histamine dihydrochloride, 500 microgram/0.5ml, vial (Ceplene®)  
SMC No. (666/10)  
Meda Pharmaceuticals Ltd  

17 December 2010  

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 NHS Scotland. The advice is summarised as follows:

**ADVICE**: following a full submission

**histamine dihydrochloride (Ceplene®)** is not recommended for use within NHS Scotland.

**Indication under review**: maintenance therapy for adult patients with acute myeloid leukaemia in first remission concomitantly treated with interleukin-2. The efficacy of histamine dihydrochloride has not been fully demonstrated in patients older than age 60 years.

In a randomised open-label study, histamine plus interleukin-2 was superior to no treatment for the endpoint of leukaemia free survival (LFS) in a sub-group of patients in first complete remission. In *post hoc* analysis of patients in first complete remission and aged less than 60 years, LFS rates at 36 months were 50% versus 30%.

Overall the manufacturer did not present a sufficiently robust clinical or economic case to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

*Chairman,*  
*Scottish Medicines Consortium*
**Indication**
Histamine dihydrochloride maintenance therapy is indicated for adult patients with acute myeloid leukaemia in first remission concomitantly treated with interleukin-2 (IL-2). The efficacy of histamine dihydrochloride has not been fully demonstrated in patients older than age 60.

**Dosing Information**
Histamine dihydrochloride 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.

*IL-2*
IL-2 is administered twice daily as a subcutaneous injection 1 to 3 minutes prior to the administration of histamine dihydrochloride; each dose of IL-2 is 16,400 IU/kg.

*Histamine dihydrochloride*
0.5 ml solution [500 micrograms] is sufficient for a single dose. Histamine dihydrochloride is administered 1 to 3 minutes after each injection of IL-2. Each 0.5 ml histamine dihydrochloride dose is injected slowly, over 5 to 15 minutes.

Histamine dihydrochloride and IL-2 are administered for 10 treatment cycles: each cycle consists of a treatment period of 21 days (3 weeks) followed by a three-week (cycles 1 to 3) or six-week (cycles 4 to 10) treatment-free period.

**Product availability date**
April 2010

Histamine dihydrochloride is an orphan medicinal product.

**Summary of evidence on comparative efficacy**
Treatment of patients with acute myeloid leukaemia (AML) involves induction of remission (typically using anthracyclines and high dose cytarabine) followed by consolidation using a variety of treatment regimens including high dose cytarabine or allogeneic stem cell transplant (SCT). In patients where allogeneic SCT is not appropriate there is no recognised maintenance treatment of patients in remission and for 75% to 80% of patients the median time to relapse is approximately one year. Histamine dihydrochloride is a synthetic immune modulator and is thought to act by improving the effectiveness of interleukin-2 (IL-2), for which efficacy has not been shown when used alone. It has a marketing authorisation for use in combination with aldesleukin (IL-2) in the maintenance treatment of AML.

The manufacturer has requested that the Scottish Medicines Consortium (SMC) considers the use of histamine dihydrochloride in AML patients aged less than 60 years who are in first complete remission.
One open-label randomised multi-centre phase III study has been conducted in adult patients with de novo or secondary AML and in first complete remission (CR1) or subsequent complete remission (CR1+) following induction or consolidation regimens. Prior induction or consolidation therapy as per standard practice at each site was allowed including autologous (but not allogeneic) SCT. Patients were also required to have a life expectancy of more than three months and an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1. The elapsed time from CR and completion of consolidation chemotherapy was not to exceed six and three months respectively. Patients were randomised (stratified by country and CR status) to the treatment arm (IL-2 plus histamine dihydrochloride) or no treatment (standard care) arm. The treatment arm comprised IL-2 16,400 IU/Kg by subcutaneous injection (sc) twice daily followed by histamine dihydrochloride 0.5mg sc twice daily (rate not exceeding 0.1mg/minute) both on days 1 to 21 for 10 cycles. Cycles 1 to 3 comprised 3 weeks treatment followed by 3 weeks off treatment and for cycles 4 to 10 the off treatment period was 6 weeks in duration. After the 18 month treatment period patients were followed up for a further 18 months.

