of ifosfamide and/or muramyl tripeptide to cisplatin, doxorubicin, and high-dose methotrexate. J Clin Oncol. 2005;23:2004-11.
[2] Meyers et al. Osteosarcoma: the addition of muramyl tripeptide to chemotherapy improves overall survival--a report from the Children's Oncology Group. J Clin Oncol. 2008;26:633-8.
[3] Pre-treatment before surgery in order to achieve the maximum reduction possible in the size of the tumour

The main inclusion criteria were as follows:
- Newly-diagnosed patients with a high-grade malignant osteosarcoma less than one month since the diagnostic biopsy;
- patients ≤ 30 years of age;
- patients with normal organ function (renal, hepatic and cardiac function).

The primary endpoint was disease-free survival[4] [5] [6] for the two treatments compared (induction treatment with or without ifosfamide and adjuvant treatment with or without MEPACT). Disease-free survival was defined as the period between randomisation and the onset of a relapse or death from any cause.

Global survival was a secondary endpoint. It was defined as the period between randomisation and death from any cause.

Results:

A total of 793 patients were recruited and treated in the study, including 115 patients with a metastatic disease (n=91) or a non-resectable tumour (n=24).
The 678 patients with a resectable, non-metastatic disease, 338 of whom were treated with MEPACT, were included in the efficacy analysis.
The patients were between 1.4 and 30.6 years of age. The primary tumour site was mainly the femur (54%) or the tibia (24.8%). High-grade osteosarcoma accounted for almost half the cases (47.5%).

Table 1: Distribution of patients according to the grade of osteosarcoma

Viable tumour **Protocol**	**Grades I/II** **High grade**	**Grades III/IV** **Low grade**	**Not specified***	**Total**
MEPACT	166 (49%)	124 (37%)	48 (14%)	338 (100%)
Without MEPACT	156 (46%)	139 (41%)	45 (13%)	340 (100%)
Total	322	263	93	678
* Includes patients whose disease has progressed prior to surgery or for whom data were not available				

Grade I: more than 50% active cancer cells; Grade II: 5 to 50% active cancer cells; Grade III: 0 to 5% active cancer cells; Grade IV: 0% active cancer cells

Three analyses were carried out:
- in 2003 with a median follow-up period of 4.8 years,
- in 2006 with a median follow-up period of 7.7 years,
- and in 2007 with a median follow-up period of 7.9 years.

[4] page 30 of the EPAR
[5] page 48 of the initial report on the study (Study report PINT 0133 Pivotal)
[6] page 62 of the study protocol including all amendments (COG INT-0133 Protocol with amendments)

Table 2: Results for disease-free survival (data for 2003, 2006 and 2007)

	2003 Data				2006 Data				2007 Data			
Treatment	N° of patients (events)	p	HR	95% CI	N° of patients (events)	p	RR	95% CI	N° of patients (events)	p	HR	95% CI
With MEPACT	338 (102)	0.0245	0.74	0.57- 0.96	338 (107)	0.0623	0.78	0.61-1.01	338 (107)	0.0586	0.78	0.61-1.01
Without MEPACT	340 (126)	--	1.00	--	340 (133)	--	1.00	--	340 (133)	--	1.00	--
HR = Hazard Ratio												

After a median follow-up period of 4.8 years, disease-free survival (primary endpoint) was better in the group treated with MEPACT in association with chemotherapy as compared to chemotherapy alone (reduction in the risk in absolute terms of 6.9%): RR = 0.74 95% CI [0.57 – 0.96]. On the other hand, there was no difference in disease-free survival after 7.7 years and 7.9 years in the two groups.

Table 3: Results for global survival (data for 2003, 2006 and 2007)

	2003 Data				2006 Data				2007 Data			
Treatment	N° of patients (death)	p	HR	95% CI	N° of patients (death)	p	RR	95% CI	N° of patients (death)	p	HR	95% CI
With MEPACT	338 (63)	0.0183	0.67	0.48-0.94	338 (73)	0.0352	0.72	0.53-0.98	338 (73)	0.0313	0.72	0.53-0.97
Without MEPACT	340 (85)	--	1.00	--	340 (100)	--	1.00	--	340 (100)	--	1.00	--
HR = Hazard Ratio												

With a median follow-up period of 7.9 years, overall survival was better in the group treated with MEPACT in association with chemotherapy as compared to chemotherapy alone (reduction in the risk in absolute terms of 7.8%): HR = 0.72 95% CI [0.53 – 0.97].
A post-hoc sub-group analysis suggests that this result for overall survival involved the following patient sub-groups: women, patients between 13 and 15 years of age, and patients with a tumour measuring more than 11 cm.

The Transparency Committee stresses the following points:
The trial design defined *a priori* is clearly a 2x2 factorial plan, for the simultaneous study of two compared therapeutic strategies:
- Mifamurtide (M) *versus* absence of M
- Doxorubicin-Methotrexate-Cisplatin(Cis)-surgery *versus* Doxorubicin-Methotrexate-Ifosfamide (I) - surgery-$Cis_{deferred}$

This supposes the absence *a priori* of an interaction between "M" and the "I-$Cis_{immediate/deferred}$" strategy.

There are two non-simultaneous randomisation procedures with an interval of at least 11 weeks between them. Only patients not withdrawn after the first eleven weeks of treatment (Cisplatin vs Ifosfamide) are included in the second part of the trial (evaluation of M), leading to a possible attrition bias.
The definition of the primary efficacy endpoint is imprecise, with the simultaneous presentation in the file of results for disease-free survival (DFS) and overall survival (OS) with no correction of the significance threshold. In the initial publication by Meyers *et al*, EFS (event-free survival) was the endpoint which was clearly specified (and which includes secondary cancers). This was the basis used to calculate the number of subjects required.
The file submitted to the FDA showed DFS as the primary endpoint, without taking account moreover of the 22 patients who, according to the company, had a non-metastatic non-resectable tumour. The results of the statistical analysis then become different, which indicates that the results are not robust.

