MEDICAL ASSESSMENT

1. Introduction/Background

This is a UK Product Licence application for eclodarabine (Leustatin*) (2-chlorodeoxyadenosine; 2-CdA). It is a purine analogue resistant to the action of adenosine deaminase (ADA). Eclodarabine was registered in the USA in February 1993 with "orphan drug" status. It is a new chemical entity in the UK.

2. Indication

Treatment of hairy cell leukaemia.

3. Dosage and Administration

3.1 Route of administration

Intravenous infusion.

3.2 Recommended dosage schedule

Eclodarabine should be administered by continuous intravenous infusion over a 7 day period in a dose of 0.09 mg/kg/day.

Use in the elderly

No evidence has been presented for reduced tolerability or altered dosage requirements in elderly patients.

Use in children

Eclodarabine is not recommended for children.

Use in impaired renal or hepatic function

No information is available.

4. Pharmacodynamics

4.1 Primary pharmacodynamics

The only information available is discussed in the Preclinical Section (p8).

4.2 Secondary pharmacodynamics

Only adverse experiences were considered. No data have been supplied on any effects on body functions, eg respiratory or cardiovascular.

5. Pharmacokinetics

Only one pharmacokinetic study is presented involving patients with hairy cell leukaemia receiving eclodarabine at the recommended dose 0.09 mg/kg/day by intravenous infusion over 7 days. Results are shown in the table below:

Number of Patients	17
Steady state serum concentration	approximately 20 nM (6 ng/ml)
Steady state volume of distribution	4.32 ± 2.69 L/kg
Clearance	approximately 640 ml/h/kg
Terminal half-life	7 hours

There was no drug accumulation over the 7-day period.

A definitive pharmacokinetic study of eclodarabine was performed by [redacted] Sweden. Twelve patients who had various lymphoid neoplasias including hairy cell leukaemia were treated with eclodarabine in a dose of 0.14 mg/kg/day during 5 consecutive days. On days 1, 3, 4 and 5 eclodarabine was administered as a 2-hour infusion. During day 2 it was given as a 24 hour infusion.

Continuous infusion

Steady State Concentration (nM)	AUC (nM x h)
22.5 ± 11.1	552 ± 258

2-hour infusion

Peak Concentration (nM)	AUC (nM x h)
198 ± 87	588 ± 185

After 2-hour infusion (using a 3 compartment model).

$\alpha t_{1/2}$ = 8 minutes
$\beta t_{1/2}$ = 1 hour 6 minutes
$\gamma t_{1/2}$ = 6.3 hours

This publication is Appendix 7, page 72. The authors said that "the long terminal half-life after a 2-hour infusion supports the use of intermittent infusions".

Absorption

This is assumed to be complete as eclodarabine is administered by intravenous infusion.

Metabolism } No studies performed in man
Excretion }

Special groups of patients

No studies have been performed to assess the elderly or those with impaired renal or hepatic function. Children do not develop hairy cell leukaemia.

Drug Interaction

No drug interaction studies have been performed with eclodarabine.

Comments

1. Limited primary pharmacodynamic and no secondary pharmacodynamic information have been supplied.

2. Two pharmacokinetic studies have shown the terminal t½ of eclodarabine to be 6.3-7.0 hours. The authors of one study stated that intermittent, 2 hourly infusions should be given. It is not clear why the sponsors chose a continuous infusion. Perhaps it was to avoid high peak blood levels with the 2 hour infusions

3. There is no information on metabolism or excretion of eclodarabine in man.

4. No information is available on drug interactions although many patients have had concurrent therapy with a variety of drugs.

6. Efficacy

A brief description of hairy cell leukaemia is given in Appendix 8, page 75. The evidence of efficacy is based on 4 open-label studies. Two pivotal studies were performed in the USA; at [redacted] and [redacted]. These 2 centres supplied 89 and 35 patients respectively (124 patients). Supportive studies were performed at the [redacted], Sweden and the [redacted], Austria. These centres had 8 and 2 patients respectively. All four studies are summarised in Appendix 9, page 75.

The 4 centres used eclodarabine to treat a variety of lymphoid neoplasms. Because impressive results had been noted in the treatment of hairy cell leukaemia at the [redacted], a protocol was prepared for the 4 centres. The diagnostic criteria and definitions of efficacy were relatively well standardised for the 2 pivotal studies. Data from the 2 European centres are not easy to assess because of variation in dosage and sometimes inadequate documentation.

All of the data for analysis from the 4 studies were retrieved retrospectively from hospital records. There was no monitoring of the clinical trials and no quality assessment.

Patient characteristics for the [redacted] and [redacted] studies are listed in Appendix 10, page ~~77~~ 76.

Diagnostic criteria for the 2 pivotal studies are listed in Appendix 11, page 77.

Important efficacy assessments are presented in Appendix 12, page 77.

All patients were assessed after a single one week course of therapy. Perhaps 2 patients had a second course.

