HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

**TRANSPARENCY COMMITTEE**

OPINION

16 July 2008

**THALIDOMIDE PHARMION 50 mg hard capsules**
**Pack of 28 (CIP: 572 677-6)**

**PHARMION LTD**

thalidomide
L04AX02

List I
Medicine for hospital prescription only.
Prescription restricted to oncology or haematology or internal medicine specialists or doctors with cancer training.
Medicinal product requiring specific monitoring during treatment:
- for all patients: a prescription requires a signature agreeing to treatment
- for women of childbearing age:
    - a prescription is limited to 1 month of treatment
    - a pregnancy test should be performed every month within the 3 days prior to the visit to the prescriber; the date and result of the pregnancy test should be entered on the patient's record card
    - dispensing should occur within a maximum of 7 days of the prescription and after the date and result of the pregnancy test have been checked

Date of centralised marketing authorisation: 16 April 2008

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

thalidomide

## 1.2 Indication

“Thalidomide Pharmion in combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.
Thalidomide Celgene is prescribed and dispensed according to the pregnancy prevention programme (see SPC).”

## 1.3 Dosage

“Recommended posology in adults:
The recommended oral dose is 200 mg per day.
A maximum number of 12 cycles of 6 weeks should be used.
Thalidomide Celgene should be taken as a single dose at bedtime, to reduce the impact of somnolence. Thalidomide Celgene can be taken with or without food.”

## 2 SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC classification 2008

L : ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
L04 : IMMUNOSUPPRESSANTS
L04A : IMMUNOSUPPRESSANTS
L04AX : : Other immunosuppressants
L04AX02 : thalidomide

### 2.2. Medicines in the same therapeutic category

2.2.1 Comparator medicines
None

### 2.3. Medicines with a similar therapeutic aim

- ALKERAN (melphalan)
- ENDOXAN ASTA (cyclophosphamide)
- ONCOVIN (vincristine)
- BICNU (carmustine)
- INTRONA (interferon alfa 2a)

High-dose corticosteroids (prednisone or dexamethasone) are used alone or in combination with cytotoxic agents.

## 3 ANALYSIS OF AVAILABLE DATA

The application includes three studies:

- one pivotal study (study IFM 99-06)
- one so-called support study (GISMM2001) comparing the combination Melphalan-Prednisone with the cobmination Melphalan-Prednisone-Thalidomide. However, the thalidomide dose used in the study corresponds to half that recommended by the marketing authorisation (which is 200 mg per day). It will therefore not be analysed.
- one study (THAL-MM-003) evaluating the combination of thalidomide with prednisone alone. It does not comply with the current marketing authorisation indication for thalidomide, which must be combined with melphalan and prednisone, and it will therefore not be analysed.

**Study IFM 99-06**[1]

Randomised, open-label, phase III study comparing Melphalan and Prednisone (MP) with Melphalan and Prednisone plus Thalidomide (MPT) and with reduced intensive treatment using Melphalan at 100 mg/m$^2$ (MEL100).

Inclusion criteria:

Patients aged 65-75 years, patients younger than 65 but ineligible for high-dose chemotherapy, previously untreated Durie-Salmon stage 2 or 3 multiple myeloma (MM), or stage 1 MM with a high risk of progression (1 bone lesion, bone pain with hyperfixation in MRI, Hb<12g/dl for men and 11g/dl for women associated with > 25% medullary plasmacytosis or raised immunoglobulin IgG > 30g/l or IgA >25g/l).

Treatments:

Group A: MP treatment (melphalan: 0.25 mg/kg/day; prednisone: 2 mg/kg/day) was given orally every 6 weeks from day 1 to day 4. Twelve cycles were administered in the absence of disease progression. The prednisone was administered by the standard methods used at each centre.

Group B: the same MP treatment given to group A was combined with oral thalidomide at the maximum tolerated dose, but not exceeding 400 mg/day. The initial dose was 200 mg/day. After 2 to 4 weeks the dose could be increased to 400 mg/day. In the absence of toxicity, thalidomide was administered throughout the MP chemotherapy until day 4 of the twelfth cycle. Thalidomide was discontinued permanently on the appearance of any symptomatic peripheral neuropathy confirmed by electromyogram.

Group C: patients were to receive 2 cycles of vincristine-adriblastine-dexamethasone (VAD) from day 1 to day 4, four weeks apart The dosage was adjusted according to age. The VAD regimen comprised a continuous 24-hour infusion of vincristine 0.4 mg and adriblastine (doxorubicin) 9 mg/m$^2$ for 4 consecutive days, and oral or IV dexamethasone 40 mg/day also for 4 consecutive days.
Four weeks after the second VAD cycle, if the patients met the criteria for more intensive therapy, peripheral blood stem cells (PBSC) were mobilised by administration of 3 g/m$^2$ of cyclophosphamide with subsequent mesna (sodium 2-mercaptoethane sulfonate) on day 0.

