

## SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion for the approval of Litak. For information on changes after approval please refer to module 8.**

### 1 Introduction

LITAK contains the active substance cladribine (2-chloro-2'-deoxy- $\beta$ -D-adenosine or 2-chloro-6-amino-9-(2-deoxy- $\beta$ -D-erythropento-furanosyl)-purine), a chlorinated purine nucleoside analogue. The applicant sought a marketing authorisation for the first-line treatment of hairy cell leukaemia. The CPMP considered the benefit risk profile positive for cladribine for the first line treatment of hairy cell leukaemia. The scientific discussion in this report focuses on this indication.

#### Hairy cell leukaemia

Hairy cell leukaemia (HCL) is a neoplasm of small B lymphoid cells with oval nuclei and abundant cytoplasm with "hairy" projections in bone marrow and peripheral blood, diffusely infiltrating bone marrow and splenic red pulp and strongly expressing CD103, CD22 and CD11c. HCL is a disseminated disease, which often is minimally symptomatic at presentation. Most patients present with splenomegaly and pancytopenia and may have few circulating neoplastic cells. At diagnosis more than 80% have thrombocytopenia, 75% have anaemia, about half have granulocytopenia (accompanied by frequent pyrogenic infections) and 80% have splenomegaly. Incidence of HCL in the Western world is estimated to be about 4-5 new cases per million per year (Bernstein, Newton et al. 1990; Au, Klasa et al. 1998; Kristinsson, Vidarsson et al. 2002). Patients are predominantly middle-aged to elderly adults with a median age of 55 years and a male predominance. The diagnosis relies upon the demonstration of the neoplastic hairy cells in blood or marrow. Monocytopenia is characteristic. Other distinctive manifestations include recurrent opportunistic infections, vasculitis or other immune dysfunction. Immediate therapy is indicated in 85% of the patients. Interferon-alpha induces partial responses in most patients but complete responses only in a minority. 2'-deoxycoformycin and cladribine induce long-lasting complete remissions in the majority of patients with HCL. Cladribine has demonstrated a high efficacy with tolerable toxicity and is now the preferred agent for first line treatment of HCL. There exists a variant type, which has a poorer response to treatments effective in typical HCL. Prolonged remissions may also follow splenectomy (Jaffe, Harris et al., 2001).

#### Cladribine

Cladribine (2-CdA) is an antimetabolite belonging to the purine nucleoside analogues. It is chemically derived from deoxyadenosine, where the hydrogen atom in the 2-position of the purine ring has been replaced by a chlorine atom. This substitution renders the molecule resistant to the deamination by adenosine deaminase. Intracellularly cladribine is phosphorylated by deoxycytidine kinase (which is present in a high concentration particularly in normal and malignant lymphoid cells). Because the lymphoid cells also have a low content of 5'-nucleotidase, there is accumulation of 2-chlorodeoxyadenosine-5'-triphosphate (CdATP). CdATP is incorporated into DNA strands, thereby blocking DNA chain elongation and inhibiting DNA repair and it will inhibit ribonucleotide reductase. Cell death then occurs from energy depletion and apoptosis.

Cladribine was originally developed by the Scripps Research Institute in the U. S. A. in the 1970s (Beutler, McMillan et al. 1997). Cladribine was first used in humans in 1981 (Carson, Wasson et al. 1982, Carson, Wasson et al. 1984). The first published experience reporting on 9 patients with intractable haematological malignancies treated in the U.S.A. in a phase I trial appeared in 1984 (Carson, Wasson et al. 1984). The first communication on two HCL patients treated with 2-CdA appeared in 1987 (Piro 1987). The outstanding activity of cladribine against HCL was thereafter confirmed and documented through a series of publications in 1990-1992 based on patients treated in the U.S.A. and Sweden (Piro, Carrera et al. 1990; Juliussen and Liliemark 1992). By February 1992, positive results from a larger confirmatory phase II trial with pre-treated and previously untreated HCL patients became available (Estey, Kurzrock et al. 1992). Large published series with more than 200 HCL patients had also become available from Switzerland, further confirming the efficacy of cladribine in HCL (Betticher, Fey et al. 1992). Although long-term results were still lacking, these reports established cladribine as a standard treatment in patients with HCL. More recently, reports with

long follow-up have confirmed the efficacy of cladribine in the treatment of patients with HCL, with long-lasting complete remissions observed in most patients (Tallman, Hakimian et al. 1996; Hoffman, Janson et al. 1997; Cheson, Sorensen et al. 1998; Saven, Burian et al. 1998; Dearden, Matutes et al. 1999; Jehn, Bartl et al. 1999; Robak, Blasinska-Morawiec et al. 1999; Zinzani, Magagnoli et al. 2000; Goodman, Burian et al. 2003).