The interaction test (although of limited power) clearly seems to be significant in the study published in 2005 by Meyers *et al*[1], rendering any interpretation of the results doubtful (the two-strata joint analysis with heterogeneous results being unacceptable on a methodological level). Secondary analysis of the results with a 4-arm comparison does not comply with an "ad hoc" hypothetical-deductive approach and lacks power, which doubtlessly explains the lack of significant results observed (see table 4 in the 2005 article). In the article published in 2008[2] and using a different statistical technique (the Cox model), the p-value for interaction is only 0.102 between M and the rest of the chemotherapy for the EFS endpoint, which is hardly convincing, especially as the authors set the significance threshold at 0.1.
The 2005 analysis, presented retrospectively in 2008 as "preliminary" does not however constitute an interim analysis (three interim analyses having already been carried out prior to publication in 2005). Thus, the many statistical analyses completed following publication in 2005 must be considered as being exploratory analyses only (where p-values can be taken into account only as a guide).
The EMA evaluation report (EPAR) referred to the inadequate monitoring procedures used for the trial, the loss of the randomisation list, and the inappropriate use of the case report forms for the notification of certain events.

3.1. Adverse effects

Withdrawals from treatment due to adverse effects were similar in the chemotherapy groups with or without MEPACT (3 patients treated with MEPACT and chemotherapy compared to 5 patients treated with chemotherapy alone).
An objective and subjective grade 3-4 hearing loss was reported in 11.5% of patients in the group treated with MEPACT in association with chemotherapy compared to 7% of patients in the chemotherapy only group.

3.2. Conclusion

The file submitted is based on a phase III, randomised, open-label study comparing the use of MEPACT in association with doxorubicin, cisplatin and methotrexate chemotherapy, with or without ifosfamide, to this same chemotherapy administered alone, in patients with an osteogenic sarcoma following surgical resection. This study was reported in two articles published by Meyers *et al* in 2005 (ref 1) and 2008 (ref 2).
After a median follow-up period of 4.8 years, disease-free survival (primary endpoint) was better in the group treated with MEPACT in association with chemotherapy, compared to chemotherapy alone (risk reduction of 6.9% in absolute terms): HR: 0.74 95% CI [0.57 – 0.96]. On the other hand, for disease-free survival after 7.7 years and 7.9 years, there was no difference between the two groups.
With a median follow-up period of 7.9 years, overall survival was better in the group treated with MEPACT in association with chemotherapy, compared to chemotherapy alone (risk reduction of 7.8% in absolute terms): HR = 0.72 95% CI [0.53 – 0.97].

The Transparency Committee stresses the following points:
- the trial design defined *a priori* is clearly a 2x2 factorial plan, for the simultaneous study of two compared therapeutic strategies:
  - Mifamurtide (M) *versus* absence of M
  - Doxorubicin-Methotrexate-Cisplatin(Cis)-surgery *versus* Doxorubicin-Methotrexate-Ifosfamide (I) - surgery-$Cis_{deferred}$

This supposes the absence *a priori* of an interaction between “M” and the “I-Cis$_{immediate/deferred}$” strategy.

- the interaction test (although of limited power) clearly seems to be significant in the study published in 2005 by Meyers *et al*, rendering any interpretation of the results doubtful (the two-strata joint analysis with heterogeneous results being unacceptable on a methodological level).
- there are two non-simultaneous randomisation procedures with an interval of at least 11 weeks between them. Only patients not withdrawn after the first eleven weeks of treatment (Cisplatin vs Ifosfamide) are included in the second part of the trial (evaluation of M), leading to a possible attrition bias.
- the definition of the primary efficacy endpoint is imprecise, with the simultaneous presentation in the file of results for disease-free survival (DFS) and overall survival (OS) with no correction of the significance threshold.
- the existence of several interim analyses with no precautions having been taken for inflation of the alpha risk (statistical analyses carried out after the article was published in 2005 must be considered as being for exploratory purposes only).

Overall, taking account of all the information set out above, the confidence level for the results reported is unsatisfactory, and further trials are necessary in order to evaluate the effect size for mifamurtide (MEPACT) and its role in the treatment of osteosarcoma.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Osteosarcoma is a life-threatening disease.
This medicinal product is intended as curative therapy.
The efficacy/adverse effects ratio is low.

Public health benefit:

Osteosarcoma is a serious clinical condition. The public health burden of osteosarcoma is however low as the disease is rare.

Improved therapeutic options for the treatment of this disease are a public health need according to the priorities established (Public Health Law, 2004, Cancer Plan, Groupe Technique National de Définition des Objectifs (GTNDO - *National group of experts defining French public health objectives*).

According to clinical data available, this product is not expected to have any impact on morbidity and mortality and quality of life compared with existing treatments.

As a result, the proprietary product MEPACT is not expected to meet an identified public health need.

Consequently, MEPACT is not expected to offer any benefit to public health for this indication.

This medicinal product is a first-line therapy.
There are treatment alternatives.

Taking account of the clinical data available based on a pivotal study in which there were methodological shortcomings relating to statistics and the standard of the study conducted (see above), the Transparency Committee considers that the level of proof of the results reported is not sufficient to evaluate the effect size of MEPACT and its role in the treatment of osteosarcoma.
On the basis of the file submitted, the actual benefit is insufficient to be paid by national solidarity.

4.2. Improvement in actual benefit (IAB)

Not applicable.

4.3. Transparency Committee recommendations

The Transparency Committee does not recommend inclusion on the list of medicines approved for hospital use and various public services.