HAUTE AUTORITÉ DE SANTÉ

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

**TRANSPARENCY COMMITTEE**

OPINION

1 December 2010

**CEPLENE 0.5 mg/0.5 ml, solution for injection**
**B/14 (CIP code: 577805 2)**

**Applicant: MEDA PHARMA**

histamine dihydrochloride

ATC code: L03AX14

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 medicine status (11 April 2005)

Date of (centralised) Marketing Authorisation “under exceptional circumstances”: 7 October 2008

This medicine was granted Marketing Authorisation "under exceptional circumstances". This means that because of the rarity of this disease it has been impossible to get complete information on this medicine. The European Medicines Agency (EMA) will review any new information on this medicine every year, and the present SPC will be updated as necessary.

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

histamine dihydrochloride

## 1.2. Background

It is the first, histamine-based immunostimulant indicated in acute myeloid leukaemia.

## 1.3. Indication

“CEPLENE maintenance therapy is indicated for adult patients with acute myeloid leukaemia in first remission concomitantly treated with interleukin-2 (IL-2).
The efficacy of CEPLENE has not been fully demonstrated in patients older than 60.”

## 1.4. Dosage

“CEPLENE maintenance therapy should be administered following completion of consolidation therapy in patients concomitantly treated with IL-2 under the supervision of a physician experienced in the management of acute myeloid leukaemia.

For dosing instructions for CEPLENE in combination with IL-2, see dosage below.

IL-2 is administered twice daily as a subcutaneous injection 1 to 3 minutes prior to the administration of CEPLENE; each dose of IL-2 is 16 400 IU/kg.
CEPLENE 0.5 ml solution is sufficient for a single dose.

CEPLENE is administered 1 to 3 minutes after each injection of IL-2. Each 0.5 ml CEPLENE dose is injected slowly, over 5-15 minutes.
CEPLENE and IL-2 treatment cycles are administered for 10 treatment cycles: each cycle consists of a treatment period of 21 days (3 weeks) followed by a three-week or six-week treatment-free period.

For cycles 1-3, each cycle consists of 3 weeks of treatment, followed by a 3-week treatment-free period. For cycles 4-10, each cycle consists of 3 weeks of treatment, followed by a 6-week treatment-free period.

The recommended dosage is presented in Tables 1 and 2.

Table 1: For treatment cycles 1-3 with CEPLENE and IL-2

| Week number (w)* | | | Treatment* |
|---|---|---|---|
| Cycle 1 | Cycle 2 | Cycle 3 | |
| w.1 to w.3 (Days 1-21) | w.7 to w.9 (Days 1-21) | w.13 to w.15 (Days 1-21) | IL-2 16 400 IU/kg followed by 0.5 ml CEPLENE. Twice daily. |
| w.4 to w.6 | w.10 to w.12 | w.16 to w.18 | Treatment-free periods (3 weeks) |

*see “dose modification” for provisions for the modification to dose and dosage schedule

Table 2: For treatment cycles 4-10 with CEPLENE and IL-2, same dosage as for Table 1 above, with the exception of number of cycles and duration of rest periods

| Week number (w)* | | | | | | | Treatment* |
|---|---|---|---|---|---|---|---|
| Cycle | | | | | | | |
| 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| w.19 to w.21 | w.28 to w.30 | w.37 to w.39 | w.46 to w.48 | w.55 to w.57 | w.64 to w.66 | w.73 to w.75 | IL-2 16 400 IU/kg followed by 0.5 ml CEPLENE. Twice daily. |
| w.22 to w.27 | w.31 to w.36 | w.40 to w.45 | w.49 to w.54 | w.58 to w.63 | w.67 to w.72 | w.76 to w.81 | Treatment-free period (6 weeks) |

*see “dose modification” for provisions for the modification to dose and dosage schedule.”

## 2. SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC Classification (2009)

| | |
|---|---|
| L | Antineoplastic and immunomodulating agents |
| L03 | Immunostimulants |
| L03A | Immunostimulants |
| L03AX | Other immunostimulants |
| L03AX14 | Histamine dihydrochloride |

### 2.2. Medicines in the same therapeutic category

Comparator medicines
None

### 2.3. Medicines with a similar therapeutic aim

None

## 3. ANALYSIS OF AVAILABLE DATA

The dossier submitted includes a non-comparative phase II exploratory study and a comparative phase III INT-0133 study . Only the results of the phase III pivotal study are analysed below.

