AWMSG Secretariat Assessment Report – Advice no. 0411
Histamine dihydrochloride (Ceplene®▼) maintenance therapy for adult patients with acute myeloid leukaemia in first remission concomitantly treated with interleukin-2

This assessment report is based on evidence submitted by Meda Pharmaceuticals on 29 October 2010

1.0 PRODUCT DETAILS

Licensed indication	Histamine dihydrochloride (HDC) (Ceplene®▼) maintenance therapy is indicated for adult patients with acute myeloid leukaemia (AML) in first remission concomitantly treated with interleukin-2 (IL-2). Efficacy has not been fully demonstrated in patients older than age 60.
Dosing	HDC solution (0.5 ml / 0.5 mg HDC) is administered subcutaneously twice daily over 5–15 minutes, 1–3 minutes after an injection of IL-2 (16,400 IU/kg). Treatment is administered for ten cycles, each consisting of a treatment period of 21 days, followed by a three-week or six-week treatment-free period. Refer to the Summary of Product Characteristics (SPC) for further information regarding dosing and recommended treatment regimen[1].
Marketing authorisation date	7 October 2008[1].
UK launch date	20 April 2010[2].

2.0 DECISION CONTEXT

2.1 Background

AML is a haematological malignancy characterised by the rapid production of abnormal immature granulocytes or monocytes (blasts) by the bone marrow. AML accounts for approximately one third of all leukaemias diagnosed in the UK; in 2007, the incidence rate was reported to be 3.8 per 100,000, with 166 new cases of AML documented in Wales[3]. AML has an overall mortality rate of almost 80%[2]. All eligible patients up to age 60 (or greater than 60 but able to receive intensive treatment) with de novo or secondary AML are encouraged to enter investigator-led studies conducted by the AML Working Group of the National Cancer Research Institute[4]. For those that are ineligible, off-study chemotherapy or best supportive care (BSC) are viable alternatives. Treatment of AML is usually divided into two phases: remission induction (commonly including anthracyclines and/or cytarabine) and consolidation (post-remission) therapy (typically repeated courses of high-dose cytarabine or equivalent)[2,5,6]. For patients younger than 60, remission is induced in a reported 60–80% of cases[7]. Beyond age 60, patients have a lower probability of achieving complete remission[7].

Depending on various factors, including age, karyotype and response to chemotherapy, the risk of AML relapse is between 35% and 76%, with 80% of relapses occurring within the first year[8,9]. Survival outcome after AML relapse is poor; more than 80% of non-transplanted patients will die within two years[9,10]. Allogeneic stem cell therapy (allo-SCT) is currently the only treatment known to significantly reduce the risk

of relapse; however few patients are eligible for this invasive procedure[2,5,6,10]. Due to the absence of a viable alternative, BSC is currently standard practice for patients not eligible for allo-SCT. In this submission, HDC, used in combination with IL-2, is presented as a maintenance treatment for patients ≤60 years of age with AML in first complete remission (CR1)[2]. The precise mechanism of action of this concomitant therapy is not currently well-defined; however, it has been suggested that HDC protects IL-2-activated, antileukaemic natural killer cells and T-cells from reactive oxygen species-induced inhibition and apoptosis[2].

The applicant company suggests that the use of HDC in the given population meets end of life (EOL) criteria; however the Welsh Medicines Partnership (WMP) is of the view that EOL criteria are unlikely to require consideration due to the quality-adjusted life years (QALYs) involved.

2.2 Comparators

WMP has identified BSC as the most appropriate comparator for AML remission maintenance therapy.