In Europe, cladribine for intravenous infusion was first approved in Sweden in November 1993 for the treatment of HCL. At the time of submission of the application, cladribine for intravenous infusion had been approved in all Member States of the Community except Ireland. In Austria, Finland, Portugal, Spain and the United Kingdom, the approved therapeutic indication also includes certain other lymphoid malignancies. Prior to commercial availability of cladribine in the Community, access to cladribine was only possible through clinical trials or compassionate use programmes. During the period of 1990 to 1993 cladribine products were received either through the U.S.A. National Cancer Institute (Cheson, Vena et al. 1991), or produced (mainly locally) in France (Bastie, Cazals-Hatem et al. 1999), Belgium (Delannoy, Ferrant et al. 1994), the United Kingdom (Hickish, Serafinowski et al. 1993), Switzerland (Betticher, Fey et al. 1992) or Poland (Robak, Blasinska-Morawiec et al. 1999).

With regard to clinical studies with cladribine, 150 articles have been published in clinical journals covering about 7,000 patients. Some of the largest published series of patients treated with cladribine have come from Scandinavia. In Sweden patients with various haematological malignancies were systematically treated with cladribine since March 1990 (Juliussen, Elmhorn-Rosenborg et al. 1992; Juliussen and Liliemark 1993). These series also included HCL patients from Sweden, Norway, Denmark and Finland (Juliussen, Heldal et al. 1995). Additional patients were recruited from Belgium, Switzerland and Germany (Juliussen and Liliemark 1992; Juliussen, Lenkei et al. 1995), with over 100 HCL patients treated by 1993. Other early series describing use of cladribine in the early 1990's have come from Germany (Jehn, Gawaz et al. 1993), Belgium (Filleul, Delannoy et al. 1994; Van Den Neste, Delannoy et al. 1996), Austria (Konwalinka, Schirmer et al. 1995), Italy (di Celle, Reato et al. 1994; Lauria, Benfenati et al. 1994; Lauria, Rondelli et al. 1997; Zinzani, Magagnoli et al. 2000), France (Meunier, Castaigne et al. 1996; Legrand, Vekhoff et al. 1997; Bastie, Cazals-Hatem et al. 1999), and the United Kingdom (Hickish, Serafinowski et al. 1993). Detailed information on the pharmacokinetics of 2-CdA became available in 1991 (Liliemark and Juliussen 1991). By 1992, the studies conducted in Sweden established the viability of the subcutaneous and the oral route (Liliemark, Albertioni et al. 1992).

#### Development of LITAK

The development of LITAK was initiated in the early 1990's by the University Hospital of Berne, Switzerland in collaboration with the Swiss Group for Clinical Cancer Research (SAKK). The aim of was to provide a more convenient schedule in terms of route of administration (subcutaneous instead of intravenous) and duration of treatment compared to the existing schedules of intravenous cladribine. The dosage regimen for subcutaneous administration of LITAK of 0.14 mg/kg body weight/day given on 5 consecutive days (total dosage per cycle 0.7 mg/kg) was chosen in order to achieve a similar exposure as that following 7-days administration by intravenous route administered at a dose of 0.09 mg/kg/day. A subcutaneous treatment daily for 5 days is expected to allow out-patient treatment and thus to be more convenient both for patients and the treating team. To enable subcutaneous administration, LITAK is provided as a higher concentrated solution of cladribine as compared to the cladribine product currently approved in the European Union. LITAK subcutaneous injection has been granted orphan medicinal product designation by the European Commission.

The applicant has submitted the results of non-clinical and clinical studies carried out by the applicant, and bibliographic references. The relevance of studies conducted using cladribine from different sources has been addressed (see Discussion on the non-clinical aspects, and Discussion on clinical pharmacology, biopharmaceutical studies). Where the results of certain studies were lacking and/or only published data were provided, the applicant has provided adequate justifications, showing that all relevant requirements as set out in the Annex I of Directive 2001/83/EC, as amended, are fulfilled, which have been assessed (see Non-clinical aspects, Discussion on the non-clinical aspects, and Clinical aspects, Discussion on clinical pharmacology, biopharmaceutical studies, and Discussion on clinical efficacy).