[1] Facon T et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet 2007, 370:1209-1218

Granulocyte colony-stimulating factor (G-CSF) was injected subcutaneously at a dose of 10 µg/kg/day from day 1 through to the last day of the leukapheresis that was initiated when the number of neutrophil leucocytes was > 4 x $10^9$/l. In the absence of any factor contraindicating intensification, patients were to receive 2 cycles of intravenous melphalan 100 mg/$m^2$ (MEL100) 2 months apart, each followed by stem cell injection.

Endpoints:

Patients in groups A and B were evaluated at 3 months, 6 months and every 6 months after that for the duration of the study. Patients in group C were evaluated before the collection of stem cells, before each melphalan cycle, a month after the first melphalan cycle and 2 months after the second.

The primary endpoint was overall survival, defined as the time from randomisation to death from whatever cause.
The secondary endpoints were as follows:

- progression-free survival (time between randomisation and the date of first documented disease progression or death from whatever cause)
- survival after progression (time from first progression to death from whatever cause)
- response rate[2]
- toxicity.

**Results**

A total of 447 patients was randomised to receive one of the three treatments.
The median age was 69.3 years (range 64-82); 40.9% of patients were 70 or over.
The available results are from an interim analysis planned in the protocol.

After 37 months' follow-up, median overall survival was 51.6 months in the MPT group, 33.2 months in the MP group and 38.3 months in the MEL100 group.
In the MPT group, the risk of death was reduced by 44% compared with the MP group (HR= 0.56; 97.5% CI 0.37 to 0.84; p=0.0012) and 42% compared with the MEL100 group (HR=0.58; 97.5% CI 0.37 to 0.89; p=0.0048).
No statistical difference was observed between the MP and MEL100 groups in terms of survival.
Follow-up data were updated after 51.5 months, or an additional 15 months approximately. MPT was found to be superior to MP in terms of median overall survival, with an absolute gain of 18.4 months (median survival for MPT: 51.6 months, MP: 33.2 months, HR=0.59, 97.5% CI 0.42-0.84, p<0.001).

[2] includes complete response, very good partial response and partial response.

Table 1: Summary of overall survival – ITT population

| **Overall survival (OS)** | **MP (N=196)** | **MPT (N=125)** | **MEL100 (N=126)** |
|---|---|---|---|
| Deceased – n (%) | 128 (65.3) | 62 (49.6) | 78 (61.9) |
| Discontinued – n (%) | 68 (34.7) | 63 (50.4) | 48 (38.1) |
| **Follow-up (months)** | | | |
| Median | 46.9 | 51.3 | 51.6 |
| 95% CI | 27.0, 39.4 | 42.7, 60.4 | 32.9, 43.7 |
| **OS duration (months)** | | | |
| Median | 33.2 | 51.6 | 38.3 |
| 95% CI | 27.0, 39.4 | 42.7, 60.4 | 32.9, 43.7 |
| **Hazard ratio (97.5% CI)[b, c]** | 1 | 0.59 (0.42, 0.84) | - |
| **p value[a]** | 0.0008 | | - |
| **Hazard ratio (97.5% CI)[b, d]** | - | 0.69 (0.47, 1.00) | 1 |
| **p value[a, d]** | - | 0.0215 | |

[a] Based on a two-tailed unstratified log-rank test of the differences in survival curves between the treatment groups.
[b] Based on a proportional hazards model comparing the likelihood functions associated with the treatment groups (MP:MPT and MP:MEL100).
[c] MPT:MP comparison. [d] MPT:MEL100 comparison.

The analysis results for the primary endpoint remained in favour of MPT when they were adjusted for the recognised prognostic factors in multiple myeloma: serum haemoglobin or albumin concentrations; WHO performance index; bone marrow plasmacytosis; serum β2-microglobulin concentration or white blood cell count. After adjustment, the death risk was reduced by 51% in the MPT group compared with the MP group (p = 0.0002) and 44% compared with the MEL100 group (p = 0.006).

Results for secondary endpoints:

Median progression-free survival was 27.6 months in the MPT group against 17.2 months in the MP group and 19.4 months in the MEL100 group. Analysis of the HRs shows that the MPT patients had their risk of disease progression or death reduced by 55% (P < 0.0001) compared with MP and 46% (p = 0.0001) compared with MEL100. As with overall survival, no significant difference was observed between the MP and MEL100 groups.
The overall response percentage was higher in the MPT (85%) and MEL100 (82.9%) groups than in the MP group (51%).