2.3 Guidance and related advice

- British Society for Haematology. Guidelines on the management of acute myeloid leukaemia in adults (2006)[8].
- National Comprehensive Cancer Network. Clinical practice guidelines in oncology: Acute Myeloid leukaemia (2010)[11].
- National Cancer Research Institute. Working parties on leukaemia in adults and children: Trial in acute myeloid leukaemia or high risk AML. AML17 (2008)[4].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFICACY

The efficacy of HDC has been evaluated in 15 clinical trials in total; however, only two (AML-1 and MP-MA-0201) pertain to its use in AML patients and were therefore presented as evidence in the company submission. AML-1 was a non-randomised, uncontrolled, open-label phase II clinical trial designed to evaluate the efficacy, feasibility and safety of concomitant HDC and IL-2 maintenance treatment for extending leukaemia-free survival (LFS) in adult patients with AML in CR1 and subsequent complete remission (CR>1)[2]. Due to the absence of a control group, the small sample size, potential effects of selection bias and concurrent chemotherapy received by some patients, efficacy results were inconclusive and this study is therefore not discussed further.

3.1 Study MP-MA-0201

MP-MA-0201 was designed to investigate the efficacy of HDC in combination with IL-2 for extending LFS in patients with AML in remission (CR1 or CR>1) subsequent to induction and consolidation chemotherapy[2,9]. MP-MA-0201 was a multicenter, randomised, open-label phase III trial comparing concomitant HDC and IL-2 treatment with BSC (i.e. no active treatment). Patients (n = 320) were randomised evenly to the treatment and control arms, which were stratified by geography and remission status[2,9]. A total of 81% (n = 129) of the treatment group and 82% (n = 132) of the control group were in CR1. A total of 59% (n = 94) of patients in the treated group and 63% (n = 101) of patients in the control group were ≤60 years old. The study was not stated to be blind due to clearly observable physiological effects of the HDC and IL-2 injections; nonetheless, staff were blinded to patient treatment[2,9]. All patients in the treatment arm received up to ten cycles (equating to approximately 18 months) of 0.5 mg HDC after a 1 microgram/kg IL-2 injection, twice daily for 21 days[9]. Treatment duration was

selected to maintain immunostimulation during the phase of highest relapse risk. Upon relapse, patients discontinued treatment. Patients were observed for at least 36 months[9].

The primary endpoint of this study was LFS duration, defined as the number of days until relapse of AML or death from any cause. Relapse was described as ≥5% blasts in the bone marrow[9]. Secondary endpoints included overall survival (OS) and Quality of Life (QoL) results[9]. In the subgroup of patients relevant for this submission (those in CR1 [n = 129]), remission was prolonged by a median of 22.7 weeks over controls (p = 0.011, log rank test; an increase of 55%). Kaplan-Meier estimates of LFS at three years were 40% for the treatment group versus 26% in the control group; a 53% relative improvement[9,12]. LFS was longest in the subgroup of patients in CR1 who were ≤60 years of age (n = 80). Remission within this group was prolonged by a median of 36.1 weeks over controls (p = 0.02, log rank test). Kaplan-Meier estimates of LFS at three years were 50% for the treatment arm versus 30% for control, or a 67% relative improvement. In the sub-group which considered only age (including both CR1 and CR>1), the log rank test for LFS was statistically significant for patients under 60 years (p = 0.02) but not for patients over 60 years (p = 0.35). It should be noted that the licensed indication is for patients in CR1 only.

No statistically significant difference in OS was observed between treatment and control arms (p = 0.16)[9]; however, a trend of increased median OS was observed in treated CR1 patients when compared with the CR1 control group (43 months versus 28 months, p = 0.12)[9]. QoL data, accumulated via the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 over the course of the trial, showed HDC and IL-2 treatment had no significant effect when compared with BSC[2,9].

4.0 SUMMARY OF EVIDENCE ON COMPARATIVE SAFETY

In study AML-1, adverse events (AEs) occurred in all patients, with ten patients reporting serious adverse events (SAEs)[2,7]. All SAEs were however deemed unrelated to use of histamine. One patient withdrew due to allergic symptoms thought to be related to a food allergy which may have been aggravated by histamine. No treatment-related deaths were recorded[2,7].