The primary endpoint was the duration of leukaemia free survival (LFS); the time elapsed from the date of randomisation to the date of relapse of AML (defined as at least 5% blast cells in the bone marrow or extramedullary leukaemia) or death from any cause in all patients. Initially there were two primary endpoints planned in the CR1 and CR1+ groups separately. Ninety-six patients per group in CR1 and 51 patients per group in CR1+ were required to provide 80% power to detect an improvement in median leukaemia free survival [LFS] of 50% and 75% in treatment versus standard care group in CR1 and CR1+ groups respectively. However after 360 patients had been recruited (n=261 in CR1 and n=59 in CR1+) it was considered unfeasible to recruit the numbers required for the CR1+ group and a protocol amendment led to the primary endpoint being changed to LFS in all patients. The primary efficacy analysis was in all randomly assigned patients and according to the intent to treat (ITT) principle.

For the primary endpoint there were 102 versus 119 relapses in the treatment and standard care arms respectively; hazard ratio for LFS 0.71; 95% confidence interval (CI) 0.54 to 0.92, p=0.01. The LFS rates (Kaplan Meier estimates) at 36 months were 34% (standard error [SE] 3.8) versus 24% (SE 3.4) and the median duration of LFS was 324 days versus 264 days. Secondary endpoints included duration of LFS in the subgroups of patients in CR1 and CR1+ and overall survival. Primary and secondary endpoints are included in the table below for all patients and those in CR1. In the CR1 patient group, median duration of LFS was 450 days versus 291 days for treatment and standard care arms respectively (HR 0.69; 95% CI 0.51 to 0.93, p=0.01). CR1 median duration of overall survival was 43 versus 28 months although this difference was not statistically significant.
### Table: Primary and secondary endpoints for all patients and those in CR1

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard ratio (95% CI)</th>
<th>Median LFS or OS (days)</th>
<th>LFS or OS rate (%) ± SE at 36 months*</th>
<th>P-value (log rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint: leukaemia free survival</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>All patients</td>
<td>Treatment n=160 Standard care n=160</td>
<td>0.71 (0.54 to 0.92)</td>
<td>324 264</td>
<td>34 ± 3.8 24 ± 3.4</td>
</tr>
<tr>
<td></td>
<td>Patients in CR1 Treatment n=129 Standard care n=132</td>
<td>0.69 (0.51 to 0.93)</td>
<td>450 291</td>
<td>40 ± 4.4 26 ± 3.8</td>
</tr>
<tr>
<td><strong>Secondary endpoint: overall survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>Treatment n=160 Standard care n=160</td>
<td>0.82 (0.58 to 1.16)</td>
<td>861 792</td>
<td>48 ± 4.0 44 ± 4.0</td>
</tr>
<tr>
<td></td>
<td>Patients in CR1 Treatment n=129 Standard care n=132</td>
<td>0.78 (0.53 to 1.15)</td>
<td>1,289 842</td>
<td>55 ± 4.4 46 ± 4.4</td>
</tr>
</tbody>
</table>

LFS= leukaemia free survival, OS=overall survival, SE=standard error, CR1=first complete remission.

* Kaplan Meier estimates

## Summary of evidence on comparative safety

All patients in the treatment arm and 95% of patients in standard care arm reported an adverse event (AE). AEs with a higher occurrence in the treatment arm and considered related to IL-2 were injection site reactions, fever, fatigue and myalgia. Those considered related to histamine dihydrochloride were palpitations, flushing and headache. Serious AE were reported in 18% versus 19% of patients in the treatment and standard care arms and most were relapse related. The number of patients with treatment related serious AEs (in the treatment arm) was seven (4.5%) who reported 9 AE. These included fever (n=3), CHF, dehydration, endocarditis, grand mal convulsion, polyarthritis and aspergillosis. There were no treatment related deaths.