## 2 Chemical, pharmaceutical and biological aspects

### Composition

LITAK contains cladribine as active substance. The product is presented as a 2 mg/ml solution for injection, for subcutaneous use. Other ingredients include water for injections as a solvent, sodium chloride for the adjustment of osmolarity and sodium hydroxide and hydrochloric acid for the adjustment of pH. LITAK is filled into colourless type I glass vials, closed with teflonised rubber stoppers and crimped with aluminium caps.

### Active substance

Cladribine is a synthetic analogue of the purine nucleoside, adenosine. Its chemical name is 2-chloro-6-amino-9-(2'-deoxy- $\beta$ -D-erythro-pentofuranosyl)-purine or 2-chloro-2'-deoxy-adenosine. It is a colourless, odourless, crystalline powder soluble in distilled water and contains three chiral centres.

The active substance is synthesised via a six-step route, starting from natural 2-deoxy-D-ribose, 2,6-dichloropurine. The critical step in the manufacture of the drug substance has been identified to be the introduction of dichloropurine in the fourth step of the synthesis. For this reason the resulting key intermediate (Intermediate 5) is tightly controlled and a release specification has been set for its appearance, optical rotation and purity, thus eliminating the presence of cladribine's potential isomers. Among the other impurities that may arise from the starting materials or the synthetic route only five have been detected in the eight batches of the active substance presented.

#### *Active substance specification*

The active substance specification includes tests for the appearance, solubility, identification (IR, UV), assay (HPLC), impurities, optical rotation, water content, total microbial count and bacterial endotoxins. The analytical methods used in the routine controls have been suitably described and validated, while the impurity limits are in accordance with the ICH guidelines and have been adequately justified.

Batch analysis data have been provided for four batches of the active substance and the results indicate that the product consistently meets the set specification.

#### *Stability*

Samples from three batches manufactured according to the proposed manufacturing process have been placed under stability study at the following conditions: 4°C, 25°C, 40°C and 50°C. The duration of the studies was 36 months at all temperatures. The parameters tested were appearance, assay, purity and levels of impurities, while the test methods employed were those used for batch release.

The storage conditions used were not in strict accordance with ICH guidelines. However, the results indicate that the drug substance is very stable and it is unlikely to be adversely affected by the divergence from ICH conditions. Therefore, the proposed re-test period and storage conditions can be accepted. In addition, the applicant has committed to carry out stability studies with commercial scale batches, stored under the ICH recommended conditions, in the packaging proposed for marketing, to confirm the non-ICH results.

### Other ingredients

All excipients are commonly used in the preparation of injectables. They are tested to, and comply with, Ph.Eur. requirements. Since the product is intended for single dose use no preservatives are included in the formulation.

The solution for injection is filled in Type I glass vials with bromobutyl rubber stoppers. Both materials are widely used in pharmaceutical products and fulfil PhEur. requirements. The stability studies performed confirmed that there is no incompatibility between the product and its immediate packaging.

## **Product development and finished product**

The aim of the pharmaceutical development was the production of a ready-to-use solution for subcutaneous use. The solubility of cladribine in water is 5 mg/ml, therefore the concentration selected for the product is within this limit, and water for injections is a suitable solvent vehicle. Sodium chloride is used to achieve isotonicity and the pH is adjusted to 7.4-7.5, because the drug substance is rapidly cleaved at the glycosidic bond at acidic pH values.

The qualitative and quantitative composition of the formulation has remained constant since the initial development with only some minor changes in the manufacturing process. Different container types have also been used during development, initially ampoules and then stoppered vials, but the glass type used and stoppers materials were identical to those for the proposed container system.

The key issue in the manufacture of the product is the method of sterilisation. Terminal heat sterilisation was precluded, since there is the potential for hydrolytic cleavage of the drug substance, and a combination of sterile filtration and aseptic preparation was therefore employed.

The manufacturing process is a standard process for the preparation of solutions for injections and consists of the following steps: preparation of the cladribine solution, sterile filtration, aseptic filling and closure of the vials. The process has been described in sufficient detail and is controlled by appropriate in process controls, which monitor among others the bioburden and the pH of the solution, the filter integrity before and after the solution filtration as well as before and after the filling of the vials.