In study MP-MA-0201, 100% (n = 157) of patients in the treatment arm experienced treatment-related AEs, whilst 96% (n = 159) of patients in the control arm experienced AEs. The number of SAEs was comparable between the two groups (treatment: 28; control: 30), with most AEs deemed to be related to relapse. The most common SAE in the treatment arm, pyrexia, was considered to be related to study drug in four of the five sufferers. Forty-eight patients (31%) in the treatment arm experienced AEs resulting in dose reduction or interruption, and thirteen patients (8%) in the treatment arm discontinued treatment because of AEs not related to relapse. The company believe that the treatment is safe to administer at home and is generally well tolerated[2]. Treatment does not appear to impact QoL when compared with patients receiving BSC, as determined by EORTC QLQ-C30[2]. The Committee for Medicinal Products for Human Use (CHMP) stated that no additional risk minimisation activities were required beyond those included in the product information[10].

5.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- In this submission, evidence included relates to HDC used in combination with IL-2 as a maintenance treatment for patients ≤60 years of age with AML in first complete remission (CR1)[2].
- As highlighted in the SPC, efficacy has not been proven in patients >60 years. The risk of developing AML increases with age; a recent population-based study conducted by Bhayat et al (2009) found that 66% of patients are over 60[13].
- Study MP-MA-0201 included 59 patients (out of a total of 320) in CR>1, which is outside of the licensed indication.
- Only 99 patients (52 in the treatment arm, 47 in the control arm) completed all ten cycles or reached equivalent cut off; however 189 of the remaining 221 had reached the primary endpoint (AML relapse)[9].
- Due to missing information, reliable risk classification based on cytogenetics could only be determined in 69% of patients, which may have led to an imbalance between the groups[9].
- Historically, IL-2 as a monotherapy has shown no efficacy in prolonging LFS in AML[2,14–21], suggesting that the benefit shown in study MP-MA-0201 is due to the concomitant administration of HDC[9]. However, CHMP stated in their assessment report for HDC that this is not unequivocally demonstrated and the pharmacological rationale, though plausible, is not completely clear[10].
- Concerns were raised by CHMP regarding the limited evidence demonstrating the efficacy of HDC[10]. The treatment was ultimately authorised by the European Medicines Agency (EMA) under "exceptional circumstances" as it was deemed that due to the rarity of the disease, complete information could not be obtained. As a result, further trials have been requested to demonstrate efficacy, including in poor prognosis subgroups, e.g. >60 years or in CR>1[10].
- AEs were very common in the company submission for both trials, but were largely in line with the patient population or associated with clinical relapse.

6.0 SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

6.1 Cost effectiveness evidence

6.1.1 Context

The company submission describes a cost utility analysis (CUA) of treatment with HDC and IL-2 versus BSC in patients with AML in CR1 and CR>1[2]. The focus of the analysis is patients in CR1 aged ≤60 years, but analyses are also provided for adult patients of any age in CR1 and all patients irrespective of remission status, based on the pivotal phase III trial (MP-MA-0201) population. A cohort of patients enters the model in remission, from which they may transition to a relapse state or death. Allo-SCT is not considered in the model, and so the results would appear restricted to those in whom transplant is not an option. OS and LFS are derived from the pivotal phase III trial and extrapolated to model outcomes and costs over a lifetime horizon. Major assumptions have been made regarding the non-drug costs of care and the use of chronic myeloid leukaemia (CML)-related utility values for the different health states as modelled, which have been subjected to one- and two-way sensitivity analysis. See Appendix 1 for further details.

6.1.2 Results

The company provided a revised economic model subsequent to the original submission. Results of the base case CUA as presented in the revised model are displayed in Table 1. The main drivers of the results are the acquisition costs of HDC and IL-2, and the more than eight-fold increase in assumed monthly background treatment costs for relapse states compared with remission states.

Table 1. Company-reported cost utility analysis results[2].