Overall response (complete response + good partial response + partial response) was 88.5% of evaluable patients in the [redacted] study and 85.7% in the [redacted] study.

The time to complete response analysis is of uncertain reliability because of incorrect timing of bone marrow biopsy and aspiration on many occasions. A combined median time for [redacted] and [redacted] would appear to be 134 days but it could have been less.

Duration of complete response of up to 751 days was noted. No patients with a complete response had a relapse during the period of these studies.

It would appear that the response of patients to eclodarabine was similar regardless of whether or not the patient had previously had chemotherapy.

Previously splenectomised patients appeared to have a poorer response than patients with a spleen (overall response; 76.5% versus 93.1%).

Clearance of hairy cells from peripheral blood occurred in around 9 days.

A more extensive description of efficacy results is given in Appendix 13, page 78-82.

Comments

- Eclodarabine appears to be very effective in the treatment of hairy cell leukaemia.
- Length of follow up of the patients was from the start of eclodarabine therapy until 30 September 1991.
- It would be desirable to have more follow-up data.

7. Safety

The safety analysis was based mainly on 124 patients in the 2 pivotal studies but some information was gained from the 10 patients in the 2 supportive studies.

The major adverse experiences associated with eclodarabine were fever and myelosuppression which were, in many cases, accompanied by infection. Most toxicities occurred within 2-4 weeks of initiation of therapy. Only rarely were they severe.

7.1 Fever

In the [redacted] study 78.7% patients experienced febrile events (temperature ≥ 37.8°C) during the study and in the [redacted] study, 54.3% patients had fever. Most fevers were termed mild. Febrile events were usually associated with cytopenia.

7.2 Myelosuppression

7.2.1 [redacted] Study

After initial periods of suppression, all haematological parameters normalised. Platelets were 100 x 10^9/L by Day 16 (median); absolute neutrophil count was 1500 x 10^8/L by Day 39 (median) and haemoglobin levels of 12.0 g/dL were achieved by day 14. The median time to normalisation of the complete blood count was 68 days for the 72 patients who achieved it.

Blood product transfusion requirements ceased by 2 months.

7.2.2 [redacted] Study

Haematological values initially declined but subsequently normalised within the first one to 2 months. Platelets were ≥ 100 x 10^9/L by 14 days from the start of the eclodarabine infusion, absolute neutrophil count was ≥ 1500 cells x 10^6/L and haemoglobin ≥ 12.0 g/dL by 35 and 48 days. The median time to normalisation of complete blood count (haemoglobin ≥ 12.0 g/dL, platelets≥ 100 x 10^9/L and absolute blood count ≥ 1500 x 10^6/L) was 48 days from the start of treatment in 25 of 28 evaluable patients (89.3%). Transfusion requirements were eliminated in evaluable, responding patients by Month 2.

7.3 CD_4 and CD_8 lymphocytes

Mean absolute CD_4 lymphocyte count decreased from 766.2/μL at baseline to values less than 300/μL during the first 9 months but increased to 447.2/μL after 15 months of study. Mean absolute CD_8 lymphocyte count decreased from 618.5/μL at baseline to 314.8/μL after the first 9 months but at one year was 516.8/μL. The CD_4/CD_8 ratio was 1.8 at baseline and ranged from 0.9 to 2.1 on study.

7.4 Incidence of infection (%):

	One Month Prior to Study	During First Month of Study
[redacted]	12.4	30.3
[redacted]	8.6	31.4

Infections were usually classified as mild to moderate and when an infectious agent was isolated, it was usually bacterial. In the second month rates of infection in patients at both centres had returned to the pre-treatment level.

7.5 Other adverse events

During the first 2 weeks of the study, 93.3% of the [redacted] and 77.1% of the [redacted] patients had at least one adverse experience, most being mild. Experiences other than fever and infection are tabled in Appendix 14, page 83).

Beyond 15 days, patients commonly complained of fatigue.

Only one adverse event (pruritus) was considered to be drug related.

7.6 Serious adverse experiences

There were 4 serious adverse experiences (apart from death).

- Ruptured spleen
- Supraventricular tachycardia
- Acute haemolysis
- Venous thrombosis.

7.7 Deaths

There were 4 deaths in the 89 patients who attended [redacted] and 2 in the 35 at the [redacted].

Cause of Death	Number
Infection	1
Underlying Heart Disease	2
Persistent Leukaemia and Infection	2
Respiratory Failure	1
	6

7.8 Supportive studies

In the Swedish and Austrian studies, the adverse event profile was similar to that of the pivotal studies ie neutropenia, febrile events and infection. The infections were associated with neutropenia during the first 5 weeks of the clinical trial. Transfusion requirements, which were frequent before therapy, were eliminated after the second month of follow-up.

One Swedish patient died of infection 9 days after completing the eclodarabine infusion.