## Summary of clinical effectiveness issues

Histamine dihydrochloride was designated an orphan product by the European Medicines Agency (EMA) in April 2005 and gained approval for the indication under review under exceptional circumstances. The company has committed to undertaking further studies to provide clinical data to assess the immunologic and anti-leukaemic activity of histamine dihydrochloride/IL-2 in adult AML patients in CR1, to study the effect in patients aged over 60 years compared to younger patients, and to assess the anti-leukaemic activity of histamine dihydrochloride/IL-2 in adult AML patients with minimal residual disease.
The phase III study demonstrated a significant effect for the treatment group versus the standard care group for LFS but not OS in patients in CR1. Currently there are no treatment options for patients with AML who are in CR1 following induction or consolidation regimens. Clinically relevant loss of quality of life was not seen in the treatment group versus the standard care group.

Currently maintenance treatment of AML is not standard practice in the UK, with the exception of allogeneic SCT. The comparator arm in the study was no treatment (standard care) and the EMA noted that this was justified “since no treatment is the standard of care and there is no evidence that IL-2 alone improves LFS”.

Subgroup analysis of patients in CR1 supports the indication under review. In addition the submitting company has requested that SMC considers the use of histamine dihydrochloride only in patients in first complete remission who are aged less than 60 years. There are limited data in this subgroup. In the subgroup of patients in CR1 and aged less than 60 years (n=80 in treatment arm and n=85 in standard care arm) the Kaplan-Meier estimate of LFS at 36 months was 50% versus 30% respectively.

No specific data were provided on the induction or consolidation regimens patients received prior to study entry (any were allowed with the exception of allogeneic SCT). The percentage of patients who had received high dose cytarabine was 66% versus 68% in the treatment and standard care groups respectively and 14% versus 11% of patients had received an autologous SCT. It is not clear whether this reflects current practice in Scotland. In addition there are no data available on subsequent treatments patients may have received following relapse, making the interpretation of OS data problematic.

The first dose of IL-2 and histamine dihydrochloride is administered in the clinic and monitoring of the patient will be necessary. The summary of product characteristics (SPC) for histamine dihydrochloride notes that training of patients and/or carers to self administer subsequent treatments is an option in patients who demonstrate a good understanding of the necessary precautions and adequate injection skills.

SMC clinical experts expressed considerable uncertainty about the clinical effectiveness of histamine dihydrochloride and indicated that the standard of care in AML has improved since the pivotal clinical study was carried out. It was suggested that data from further clinical studies are needed before its potential place in therapy can be established.

**Summary of comparative health economic evidence**

The manufacturer submitted a cost-utility analysis, based on a Markov model, comparing histamine dihydrochloride plus IL-2 with no active treatment. In the treatment pathway the role evaluated was in first complete remission (CR1), and the patient group was stated as being below the age of 60 years.

The transition probabilities for the model were based on a subgroup analysis of the main clinical study which appeared to relate to CR1 patients aged between 40 and 60 years. Probabilities
reflected Kaplan-Meier plots for the first 66 months and an assumed extrapolation function beyond that time. The time horizon was over the lifetime of the patient.

Utilities were taken from an evaluation of chronic myeloid leukaemia on the basis of its assumed similarities to AML in terms of impact on quality of life. EORTC (European Organisation for the Research and Treatment of Cancer) quality of life data were collected in the clinical study and the manufacturer subsequently provided estimates based on mapping the EORTC QLQ-30 onto utility values.

Apart from medicines costs the model also took account of costs of drug administration, drop-outs from treatment, and serious adverse events. Cost implications for later stages of treatment were based on a published paper from a previous trial in AML; this had to be updated and converted from US dollars.

Based on these assumptions, the manufacturer estimated that over 30 years the added cost would be £29,053 (£41,510 for histamine dihydrochloride plus IL-2 versus £12,457 for standard care) and a quality adjusted life year (QALY) gain of 3.042 (6.564 versus 3.522). Histamine dihydrochloride plus IL-2 was associated with a gain in survival of 3.84 years. The incremental cost per QALY was estimated to be £12,617. When the results were re-estimated using EORTC QLQ-30 data collected in the trial the cost per QALY rose to between £16,073 and £19,028. The lower figure was based on an added cost of £29,053 and a QALY gain of 1.81.