### 3.1. Safety

In the pivotal study (study IFM 99-06) severe adverse events were reported for 38.7% (48/124) of patients in the MPT group and 29.5% (57/193) in the MP group.
In the MPT group, pulmonary embolism (3.2%), deep vein thrombosis (3.2%), hyperthermia (2.4%), lung infections (2.4%) and back pain (2.4%) were the most common severe adverse effects.
Treatment discontinuation associated with adverse events was more common in the MPT group than in the MP group: 42.7% vs 7.8%. Peripheral neuropathy (8.9%), neutropenia (5.6%) and paraesthesia (4%) were the main adverse events leading to treatment discontinuation in the MPT group.

## 3.2. Conclusion

The efficacy and safety of thalidomide as first-line treatment for multiple myeloma in patients aged over 65 years were evaluated in a randomised, open-label, phase III study comparing Melphalan-Prednisone (MP) with Melphalan-Prednisone-Thalidomide (MPT) and reduced intensive treatment using Melphalan at 100 mg/$m^2$ (MEL100).
The interim analysis after median follow-up of 37 months showed that the addition of Thalidomide to the reference combination of Melphalan and Prednisone (MPT) led to a 21.4 month increase in the median overall survival compared with the reference combination of Melphalan and Prednisone (MP) used alone (MPT median survival: 53.6 months for MPT vs 32.2 months for MP; HR = 0.56, 97.5% CI 0.37 to 0.84, p=0.0012).
This advantage in terms of survival was found in a further analysis of overall survival based on data covering a further 14.5 months of follow-up: median prolongation 18.4 months (MPT median survival: 51.6 months, MP: 33.2 months, HR=0.59, 97.5% CI 0.42-0.84, p<0.001).
MPT also proved to be significantly superior to MP alone on secondary efficacy endpoints: progression-free survival (27.6 vs 17.2 months) and response rate (85% vs 51%).
Treatment discontinuation associated with adverse events was more common in the MPT group than in the MP group: 42.7% (53/124) vs 7.8% (15/193). Peripheral neuropathy (8.9%), neutropenia (5.6%) and paraesthesia (4%) were the main adverse events leading to treatment discontinuation in the MPT group.

## 4 TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual benefit

Multiple myeloma is a blood disease that is almost always fatal with short median survival (3-5 years).
The efficacy/safety ratio is high.
The treatment is intended for palliative use.
It is for use as first-line treatment.
There are alternative medicinal treatments.

Public health benefit:

The public health burden caused by multiple myeloma in the population concerned by the indication under consideration is moderate.

Having treatments available to improve the survival of multiple myeloma patients is a public health need.

In light of the available data, thalidomide, in combination with melphalan and prednisone (MPT) is expected to have a major theoretical impact in terms of reducing the morbidity and mortality associated with multiple myeloma in patients over 65 years of age, compared with their current therapeutic management. However, there are no data to evaluate the quality of life of the patients treated.

The population impact expected in practice can only be moderate, given the small number of patients concerned and the adverse events that may occur and jeopardise the continuation of treatment.

Thalidomide combined with melphalan and prednisone may help to meet an identified public health need.

Accordingly, THALIDOMIDE PHARMION in combination with melphalan and prednisone is expected to benefit public health in this indication. This benefit is moderate.

The actual benefit is substantial.

### 4.2. Improvement in actual benefit

THALIDOMIDE PHARMION in combination with melphalan and prednisone provides a substantial improvement in actual benefit (level II) in terms of efficacy compared with the combination of melphalan and prednisone alone, as first-line treatment of patients with multiple myeloma, aged over 65 years or ineligible for high dose chemotherapy.

### 4.3. Therapeutic use

The current classification of myeloma drawn up on the criteria of the International Myeloma Workshop Group[3] distinguishes between two categories of patients: asymptomatic patients, for whom mere surveillance is generally sufficient, and symptomatic patients (with bone disease, renal failure, hypercalcaemia, anaemia, intercurrent infections, amylosis) who require management adjusted to their age and comorbidities.

[3] International Myeloma Working Group. Criteria for the classification of monoclonal gammapathies, multiple myeloma and related disorders: a report of the International Myeloma Workshop group. Br J Haematol 2003:120;749-757.