### 3.1. Efficacy

**Study MP-MA-201**[1]

An open, randomised, phase III study comparing CEPLENE plus interleukin-2 (IL-2) treatment versus no treatment in 320 patients with acute myeloid leukaemia (AML) in complete remission after consolidation therapy.

Treated group:
Combination of recombinant IL-2 (PROLEUKIN, 16,400 IU/kg or 1 µg/kg, 2 subcutaneous injections per day) and CEPLENE (0.5 mg, 2 subcutaneous injections per day); the IL-2 was injected 1 to 3 minutes before the CEPLENE, which was administered by slow injection (5 to 15 minutes).
The treatments were administered at home over 10 three-week cycles, i.e. approximately 18 months, or until relapse or death.
The first 3 treatment cycles were separated by a 3-week interval without treatment and the following cycles were separated by a 6-week interval without treatment.

Primary efficacy endpoint: relapse-free survival.
The duration of relapse-free survival was defined as the interval between the date of randomisation and the date of relapse or death from any cause.
Relapse was defined as at least 5% blasts in the bone marrow, not secondary to the process of regeneration after myelosuppressive therapy, or the occurrence of extramedullary leukaemia.

Secondary endpoints:
- proportion of patients in each group with relapse at 12, 18, 24, 36 and 48 months;
- overall survival, defined as the interval between randomisation and death from any cause;
- quality of life evaluated using the EORTC QLQ-C30 questionnaire;
- tolerance.

[1] Brune M, Castaigne S, Catalano J, Gehlsen K, Ho AD, Hofmann WK et al. Improved leukemia-free survival after postconsolidation immunotherapy with histamine dihydrochloride and interleukin-2 in acute myeloid leukemia: results of a randomized phase 3 trial. Blood 2006; 108(1):88-96.

**Results:**
The mean age of the patients was 55 years; approximately 60% were ≤ 60 years.
All the patients were in good general health.
After the consolidation therapy 81.6% of the patients included were in their first complete remission “CR1” (patients not previously treated) and 18.4% were in complete remission obtained after one or more relapses “CR1+”.

In the total study population, the median relapse-free survival (primary endpoint) was 324 days in the CEPLENE plus IL-2 group versus 264 days in the untreated group, which is an absolute gain of 2 months (p = 0.008 in the stratified log-rank test).
The percentage surviving relapse-free at 3 years was as follows:
- for all patients included: 34.0% in the CEPLENE/IL-2 group versus 24.7% in the untreated group, p = 0.06;
- in the CR1 subgroup used for the Marketing Authorisation: 40% in the CEPLENE/IL-2 group versus 26% in the untreated group (p = 0.02). The absolute gain in median relapse-free survival is 5.7 months;
- in the CR1+ subgroup: 15% in the CEPLENE/IL-2 group versus 10% in the untreated group, NS.

Table 1: Proportion of patients in CR1 surviving without relapse

| | CEPLENE + IL2 (n = 129) | Controls (n = 132) | p |
|---|---|---|---|
| Inclusion | 100% | 100% | |
| 6 months | 72,1% | 66.7% | 0.34 |
| 12 months | 52.5% | 43.9% | 0.17 |
| 18 months | 47.8% | 36.2% | 0.06 |
| 24 months | 44.7% | 31.6% | 0.03 |
| 36 months | 39.9% | 26.2% | 0.02 |

There was no difference in overall survival between the two groups: the proportion of patients surviving at 3 years was 48% in the treated group versus 45% in the untreated group, NS.
The quality-of-life data did not reveal any difference between the two groups.

Analysis according to prognostic factors:
A post-hoc method employing a significance level of 0.1 for the selection of confounding variables was used, the prespecified model having failed to show interactions with a level of 0.05.
Multivariate analysis using the Cox model suggests a prognostic influence of age, sex, and leukaemia subtype.

Table 2: Cox model analysis for relapse-free survival

| Variable | Estimation | Standard error | Relative risk | 95% CI | p |
|---|---|---|---|---|---|
| Treatment (active/control) | 0.364 | 0.137 | 1.44 | (1.10, 1.88) | 0.0079 |
| Age (≤ 60 / > 60 years) | 0.377 | 0.149 | 1.458 | (1.09, 1.95) | 0.01 |
| Favourable karyotype (yes / no) | 0.162 | 0.288 | 1.2 | (0.67, 2.07) | 0.57 |
| Intermediate karyotype (yes / no) | -0.018 | 0.165 | 1 | (0.71, 1.36) | 0.91 |
| Unfavourable karyotype (yes / no) | 0.406 | 0.23 | 1.5 | (0.96, 2.36) | 0.08 |
| Sex (M / F) | -0.300 | 0.143 | 0.7 | (0.56, 0.98) | 0.04 |
| AML subtype M0/M1/M5/M6/M7 (yes / no) | -0.306 | 0.269 | 0.7 | (0.44, 1.25) | 0.26 |
| AML subtype M2/M3/M4 (yes / no) | -0.583 | 0.266 | 0.6 | (0.33, 0.94) | 0.03 |
| Interval between remission and randomisation (≤ 6 / > 6 months) | -0.310 | 0.177 | 0.7 | (0.52, 1.04) | 0.08 |