The main weaknesses identified were as follows:

- The manufacturer initially did not provide data to support the appropriateness of the methodology chosen for the extrapolations in the analysis. However, results were subsequently provided to show that the results were relatively insensitive to the alternative methods of extrapolation being used. SMC had concerns over the magnitude of the survival gain estimated in the economic model compared with the outcomes seen in the clinical study. It should also be noted that the incremental cost per QALY for a 5-year time horizon was £40,880; this time horizon would limit the extrapolation required.
- The analysis was based on a relatively small subgroup of the overall trial population (CR1 and between 40-60 years) and the overall trial appeared to have poorer than expected outcomes in the control group.
- SMC had concerns that use of quality of life data from chronic myeloid leukaemia patients may have introduced bias. EORTC quality of life data from the trial could have been converted into utility values but this was not undertaken in the original submission. The manufacturer supplied this subsequently and the cost per QALY increased.
- SMC also had concerns that the outcomes for patients treated with standard care were poorer than might be expected with current practice and that adjustment for this would worsen the cost-effectiveness ratios.

Due to the issues outlined above the economic case has not been demonstrated.

### Summary of patient and public involvement

A Patient Interest Group Submission was not made.
“Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet” were published in 2010. They include guidance on induction and post remission therapy. In patients aged less than 60 years post remission therapy treatments include high dose cytarabine, allo- and auto-SCT. They noted that maintenance chemotherapy is generally not routinely administered outside of clinical trials for patients with non-acute promyelocytic leukaemia (APL) AML. In patients aged over 60 years no clear recommendations for post remission therapy are given.

The British Committee for Standards in Haematology published “Guidelines on the management of acute myeloid leukaemia in adults” in 2006. In younger patients post remission treatments include consolidation chemotherapy and autologous, allogeneic-related or unrelated donor transplantation. They note that there is no evidence that maintenance therapy is of benefit in patients with AML who have undergone intensive consolidation therapy with the possible exception of APL.

Neither guideline discusses the use of histamine dihydrochloride although their publication may predate the licensing of histamine dihydrochloride.

### Additional information: comparators

There are no licensed treatments options following induction or consolidation of remission in patients with acute myeloid leukaemia. No active treatment is the standard of care.

### Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per cycle (£)</th>
<th>Cost for 10 cycles (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>histamine dihydrochloride</td>
<td>0.5mg subcutaneous injection twice daily on days 1 to 21 of cycle</td>
<td>3,544</td>
<td>35,440</td>
</tr>
<tr>
<td>aldesleukin (IL-2)*</td>
<td>16,400 IU/kg subcutaneous injection twice daily on days 1 to 21 of cycle</td>
<td>2,176</td>
<td>21,760</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>5,720</strong></td>
<td><strong>57,200</strong></td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 20 September 2010.

*The cost for aldesleukin is based on 70kg weight and use of one vial per day.
For patients in first complete remission aged <60 years, the manufacturer estimated an NHS cost impact of £832k in year 1 rising to £1.1m in year 5 based on 35 new patients becoming eligible each year. The medicines cost impact was £834k in year 1 rising to £1.2m by year 5. The clinical experts consulted by SMC indicate that assumptions about market share may be high and the actual budget impact would be lower than these estimates suggest.
References

The undernoted references were supplied with the submission.


Meda Pharmaceuticals. Multicenter randomized open-label study to evaluate the safety and efficacy of immunotherapy with subcutaneous CepleneTM (histamine dihydrochloride) plus ProleukinTM (interleukin-2) versus no treatment in patients with acute myeloid leukaemia in first or subsequent complete remission. 2006.

This assessment is based on data submitted by the applicant company up to and including 13 December 2010.

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.

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.