### *Product specification*

The product specification includes tests for appearance, pH, identification of the active and the solvent, purity (HPLC), impurities (HPLC), assay (HPLC), extractable volume (Ph.Eur.), sterility (Ph.Eur.), particulate contamination (Ph.Eur.) and bacterial endotoxins (Ph.Eur.).

Batch analysis data from three pilot scale and one commercial scale batches have been presented. All batches met the proposed specification and indicate consistent and reproducible manufacture of the product to the required quality.

### **Stability of the product**

Stability data have been provided for one commercial and three pilot batches. The pilot scale batches were stored, for up to 48 months, at 4°C, 25°C, 40°C and 50°C. The testing parameters were appearance, pH, assay and purity. The analytical methods used were the same as for batch release.

The samples from the production scale batch have been stored for up to 24 months, under the following conditions that are in accordance with ICH recommendations: 4±2°C, 25±2°C, 60±5% RH, 30±2°C, 60±5% RH, 40±2°C and 75±5% RH.

The summary of the results indicates that no change was observed in the quality of the product at 4°C and 25°C. Above 30°C degradation of the active ingredient was noted, but even at 40°C the specifications were met up to and including 18 months.

The sterility of the pilot batches stored at 4°C was reassessed after four years storage and showed no microbiological contamination.

In summary the stability data support the product shelf life as stated in the SPC under the approved conditions.

### **Discussion on chemical, pharmaceutical and biological aspects**

The quality of LITAK has been adequately established. The active substance is stable; it is well characterised and documented. The excipients and the packaging material are commonly used in this kind of formulation and are well documented. The manufacturing process of the finished product has been adequately described. Stability tests indicate that the product is chemically stable for the proposed shelf life.

However at the time of the CPMP opinion a number of minor quality issues were unresolved, which the applicant gave a commitment to resolve, as follow-up measures.

### 3 Non-clinical aspects

#### Pharmacology

Cladribine (2-chloro-2'-deoxyadenosine) is a prodrug that is phosphorylated intracellularly via deoxycytidine kinase (dCK). Unlike its non-chlorinated analogue 2'-deoxyadenosine, it cannot be deaminated by adenosine deaminase (Carson, Wasson et al., 1980). Phosphorylation of cladribine to its mono-, di- and subsequently triphosphate (2-chlorodeoxyadenosine-5'-triphosphate, 2-CdATP), results in accumulation of the active nucleotide (2-CdATP), particularly in cells with high dCK activity and a low level of deoxynucleotidases. These latter features are characteristic of lymphoid cells and various malignant cells derived from the haematopoietic system. Incorporation of CdATP into DNA of proliferating cells and the consequent blockage of DNA synthesis and inhibition of DNA repair results in cell death. Cladribine is also cytotoxic in resting cells (Carson, Wasson et al., 1983), through induction of apoptosis, and consequently may be effective in indolent diseases that do not respond adequately to conventional chemotherapy.

#### Primary pharmacodynamics

The applicant presented a review of the pharmacodynamics of cladribine investigated *in vitro* (Wataya, Hirota et al. 1989; Nagourney, Evans et al. 1993; Fridborg, Nygren et al. 1995; Carson, Wasson et al. 1983; Huang, Ashmun et al. 1986; Avery, Rehg et al. 1989; Mohammad, Katato et al. 1998; Cory, Nelson et al. 1997; Hentosh, Tibudan et al. 1997; Carrera, Yamanaka et al. 1989; Petzer, Bilgeri et al. 1991; Piga, Ganeshaguru et al. 1989; Depenbrock, Wenger et al. 1995; Hutton and von Hoff 1986; Robak and Korycka 1996; Ballarino, Castello et al. 1996; Begleiter, Wang et al. 1996; Barbieri, Abbraccio et al. 1998; Barbieri, Franceschi et al. 1998; Yuh, Tibudan et al. 1998; Leoni, Chao et al. 1998; Wyczechowska, Ruckemann et al. 1999; Genini, Adachi et al. 2000; Genini, Budihardjo et al. 2000; Nomura, Inanami et al. 2000; Godlewski, Motyl et al. 2001) and *in vivo* (Carson, Wasson et al. 1980; Mohammad, Katato et al. 1998; Huang, Ashmun et al. 1986; Schmid, Oberhuber et al. 1994; Nawrocki, Grieb et al. 1996; Schmid, Hechenleitner et al. 1998; Ryba, Grieb et al. 1993).