	HDC and IL-2	BSC	Increment
CR1, ≤60 years age (base case)			
Costs	£41,819	£13,060	£28,760
QALYs	5.752	3.038	2.668
ICER	**£10,778 per QALY gained**		
CR1, any age			
Costs	£42,485	£11,784	£30,700
QALYs	4.252	3.159	1.093
ICER	**£28,084 per QALY gained**		
All patients in MP-MA-0201			
Costs	£37,522	£9,226	£28,296
QALYs	3.660	3.072	0.588
ICER	**£48,083 per QALY gained**		

BSC= best supportive care; CR1= First complete remission; ICER= Incremental cost effectiveness ratio; IL-2= Interleukin 2; QALY= Quality-adjusted life year

One-way sensitivity analyses indicate that the ICER in CR1 patients aged ≤60 years increases to £15,300 per QALY gained when background costs of treatment in remission are increased to £300 per month, and the ICER approaches £2,000 per QALY gained as the background costs of care in relapse state approach £1,750 per month[2]. The model is insensitive to AE costs explored in the range £0 to £1,000 per event per month. Using a five-year time horizon demonstrates the sensitivity of the model to the assumed time horizon of analysis; the reported ICER in CR1 patients aged ≤60 years increases to £44,210 per QALY gained, in CR1 patients of any age the ICER increases to £88,764 per QALY gained, and in all patients the ICER increases to £119,762 per QALY gained.

Two-way sensitivity analyses indicate that the ICER increases as the difference in utility values for remission and relapse states decreases and the lower the utility values assumed. Alternative utility estimates have been considered by mapping health-related QoL data obtained from AML patients in the pivotal MP-MA-0201 trial to the EQ-5D instrument. Using this approach, the reported lifetime ICERs increase to £13,624 per QALY gained for patients in CR1 aged ≤60 years, to £33,962 per QALY gained in all CR1 patients, and to £67,248 per QALY gained in all patients.

No sensitivity analyses have been presented to explore the relative impact of treatment on LFS and OS. Probabilistic sensitivity analyses to explore the combined uncertainty in a limited range of parameter values have subsequently been provided by the company, and indicate probabilities of cost-effectiveness of 87% and 94% at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, respectively; however please note section 6.1.3.

6.1.3 WMP critique of the company's economic evidence

There are a number of limitations to the economic evidence presented in the company submission which, collectively, render the modelled outputs subject to considerable uncertainty. These include:

- For the base case analyses, the company has elected to use utility values obtained from a published cost effectiveness analysis of imatinib in the treatment of CML, rather than those mapped from health-related QoL estimated in patients with AML during the MP-MA-0201 trial. The CML-related utility values used in the base case analysis generate more favourable incremental cost effectiveness ratios compared with the mapped utility values. There is little to support the use of the CML-related utility values in preference to those derived from AML patients.
- The cost of IL-2 in the base case analysis is on a per injection basis, assuming no vial wastage. This would not be possible in practice due to the short shelf life of 24 hours following reconsititution[22]. The costs of HDC and IL-2 treatment assumed in the base case model are therefore likely to be biased, and additional analyses provided by the company indicate that the ICER may increase to £16,929 per QALY (in the CR1 ≤60 years patient group) when more plausible acquisition costs are considered. This increases further, to around £21,500 per QALY gained, when different sources of utility estimates are also considered.
- The modelled six-month probabilities of LFS and OS drive the relative rates of relapse and survival in the short- and long-term. There has been no explicit exploration of the assumed six-month probabilities of LFS and OS for HDC–IL-2 and the comparator. It is of note that there were no statistically significant differences observed in OS between treatment and the comparator, and that the confidence intervals around the hazard ratios for LFS in relevant subgroups were wide.
- It is uncertain whether or not AEs of treatment have been adequately represented in the model in terms of disutility.
- The probabilistic sensitivity analysis (PSA), used to explore combined uncertainty in multiple parameters, has been applied to a base case scenario which is not considered to be correctly specified (as discussed above). Furthermore, effectiveness parameters (i.e. those relevant to LFS and OS) are not among those varied in the PSA. The sensitivity analyses therefore do not fully address key areas of uncertainty in the model.