7.9 Clinical chemistry

7.9.1 Liver function tests

7.9.1a SGOT

Summarised data from [redacted] and [redacted] centres combined are in Appendix 15, page 84. Although 124 patients were entered, only 92 had a baseline test. During the first week of the study it is impossible to tell whether the same or different patients had SGOT measured. Not many patients were assessed during the critical first 2 months. Mean levels did not appear to alter much from baseline during this time.

7.9.1b Total bilirubin (Appendix 16, page 86).

Most patients (118/124) had a baseline measurement. During the week of treatment barely half of the patients were tested on any day. There was a rise in mean total bilirubin around the end of the week of treatment and this continued for 2 months. On the 13th day (when only 7 patients were assessed) the mean plasma level was almost 7 times the baseline value.

7.9.1c Alkaline phosphates (Appendix 17, page 88).

Most patients (121/124) had a baseline measurement. It is not obvious which patients had measurements at later times. The mean value had doubled at 2 weeks and was lower but variable for 6 months.

7.9.2 Renal function

7.9.2a Serum creatinine (Appendix 18, page 90).

Most patients (119/124) had a baseline measurement. During the first 3 months only around a 5th of patients were assessed on the days stated. There appeared to be no adverse trend in mean values.

7.10 Additional information

Discussions with the sponsor company have revealed that it was intended to check clinical chemistry on the first and fourth days of eclodarabine administration in the [redacted] study and only before each course in the [redacted] study. Thus deviations from normal were likely to have been due to checking blood sample on ill patients. When the data for 2 seriously ill patients were removed from the bilirubin analysis, there was no longer a significant shift in the mean values.

Comments

The major adverse event was neutropenia with associated fever and sometimes a proven infection. Complete blood counts returned to normal within 68 days. Infections were usually mild and commonly bacterial. These events were usually manageable.

The sponsoring company stated that "there were no perturbations of renal or hepatic function". This statement was not borne out by the data presented. Further enquiries revealed that the data had been poorly presented and that for most patients there had been no significant deviations. Nevertheless there was probably an inadequate frequency of assessing hepatic and renal function in all patients.

8. Expert Report

The expert, [redacted] has treated 17 patients with eclodarabine in a dose of 0.1 mg/kg/day by intravenous infusion for 7 days.

[redacted] reviewed the results of each study centre and also gave an overview. [redacted] complete report is presented as Appendix 19, page 92.

9. Product Particulars

A summary of product particulars (SPC), the proposed UK Data Sheet and MLA 201 are part of the application.

9.1 SPC

9.1.1 Section 4.2. Posology

In view of the known plasma t½ of up to 7 hours, perhaps 2-hour infusions daily will be more appropriate.

9.1.2 Section 4.5. Interaction with other medicaments

Allopurinol was administered empirically to all patients in this submission and it would appear that there were no interactions.

9.1.3 Section 4.8.3

It is clearly stated that the clinical information in the SPC is based on 124 patients in 2 trials (these are the pivotal studies).

9.1.4 Section 5.2. Pharmacokinetic properties

No mention is made of the published 2-hour infusion study.

9.2 Data Sheet

9.2.1 Uses

A) Leustatin can be used for primary and secondary hairy cell leukaemia.

B) (HCL) should be put after hairy cell leukaemia as HCL alone is used alone in later parts of the text.

9.2.2 Preparation of a single daily dose

The dosage of 3.6 mg/m^2/day should be considered.

9.2.3 Interaction with other medicaments

None is known but it is unlikely that any were sought.

9.2.4 Effect on renal and hepatic function

All patients should have hepatic and renal function measured regularly - not just those with known impairment.

9.2.5 Pregnancy and lactation

Leustatin should be contraindicated in pregnancy. It would be simpler for nursing mothers not to breast feed rather than be excluded from receiving eclodarabine.

9.3 MLA 201

9.3.1 Preparation of a single dose

This wrongly includes a paragraph on warnings.

9.3.2 Pharmacokinetic particulars

The source is unknown for a mean terminal half-life of 5.4 hours.

10. Conclusions

Eclodarabine (Leustatin*) is a purine analogue which is resistant to the action of adenosine deaminase. In poorly controlled, open clinical trials it has been shown to be very effective in the treatment of hairy cell leukaemia in a dose of 0.09 mg/kg/day as a continuous infusion for 7 days. A predictable myelosuppression was associated with fever and some proven infections. The marrow toxicity was not too severe and recovery usually occurred by around 2 months.

Although treatment was usually given by continuous intravenous infusion over a 7 day period 2 pharmacokinetic studies showed that the plasma half-life is 6-7 hours. A 2-hour infusion daily for up to 7 days has been suggested.

It is of concern that nothing is known of the metabolism or excretion of eclodarabine in man. Liver and kidney function should be monitored in all patients treated with eclodarabine.

The clinical trials stopped in September 1991. An update of patients' progress would be useful.

11. Recommendation

Because of lack of information on metabolism and excretion of eclodarabine, inadequate monitoring of renal and hepatic function during the clinical trials and insufficient information on long-term follow-up it is considered that a product licence should not be granted.