#### Studies *in vitro*

The cytotoxicity of a number of anticancer drugs, including cladribine, was investigated in primary cultures of normal human peripheral blood mononuclear cells (PBMC), or tumour cells from patients with acute or chronic lymphocytic leukaemia (ALL or CLL). Cladribine showed good potency in these cells, with  $IC_{50}$ 's in PBMC, ALL and CLL being 0.016 µg/ml, 0.30 µg/ml and 0.75 µg/ml, respectively (Fridborg, Nygren et al. 1995).

The inhibitory effects of cladribine on the growth of human haematopoietic (T-, B-, non T- and non B-lymphoblastic) cell lines, and the protective effect of the nucleoside transport inhibitors dipyridamole and NBTI were reported. All cell lines were protected to some extent (1.7 - 16-fold) by dipyridamole and NBTI (Avery, Rehg et al. 1989).

Bryostatin induces differentiation of CLL *in vitro* to a hairy cell stage. The effects of cladribine in this type of model were investigated using an EBV-negative CLL line (WSU-CLL) from a patient resistant to chemotherapy including fludarabine, which was exposed to bryostatin (100 nM) for 72 hours. Subsequent treatment with cladribine (11.2 µM) resulted in complete growth inhibition, which was greater than with either agent used alone. Growth inhibition was dose-dependent, with 5.6 and 11.2 µM cladribine showing 21.3 and 57% inhibition, respectively, on day 4; 16.8 and 22.4 µM were toxic (Mohammad, Katato et al., 1998).

The potency of cladribine was compared with that of cytosine arabinoside, 6-thioguanine, 5-fluorouracil and hydroxyurea in a number of human cell lines (leukaemia and lymphoma cells from patients, normal bone marrow cells and normal peripheral blood cells). The ratio of the  $ID_{50}$  in normal human peripheral blood lymphocytes to that in a T-lymphoblastoid cell line was calculated for each of the compounds. The ratio for cladribine was 1, whilst each of the other compounds had a ratio of > 500. Cladribine was therefore equipotent in resting and proliferating cells (Carson, Wasson et al. 1983).

CLL cells and normal peripheral blood lymphocytes express both caspase-3 and apoptotic protease activating factor 1 (Apaf-1). Incubation of lymphocytes with cladribine induced caspase-3 activation prior to the degradation of DNA and cell death. Stimulation of the caspase proteolytic cascade by CdATP may help explain the effects of cladribine on non-dividing lymphocytes (Leoni, Chao et al., 1998).

The induction of apoptosis in quiescent human PBMC by cladribine and 2-chloro-adenosine (2-CA) were investigated *in vitro*. It appeared that at least three pathways may be involved, and that the two compounds did not share the same pathways (Barbieri, Abbracchio et al, 1998). In a subsequent study, the effect of altering the structure of these compounds on their apoptotic effect in PBMC was investigated. Structural alterations abolished the effect of 2-CA, and significantly decreased that of cladribine (Barbieri, Franceschi 1998).

The analysis of the effect of cladribine on cell cycle kinetics showed an accumulation of cells in the S phase, the accumulation becoming more marked with longer periods of exposure and with higher concentrations (Huang, Ashmun et al., 1986).

#### Studies *in vivo*

The activity of cladribine against L1210 murine leukaemia *in vivo* was reported following intraperitoneal (i.p.) injections at various concentrations, either once a day for 6 or 2 days or at 3 hourly intervals on day 1, 5, 9. The surviving mice were observed for 60 days. There was an increase in the life span of the treated mice. At concentrations of 4, 6 and 9 mg/kg/injection, the median increase in life-span was 25, 50 and 75%, respectively. The maximal tolerated dose (50 mg/kg/injection) given daily for 6 days produced an 80% increase in life span, corresponding to a reduction by 1 order of magnitude in tumour cell burden by the end of treatment (Carson, Wasson et al., 1980).

The effects of cladribine on the survival of mice inoculated with L1210 leukaemia cells have been described in another published study. Cladribine administered i.p. at doses up to 30 mg/kg/day for 7 days prolonged survival in a dose-dependent manner, to a maximum of over 100% (Huang, Ashmun et al., 1986).

In a xenograft model of CLL in WSU-CLL-bearing mice, the maximum tolerated doses of cladribine and bryostatin (30 mg/kg s.c and 75 mg/kg i.p., respectively) were given either alone or in combination. The survival, tumour growth inhibition ratio, tumour growth delay and log<sub>10</sub> kill of the mice treated with bryostatin followed by cladribine were significantly better than in the control and other scheduled groups (Mohammad, Katato et al., 1998).