6.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published cost effectiveness analyses of HDC and IL-2 in the treatment of AML.

7.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

7.1 Budget impact evidence

7.1.1 Context and methods

Based on Cancer Research UK data, there were 166 new cases of AML in Wales in 2007[3]. Based on company-sought expert opinion, the company estimates that 44% of AML patients undergo intensive chemotherapy, of which 70% may achieve CR1, and of these 75% may not be candidates for allo-SCT. This equates to 23% of patients (i.e. 38 patients) diagnosed with AML who may be eligible for treatment with HDC and IL-2. This annual incidence figure is assumed to remain constant throughout the next five years.

Uptake in these patients is assumed to be 100%. Mortality rates, discounted drug treatment costs and other background costs are derived from the economic model discussed in section 6.

7.1.2 Company-reported budget impact analysis[2]

	2010	2011	2012	2013	2014
Net patient numbers	38	64	83	100	115
HDC and IL-2 costs*	£914,795	£681,846	£437,070	£427,681	£418,781
No treatment cost*	£56,866	£70,932	£78,057	£87,910	£92,656
Incremental costs*	**£857,929**	**£610,914**	**£359,014**	**£339,771**	**£326,125**
IL-2= Interleukin 2 *These estimates appear flawed, see 7.1.3					

7.1.3 WMP critique of the company's budget impact estimates

The company estimates of budget impact appear incorrect based on the stated assumptions that have been applied. In each subsequent year, there are 38 new patients to add to the cumulative total, which would result in an increasing budget impact in each subsequent year, rather than a decrease as reported here.

The costs of treatment are based on discounted costs derived from the economic model; however, these have not been amended in line with the company's revised economic model. Therefore, all cost and effectiveness related limitations (i.e. underestimation of administration and IL-2 costs; uncertainty regarding LFS and OS) highlighted in section 6.0 would feed through to the budget impact analysis. Collectively, the figures quoted above appear flawed and unreliable.

7.2 Comparative unit costs

The company has focused its submission on patients in CR1 aged ≤60 years in whom other interventions (i.e. allo-SCT) are not appropriate. Therefore, there are no relevant comparative interventions and costs beyond BSC. Table 2 presents acquisition costs of HDC and IL-2 for one cycle and for the maximum of ten cycles that may be delivered over an 18-month period, assuming a patient weight of 70 kg and based on Monthly Index of Medical Specialities (MIMS) list prices[23].

Table 2. Example acquisition costs for HDC and IL-2 treatment

Regimen	Cost per cycle	Cost per full course
HDC 500mcg twice daily + IL-2 16,400 IU/kg twice daily for 21 days per cycle	£3,543.96 + £2,352 = £5,895.96	£58,959.60 (based on 10 x 3-week cycles over 18 months)
IL-2= Interleukin 2; MIMS= Monthly Index of Medical Specialities *See the individual Summaries of Product Characteristics for recommendations[1,22]. IL-2 costs calculated from MIMS list prices[23], assuming a maximum usable vial life of 24 hours following reconstitution[22].*		

8.0 ADDITIONAL INFORMATION

8.1 Shared care arrangements

WMP is of the opinion that HDC is not suitable for shared care within NHS Wales.

HDC 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 AML.

8.2 Ongoing studies

Upon licensing, CHMP requested the following studies to be performed[10]:

- A multicenter, open-label clinical pharmacology study to evaluate the biomarkers and pharmacologic endpoints of HDC plus low dose IL-2 in approximately 100 adult patients stratified by age greater or less than 60 with AML in CR1, with well characterized morphologic, cytogenetic and molecular profiles.
- An open-label clinical study to evaluate minimal residual disease for the assessment of the anti-leukaemic activity of HDC plus low dose IL-2 in approximately 150 adult patients stratified by age greater or less than 60 with AML in CR1[10].