Relapse-free survival was longer in the treated group for patients aged ≤ 60 years (543 days versus 290 days, n = 195) but not for patients > 60 years of age (268 days versus 237 days, n = 125).
Female sex (581 days versus 295 days, n = 148) and AML type [M2, M3 or M4] (424 versus 295, n = 181) are factors predictive of success.

In trial MP-MA-201, the only methodologically valid result is that obtained for the primary endpoint (relapse-free survival) using the stratified log-rank test.
The other analyses are of an exploratory nature (particularly those for other endpoints) or analyses of sensitivity (particularly those concerning the primary endpoint but using other statistical techniques, i.e. Cox model including adjustment variables).

### 3.2. Adverse effects

30% of the patients discontinued treatment on account of adverse events; in 11% there was a connection with the treatment. The frequency of serious adverse events was comparable in the two groups (18% for the treated patients versus 19% for the controls).
Adverse events of grade 3-4 were observed in 50.3% of the patients in the treated group versus 34.6% in the untreated group. These events were chiefly thrombocytopenia (17% versus 10% in the untreated group) and headache (6% versus 0% in the untreated group).
The most frequent adverse events in the treated group were flushing (84% versus 0%), headache (56% versus 14%), fatigue (42% versus 17%), fever (39% versus 17%), and reactions at the injection site, particularly granuloma (45%) and erythema (35%).

### 3.3. Conclusion

The efficacy and tolerance of CEPLENE were evaluated in an open, randomised, phase III study that compared CEPLENE plus interleukin-2 (IL-2) treatment versus no treatment in 320 patients with acute myeloid leukaemia (AML) in complete remission after consolidation therapy.
The mean age of the patients was 55 years; approximately 60% of them were ≤ 60 years.
On inclusion, 81.6% of the patients were in their first complete remission “CR1” (patients not previously treated) and 18.4% were in complete remission obtained after one or more relapses “CR1+”.
In the total study population, the median relapse-free survival (primary endpoint) was 324 days in the CEPLENE/IL-2 group versus 264 days in the untreated group, which is an absolute gain of 2 months (p = 0.008).
The percentage surviving relapse-free at 3 years was as follows:
- for all patients included: 34.0% in the CEPLENE/IL-2 group versus 24.7% in the untreated group, p = 0.06;
- in the CR1 subgroup used for the Marketing Authorisation: 40% in the CEPLENE/IL-2 group versus 26% in the untreated group (p = 0.02). The absolute gain in median relapse-free survival is 5.7 months;
- in the CR1+ subgroup: 15% in the CEPLENE/IL-2 group versus 10% in the untreated group, NS.

There was no difference in overall survival between the two groups, either in the total groups or in the subgroups.
The Committee stresses that the only methodologically valid result is that obtained for the primary endpoint (relapse-free survival) using the stratified log-rank test. The other analyses are of an exploratory nature or analyses of sensitivity.

As regards tolerance, the most frequent adverse effects are flushing, headache, and reactions at the injection site. The most frequent serious adverse event is thrombocytopenia.

## 4. TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual benefit

Acute myeloid leukaemia (AML) is a heterogeneous group of malignant haemopathies characterised by clonal proliferation of abnormal myeloid precursors and impairment of normal haematopoiesis. It is a life-threatening disease.
This proprietary medicinal product is intended as curative therapy.
It is a maintenance treatment for patients in first remission after induction/consolidation therapies.

Public health benefit:

Acute myeloid leukaemia is a serious, life-threatening disease. However, given the limited number of patients who might benefit from the treatment (under 60 years of age, in first remission, and treated simultaneously with IL-2), the burden is small.
Improving the management of cancer patients is a public-health priority that figures in the law of 9 August 2004 and the cancer plan for 2009-2013.
On the basis of the available data, the impact of CEPLENE on morbidity (relapse) is small and cannot be ascribed to CEPLENE alone. CEPLENE does not show any impact on mortality (overall survival) or on patients' quality of life either. Furthermore, it is not expected that CEPLENE will have any impact on the organisation of care. CEPLENE thus does not meet the stated public-health need.
In conclusion, CEPLENE does not show the expected public-health benefit in the treatment of adult patients with AML in first remission who are simultaneously treated with IL-2.