Immunosuppressive activity was investigated in a rat experimental small bowel transplantation model. Cladribine itself did not appear to have immunosuppressive properties, but was highly effective when combined with cyclosporin A, preventing rejection in 4/5 animals (Schmid, Oberhuber et al., 1994).

A similar finding was noted following cardiac allograft in rats, where cladribine alone did not prolong mean survival time (7 days) of control grafts without immunosuppression, but when combined with cyclosporin A, prolonged graft survival for up to 20 days (Nawrocki, Grieb et al., 1996).

The synergistic immunosuppressive properties of cladribine and cyclosporin A were also demonstrated following liver or heart transplant in an allogeneic rat model. Cladribine alone (i.v. 0.1 mg/kg/day) had no effect, but when combined with cyclosporin A (p.o. 10 mg/kg/day), 80% of the liver grafts and 60% of the heart grafts were not rejected (Schmid et al., 1998). In rabbits with experimental sub-arachnoid haemorrhage, cladribine (0.3 mg/kg/day s.c. for 5 days) had similar immunosuppressive effects as cyclosporin A in preventing cerebrovascular changes (Ryba, Grieb et al., 1993).

#### Secondary pharmacodynamics and safety pharmacology

Specific secondary pharmacodynamic or safety pharmacology studies have not been submitted.

#### Pharmacodynamic interactions

The applicant did not carry out specific pharmacodynamic interaction studies with LITAK. Cross-reactions with other antineoplastic agents *in vitro* (e.g. doxorubicin, vincristine, cytarabine, cyclophosphamide) and *in vivo* have not been observed. However, an *in vitro* study revealed cross-

resistance between cladribine and nitrogen mustard (chlormethine) (Nagourney, Evans et al. 1993). In one *ex vivo* study with patients with acute myelogenous leukaemia, a synergistic model of drug interaction between cladribine and cytarabine was observed (Gandhi, Estey et al., 1996). Cladribine showed a synergistic effect with chlorambucil in chronic lymphocytic leukemia (CLL) *in vitro*. Treatment with chlorambucil for 6 h followed by cladribine for 18 h produced a 2.3 to 7.5-fold synergistic cytotoxic effect (Begleiter, Wang et al., 1996).

The effects of cladribine were studied *in vitro* in combination with interferon- $\alpha$  or interferon- $\gamma$  on the clonal growth of granulocyte-macrophage progenitor cells (CFU-GM) from normal volunteers and patients with chronic myeloid leukaemia (CML) and clonogenic blasts (CFU-L) from patients with acute myeloid leukaemia (AML). Cladribine and interferon- $\alpha$  showed the greatest additive effect on the growth of CFU-L blasts at concentrations of 80 nmol/l and 104 U/ml, respectively. Similar results were reported on the effect on myeloid progenitors (CFU-GM) *in vitro* of cladribine combined with interferon- $\alpha$  with and without addition of interleukin-1 (IL-1) and/or granulocyte macrophage colony stimulating factor (GM-CSF). Cladribine dose-dependently inhibited CFU-GM growth. At the lower doses of cladribine (15.6 nmol/l to 62.5 nmol/l), combination with interferon- $\alpha$  had a synergistic inhibitory effect, whereas at the higher doses (up to 1  $\mu$ mol/l) there was no synergistic effect. The addition of IL-1 and/or GM-CSF had no effect on the inhibitory effect of cladribine (Robak and Korycka, 1996).

### **Pharmacokinetics**

The applicant submitted a review of the pharmacokinetics of cladribine investigated in pre-clinical and clinical studies (Liliemark and Juliusson 1991; Liliemark, Albertioni et al. 1992; Betticher, Fey et al. 1993; Liliemark and Juliusson 1994; Albertoni, Hassan et al. 1995; Liliemark and Juliusson 1995; Reichelova, Juliusson et al. 1995; Sonderegger, Betticher et al. 1996; Betticher, Hsu Schmitz et al. 1997; Sonderegger 1998; Sonderegger, Betticher et al. 2000).

#### Absorption

Absorption of cladribine has not been well studied in animals. A single-dose study using rat liver perfused for 3.5 h has been described. Comparative pharmacokinetics in mouse and man following subcutaneous administration have been reported. This latter study was conducted because significant differences had been observed in toxicity between mouse and man in Phase I studies (Albertioni, Hassan et al. 1995).