Based on these requirements, the company commenced a phase IV, international, multicentre, open-label study to evaluate the quantitative and qualitative pharmacodynamic effects of HDC and IL-2 remission maintenance therapy in adult patients with AML in CR1 in April 2009[24].

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Appendix 1. Additional health economic analysis information

Table 1A. Health economic analysis detail[2].

	Base case model	Appropriate?
Comparator(s)	Histamine in combination with IL-2 is compared against BSC as maintenance therapy for adult patients with acute myeloid leukaemia in CR1.	Yes, as requested by WMP.
Population	Base case relates to adult patients aged ≤60 years who are in CR1 (age 55 years at start of treatment, as per the approximate mean age of patients enrolled in the pivotal trial MP-MA-0201), which the company consider to be the target population. The pivotal trial MP-MA-0201 from which the population is modelled included adult patients of any age and also included patients in first or subsequent remission. Additional analyses have been provided in patients in CR1 of any age and in all patients irrespective of remission number. All patients had achieved complete remission and had completed consolidation therapy.	Yes, the modelled population reflects the licensed indication. The licensed indication indicates that the efficacy of histamine has not been fully demonstrated in patients aged over 60 years[1]. The submission indicates that patients aged ≤60 years are the focus of the analysis. In addition, as allo-SCT is not considered in the model, the results would appear to relate only to those in whom allo-SCT is not an option.
Analysis type	CUA based on a Markov model with a one-month cycle. Patients in remission commence treatment with histamine and IL-2 or receive BSC. Within the remission state, patients may experience serious adverse events associated with treatment or not. They may move from the remission state to either a relapse state or death.	CUA is the preferred type of analysis. A simple clinical pathway is described for the target population. Allo-SCT appears not to be permitted, although the model provided by the company is designed to enable its incorporation. Salvage treatment following relapse is not considered.
Perspective	Considers direct medical costs only, from perspective of NHS Wales.	Yes.
Time horizon	The base case analysis is based on a 25-year lifetime horizon, relying on extrapolation of 66-month survival data from the main clinical trial. Five-year time horizon explored in scenario analysis (to reflect length of follow-up in the main clinical trial).	A lifetime horizon would be appropriate. The revised model indicates that around 91% of patients have died by 25 years. Patients are modelled with a starting age of 55 years, as per the median age of patients in the main clinical trial. The model is sensitive to the assumed time horizon. Using a five-year horizon in the latest version of the model generates an ICER of £44,210 per QALY gained.
Discount rate	3.5% applied to both costs and outcomes	Yes.
Efficacy	It is reported that LFS and OS data for the subgroup of patients in the MP-MA-0201 trial with CR1 aged ≤60 years have been extracted from Kaplan-Meier curves using digital software to estimate six-month probabilities of LFS and OS. Trial data were available for up to 66 months of follow-up, and progression rates were reported to be different over the first 12 months of follow up compared with the post 12-month period. LFS and OS were extrapolated beyond the time horizon of the trial, using constant six-month probabilities, based on post 12-month data. Life tables (weighted by the gender distribution in the trial) have been used to incorporate all-cause mortality for the period beyond the trial follow up. This approach was repeated for the subgroup of patients of any age in CR1, and for all patients irrespective of remission number. The model is capable of extrapolating the survival data using Weibull and other types of functions.	The LFS and OS data in the subgroup of CR1 patients aged ≤60 years are referenced to data on file and have not been verified. OS in the first five years is already accounted for in the trial data. Life tables are used to provide all-cause mortality beyond five years, but it is unclear whether or not there is the potential for double counting when considered alongside the extrapolated trial data. The company has not provided analyses using other extrapolation functions; however, it appears from a revised model that the use of other functions (e.g. Weibull) results in marginally more favourable model outputs. The extrapolation function used by the company, therefore, seems appropriately conservative.. No sensitivity analyses have been considered around the key effectiveness parameters related to LFS and OS.
Adverse events	The submission states that treatment-related grade 3 or 4 adverse events reported in at least 5% of patients in the MP-MA-0201 trial are assumed to impact on quality of life and costs and that these are applied in the model irrespective of the model cycle length.	Adverse events are treated in the model in the same way, irrespective of type. Although the submission reports that costs and quality of life associated with adverse events are considered, few details are provided (see below). It is unclear if/how costs associated with adverse events have been applied in relation to length of impact of the adverse event.

