LICENSING DIVISION

[redacted]

MARKETING AUTHORISATION APPLICATION (ABRIDGED)

MEDICAL ASSESSMENT

LICENCE No.:	PL: 00242/0338
PROPRIETARY NAME:	Leustat Injection 1mg/ml
ACTIVE(S):	cladribine
COMPANY NAME:	Janssen-Cilag Ltd.
EC ARTICLE:	4.8a Hybrid
LEGAL STATUS:	POM

1. INTRODUCTION AND BACKGROUND

This medically-targeted abridged application concerns an amendment of the existing Marketing Authorisation for Leustat (PL 00242/ 0232) used for the treatment of Hairy Cell Leukaemia, in order to include an additional therapeutic indication: secondary treatment of B-cell Chronic Lymphocytic Leukaemia (CLL).

2. INDICATIONS

The new indication is:

Treatment of patients with B-cell chronic lymphocytic leukaemia (CLL) who have not responded to, or whose disease has progressed during or after, treatment with at least one standard alkylating agent containing regimen.

3. DOSE & DOSE SCHEDULE

For use in adults and elderly only.

[redacted]

In patients with CLL, the recommended treatment consists of a continuous intravenous infusion of Leustat for 2 hours on days 1 to 5 of a 28 day cycle at a dose of 0.12 mg/kg/day (4.8 mg/m^2/day). The patient's response should be determined every two cycles. It is recommended that Leustat be administered in responding patients for 2 cycles after maximum response has occurred, up to a maximum of 6 cycles. Therapy should be discontinued after 2 cycles in non-responding patients. Response is defined as a 50% or more lymphocyte reduction.

4. TOXICOLOGY

No significant changes occurred in the pharmacological and toxicological profile of cladribine since the original submission.

No new toxicology data have been requested.

5. CLINICAL PHARMACOLOGY

No new data were requested. The clinical expert briefly reviewed the pharmacodynamics of cladribine, a purine nucleoside analogue. In addition, a published review on the clinical pharmacology of the agent is provided.

6. EFFICACY

6.1 UNCONTROLLED STUDIES

The present application relies on the results of a recently completed study of cladribine on CLL, supplemented by published scientific data demonstrating the efficacy of cladribine in the proposed indication.

UK Study P-104

This is an open-label study, including 34 patients, of whom 8 were Binet (classification) stage A and progressing, 13 were stage B and 13 were stage C. All received daily therapy as a two hour infusion: 0.012 mg/kg/d over days 1-5 in a 28 day cycle. Patient demographics are shown in Table A of the Clinical Expert Report, and the guidelines for stopping or delaying treatment were well defined (Table B).

Main efficacy parameters were degree of remission (CR, PR or none), time of onset and duration of remission.

Table 1 provides a descriptive overview of the trial (design and results).

According to [redacted], 7/34 (20%) achieved complete response (CR), 19/34 had a partial response (PR) (56%), 5 didn't respond at all and three others could not be classified. This results in an overall response of 76%. For the majority of patients (22/34), haematological CR or PR was seen at the end of the first cycle. At cut-off date, 2 with CR relapsed after a remission duration of 63.6 and 64.9 weeks

[redacted]

respectively. From those with PR, 8 relapsed (42%) after a median duration of remission of 38.5 weeks.

Published studies

Seven open, non-randomised studies have been published on the efficacy and safety of cladribine in patients with B-CLL. Five studies enrolled previously treated patients: most had received multiple chemotherapy schemes and many were considered refractory or resistant to treatment. In total, 351 patients were involved, of whom 119 received continuous iv infusion of cladribine at 0.1mg/kg/day, 7 or 5 days per cycle. The others received 2-hour iv bolus infusions.

A detailed summary is made available by the Clinical Expert. Response rates varied across the studies (CR and PR) and were in range of 27-85% for the overall response (assessment defined according to [redacted]). For previously treated patients, the overall response ranged from 27-57%, while this range was from 55-85% for previously untreated patients. Also, there seems to be an association with lower disease stage (Binet or Rai classification), previous fewer treatment regimens and previous response to therapy.

Comment:

Cladribine has shown to be effective in CLL, with a better response in those previously untreated. However, the Applicant has wisely decided that more data are needed for approval of this indication. Therefore, at this time Marketing Authorisation is only requested for rescue therapy in those resistant to standard therapy.

For second line therapy, response rate is to be expected as 27-57%, with a median duration of remission reported as 12-16 months.

7. SAFETY

7.1 SUMMARY ADVERSE REACTIONS - PATIENTS

UK study P-104

A total of 183 ADR were reported (52 duplicate), and more than half were unlikely linked to cladribine (54%). Most events were mild to moderate, with only 18% rated as marked.

Up to cut-off date, nine patients (26%) died.

Bone-marrow suppression was the dose-limiting adverse effect.

An excellent overview of the ADR has been given by the Clinical Expert

[redacted]

[redacted] *study*

Safety data are available on 124 CLL patients. Nature of the ADR are well reported by the clinical expert in his report page 19

[redacted] *studies and published studies*

Excellent review is available in the Expert Report

Comment:

Overall, myelosuppression is the predominant and dose-limiting toxicity of cladribine. As a result, high incidence of serious infections is to be expected.

In addition, there is a potential for neurotoxicity, haemolytic anaemia and secondary tumours

8. EXPERT REPORTS

A brief statement on the pharmaco-toxicological documentation has been provided.

The Clinical Expert Report was well detailed, concise and critical in nature. The expert is a leading Clinical Haematologist.

9. PATIENT INFORMATION LEAFLET

The PIL has been well constructed, in accordance with current regulations

10. LABELLING

The labels should be marked with the correct PL number.

11. APPLICATION FORM

The administrative details are duly completed.

12. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC is an adaptation from the one already approved for hairy-cell leukaemia. However, for point 8 (Marketing Authorisation Number) the cross-reference PL number was provided in error.

13. DISCUSSION

This is a well received application to license the use of cladribine as a second line therapy in patients with CLL. The applicant provided documentation from recent

[redacted]

literature on the efficacy/safety of the product in these circumstances, and independently sponsored a UK phase II study on the subject. All trials mentioned are open-label, non-controlled, but this can be considered standard and acceptable in cases of haematological malignancies.

A minor detail needs to be changed in SPC and labels.

14. RECOMMENDATION

That a licence be granted on condition of changing PL numbers noted in SPC and labels.

[redacted]
Senior Medical Assessor
[redacted]

Date: 28 August 1997

[redacted]