First-line treatment includes the following alternative: is the patient eligible or not for intensive treatment after induction chemotherapy has led to complete or partial remission? It has been shown that intensification followed by an autologous transplant significantly increases survival to 5 years in patients below the age of 70.[4] After intensification, consolidation treatment can increase the remission rate (i.e. reduce the tumour mass), prolong response duration and improve survival. This was demonstrated for thalidomide by the French myeloma intergroup (IFM) in a randomised trial (IFM 99-02)[5]. Patients aged over 65 or ineligible for intensification are treated with drug combinations including at least an alkylating agent such as melphalan (M) and a corticosteroid such as prednisone (P): this is the standard MP regimen (28-day cycles including 4 days of treatment with 0.25 mg/kg M and 1 mg/kg P). This, known as the Alexanian[6] regimen, provided less than 50% good responses (monoclonal peak reduction > 50%) and was improved by the IFM group by adding thalidomide (T). The proportion of good responses then rose to almost 80%.
In light of the available results, the addition of thalidomide to the combination of melphalan and prednisone is therefore a new first-line treatment method for multiple myeloma in patients over 65 or ineligible for high-dose chemotherapy.

### 4.4. Target population

The target population for THALIDOMIDE PHARMION comprises patients with untreated symptomatic multiple myeloma, aged over 65 years or ineligible for high dose chemotherapy.
According to data from the Health Monitoring Institute (InVS)[7], the incidence of multiple myeloma in France rose from 3,565 new cases per year in 2000 to 4,516 in 2005.
Of these patients, 3,327 were aged 65 or over.
The percentage of non-symptomatic patients who therefore only require surveillance is estimated at between 15[8, 9] and 20%[10].

The target population for THALIDOMIDE PHARMION is therefore approximately 2,600 to 2,800 patients per year.

### 4.5. Transparency Committee recommendations

The Transparency Committee recommended inclusion on the list of medicines approved for hospital use and various public services.

[4] Kristinsson SYet al. Patterns of Survival in Multiple Myeloma: A Population-Based Study of Patients Diagnosed in Sweden From 1973 to 2003. J Clin Oncol 25:1993-1999, 2007
[5] Attal M, Harousseau JL,Leyvraz S et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood 2006;108:3289-3294.
[6] Alexanian R, et al. Melphalan therapy for plasma cell myeloma. Blood 1968;31:1-10
[7] Evolution de l'incidence et de la mortalité par cancer en France de 1980 à 2005 ; Fiche Myélome Multiple et Maladies Immunoprolifératives INVS 30/01/2008 :
http://www.invs.sante.fr/surveillance/cancers/estimations_cancers/donnees_localisation/myelome/myelome.pdf
[8] TNS Health Care. Prise en charge des myélomes multiples. May 2007 and April 2008
[9] Rajkumar SV. MGUS and Smoldering Multiple Myeloma: Update on Pathogenesis, Natural History, and Management. Amer Soc Hematol; Hematogy 2005:340-345.
[10] He Y, Wheatley K, Clark O, Glasmacher A, Ross H, Djulbegovic B. Early versus deferred treatment for early stage multiple myeloma. Cochrane Database of Systematic Reviews 2003, Issue 1.

# Appendix

## Classification

The Durie-Salmon classification is based on tumour mass. It comprises three stages and one sub-classification[11].

**Stage I** – Myeloma of low tumour mass

All the following criteria are present:

1 - Haemoglobin > 100 g/l
2 - Serum calcium < 120 mg/l (3 mmol/l)
3 - Normal bone structure or solitary bone plasmacytoma only
4 - Low M-component production rates:
    IgG < 50 g/l
    IgA < 30 g/l
    Bence Jones protein < 4 g/24 h

**Stage II** – Myeloma of intermediate tumour mass

Neither stage I nor stage III

**Stage III** – Myeloma of high tumour mass

One or more of the following criteria:

1 - Haemoglobin < 85 g/l
2 - Serum calcium > 120 mg/l (3 mmol/l)
3 - Multiple bone lesions
4 - High M-component production rates:
    IgG > 70 g/l
    IgA > 50 g/l
    Bence Jones protein > 12 g/24 h

Sub-classification:

Stage A: Relatively normal renal function (serum creatinine < 20 mg/l or 180 µmol/l)
Stage B: Abnormal renal function (serum creatinine > or = 20 mg/l or 180 µmol/l).

## Prognostic staging

The International Staging System[12] uses 3 groups based on serum β2-microglobulin and albumin levels. For values of <3.5 mg/l and ≥35 g/l respectively, patients are classed in group I and are generally not given active treatment; all other patients, classed in group III (β2-microglobulin ≥ 3.5 mg/l) or group II (neither I nor III), receive active treatment, unless there are particular contraindications.

[11] http://www.oncolor.org/referentiels/hemato/myelome_classif.htm

[12] Greipp PR, San Miguel JF, Durie BG, et al. International staging system for multiple myeloma. J Clin Oncol 2005; 23:3412–3420