The efficacy/adverse effects ratio of the combination CEPLENE + IL-2 is low.
No alternative medicinal products exist; the non-pharmacological alternative is an allograft in patients who are eligible or an autograft.

In view of the methodological weaknesses of the presented study (see Efficacy section), but bearing in mind both the absence of any pharmacological alternative and also the effect observed compared with current management, the Transparency Committee provides a moderate actual benefit to the combination CEPLENE + IL2.

### 4.2. Improvement in actual benefit (IAB)

The combination CEPLENE + IL2 does not provide an improvement in actual benefit (IAB V) in the management of adult patients over 60 years of age with acute myeloid leukaemia in first remission. The Committee considers this combination to be a useful therapeutic tool.

### 4.3. Therapeutic use[2] [3]

The standard treatment for AML in adults usually consists in an induction therapy followed by intensive therapy. The induction therapy combines an anthracycline (usually daunomycin) and cytarabine administered at a high dose, with or without 6-thioguanine. This treatment is repeated every 4 weeks until complete remission (CR)[4], which can be obtained in 70-80% of patients.
The intensive (or consolidation) therapy carried out after the induction chemotherapy is aimed at eradicating any microscopic presence of leukaemia cells (usually through repeated doses of high-dose aracytine). Except in patients with favourable cytogenetics [t(15;17), t(8;21), and inv(16)], an allograft must always be considered after consolidation chemotherapy in the case of patients under 50 years of age in CR for whom there is an HLA-

[2] http://hematologie.net/hematolo/UserFiles/File/REFERENTIEL%20COMPLET%20VERSION%20FINALE%20SFH20082009(1).doc
[3] EPAR on CEPLENE 2008
[4] haemogram: no circulating blasts, PMN >1 x $10^9$/l, platelets > 100 x $10^9$/l, cell-rich bone-marrow smear with less than 5% blast cells and no clinical signs or symptoms of the disease

identical donor in the family. Allogeneic grafting of haematopoietic stem cells in CR1 gives the best antileukaemic efficacy with the lowest rate of relapse, but the mortality associated with the procedure is higher than after an autograft or intensive chemotherapy.
The majority (75-80%) of patients who have not received an allograft relapse within a median period of about a year after first complete remission.
In cases where an allograft is not an option, there is no expert consensus regarding an effective therapy for maintaining remission beyond the end of the consolidation chemotherapy.

The combination of CEPLENE + IL-2 is a new method of maintenance treatment for AML in patients under 60 years of age in their first complete remission who will not receive an allograft or autograft. The place of this combination in the therapeutic strategy remains to be determined.

### 4.4. Target population

The target population of CEPLENE + IL-2 is patients with AML in their first complete remission who are not eligible for an allograft and who are $\leq$ 60 years of age.

According to a DATAMONITOR investigation[5] provided by the company, the incidence of AML in France in 2009 was evaluated as 2319 patients.
47% of them are reported to be under 60 years of age and 53% over 60 years of age.
Only 91% receive induction treatments under 60 years of age and 66% beyond that age.
The first complete remission rates are 75 to 80%.
Of these, around 25% are eligible for a stem cell transplant under 60 years of age and 8% beyond that age.
Treatment with CEPLENE + IL-2 is aimed at patients under 60 years of age, as its efficacy over the age of 60 has not been adequately established. The estimated target population is therefore 500 to 600 new patients per year.

Currently, the Intergroupe Français des leucémies aiguës myéloblastiques [French intergroup for acute myeloblastic leukaemia] (GOELAMS [East-west group for the study of acute leukaemia and other blood diseases] and ALFA [Acute Leukemia French Association] group) recommends inclusion of all acute myeloblastic leukaemia patients in a prospective protocol, which in addition to autografts and allografts gives considerable attention to new compounds of the tyrosine-kinase inhibitor type. It is thus anticipated that the number of patients who will be offered the combination CEPLENE + IL-2 will be small (250 to 300 patients per year according to the experts).

### 4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the indication and at the dosage in the Marketing Authorisation.

The Committee will re-assesses the actual benefit of the combination CEPLENE + IL-2 after the next re-assessment by the EMA.

[5] DATAMONITOR – DMHC2499 – 09/2009