Table 1A. Continued

	Base case model	Appropriate?
Utility values	The company reported a lack of AML-specific utility data within the literature. In the base case analysis, utility values for patients in remission are assumed the same as those reported in the literature the chronic phase of CML. For the post-relapse state, utility values reported in the literature for blast phase of CML were assumed. The company had contacted a number of UK haematologists for validation of this approach, and had undertaken two-way sensitivity analyses to explore the impact of these assumptions. Health-related quality of life data were collected in the MP-MA-0201 trial using the EORTC QLQ-C30 instrument. Two means of mapping these data to the EQ-5D™ instrument to generate utility values were also conducted and results presented as sensitivity analyses.	There would appear to be a degree of uncertainty associated with the assumed utility values. The base case models use utility values related to the remission and relapsed states of CML. Although these have reportedly been validated by four clinical experts, there are issues with using utility values based on health professional opinion, and it is not clear that there is consensus among the experts approached by the company. Furthermore, there is no specific consideration of the potential disutility associated with twice-daily injections required for administration of histamine and IL-2. Although the submission suggests that health-related quality of life associated with adverse events is considered, there are no details of a disutility associated with adverse events being applied within the submission or the model, which would appear to favour treatment with histamine and IL-2 over the comparator. Two-way sensitivity analysis has been conducted around the utility values associated with remission and relapse, but not in relation to adverse events. The company submission stated that utility values obtained from mapped AML patient health-related quality of life via two alternative (published) means were not used in the base case analysis, as there is a great degree of uncertainty around mapping such values. However, the company has subsequently acknowledged that the mapped values may be more appropriate. The use of the mapped utilities, based on data from AML patients, results in incremental cost effectiveness ratios that are greater than those estimated in the base case analysis. The base case analysis may therefore be biased in favour of HDC + IL-2 treatment.
Resource use and costs	Resource use relates to drug acquisition and management of adverse events as well as non-drug resources such as in/outpatient hospital visits, monitoring, etc. Treatment costs are based on MIMS list prices[23]. A published study that provided estimates of costs for remission and non-remission states of elderly AML patients, based on 1992 costs ($US)[25], has been used to provide estimates beyond drug costs. Adverse event costs are simply assumed to be £100 per event per month. One-way sensitivity analysis has been conducted around costs.	The published costs for remission and relapse states are inflated and converted to pounds sterling, but the extent to which the items of resource use making up these costs, based on practice in 1992 in the Netherlands, would be representative of current UK practice is unclear. One-way sensitivity analyses have been reported for background costs and adverse event costs. No administration costs are considered for histamine and IL-2 treatment, which require subcutaneous injection twice daily for 21 days in each treatment cycle, up to a maximum of ten cycles. In addition, once reconstituted, IL-2 has a short half-life of 24 hours[22], but IL-2 costs in the base case analysis are based on the assumption of no vial wastage. This is likely to substantially underestimate actual treatment costs in practice and bias the modelled cost effectiveness in favour of HDC and IL-2 treatment.

Table 1A. Continued

	Base case model	Appropriate?
Model provided?	Yes.	The model originally provided by the company did not generate the cost and outcome estimates reported in the company submission. A revised model has subsequently been provided.

Allo-SCT= Allograft stem cell therapy; AML= Acute myeloid leukaemia; BSC= Best supportive care; CML= Chronic myeloid leukaemia; CR1= First complete remission; CUA= Cost utility analysis; EORTC QLQ-30= European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30; IL-2= Interleukin 2; LFS= Leukaemia-free survival; MIMS= Monthly Index of Medical Specialities; OS= Overall survival; WMP= Welsh Medicines Partnership