One study reported the pharmacokinetics in mice and humans following s.c. administration (Reichelova, Juliusson et al. 1995). Cladribine was administered s.c. to female NMRI mice at approximately one half of LD<sub>10</sub> (135 mg/m<sup>3</sup>). Results were compared with a study in humans treated at the MTD (4.8 mg/m<sup>2</sup>) (Liliemark, Albertioni et al. 1992). The plasma concentration/time curve could be fitted to a 2-compartment model in both species, but the slopes were much steeper in mice. The half-lives of drug disposition and elimination in mice were 11.4 and 150 minutes, respectively. The corresponding values in man were much longer, at 1.47 and 13.3 hours. The t<sub>max</sub> was similar (15 mins in mouse, 20 mins in man), but a much higher C<sub>max</sub> occurred in mice. The ratio of the LD<sub>10</sub> dose in mice to the MTD in humans was 50, and the area under the curve determined in mice at approximately one-half of the LD<sub>10</sub> was about 49 times higher than the AUC found in patients at the MTD (Table 1).

**Table 1. Pharmacokinetic parameters in mice (Reichelova, Juliusson et al., 1995) in comparison to those in human (Liliemark, Albertioni et al., 1992) following a s.c. dose of 0.14 mg/kg of cladribine**

	Mice (mean of n=3)	Humans (mean of n=10)
$t_{1/2\alpha}$ (h)	0.19	1.47
$t_{1/2\beta}$ (h)	2.50	13.3
Peak concentration ( $\mu\text{M}$ )	54.80	0.32
Time of peak concentration (h)	0.25	0.34
CL ( $1\text{h}^{-1} \text{m}^2$ )	14.40	25.9
AUC ( $\mu\text{M} \times \text{h}$ )	32.80	0.80

### Distribution

Plasma protein binding of cladribine was studied *in vitro* using solutions of human serum albumin (HSA, 40 g/l) or  $\alpha_1$ -acid-glycoprotein (0.7 g/l), or *in vivo* in blood from patients treated with cladribine, or in blood from volunteers spiked with cladribine (25 to 1000 nmol/l). In the HSA solution, 24.3% was bound, but < 5% was bound in the  $\alpha_1$ -acid-glycoprotein solution. In patients, 25% was bound, and in volunteers, 21.1%, although there was a wide range (5.6 to 50.8% in patients and 9.7 to 32.7% in volunteers). Binding did not appear to be concentration-dependent (Albertioni, Hemgren et al. 1994). Plasma protein binding of cladribine in mouse plasma was only about 6% to 10% at concentrations of 0.5 to 50  $\mu\text{M}$  (Reichelova, Juliusson et al. 1995).

### Metabolism and excretion

The metabolism of cladribine (2, 20 or 200  $\mu\text{g/ml}$ ) in perfused rat liver was investigated. The major metabolite, 2-chloroadenine, increased proportionally with dose and time. There was a 50% first pass effect. Less than 1% of the dose was recovered intact in the bile, and less than 1% was recovered as 2-chloroadenine. Elimination half-life was concentration-dependent (Albertioni, Hassan et al. 1995).

### **Toxicology**

The applicant submitted the results of studies investigating single and repeated dose toxicity of cladribine using the intraperitoneal route in mice and monkeys (Carson, 2002).

#### Single dose toxicity

Female CDF 1 mice were administered single i.p. doses of a 0.1% solution of cladribine and observed for 30 days. There was no mortality up to 90 mg/kg. The  $\text{LD}_{50}$  was 150 mg/kg and the  $\text{LD}_{90}$ , 180 mg/kg. No other parameters were evaluated in this study (Carson 2002).

#### Repeat-dose toxicity

Female CDF 1 mice were administered i.p. doses of a 0.1% solution of cladribine at 50, 75, 100 or 125 mg/kg/day for 5 days, and observed for 30 days. The MTD was 50 mg/kg/day. The  $\text{LD}_{50}$  was 75 mg/kg/day and the  $\text{LD}_{90}$ , 100 mg/kg/day. No other parameters were evaluated in this study. In another i.p. study, female CBA/CeJ mice were administered 60 mg/kg cladribine every 3 hours for 3 doses on days 0, 3, 6 and 9. Leukopenia, mild lymphoid depletion and atrophy occurred by Day 3. Acute tubular necrosis, dilation, degeneration, and interstitial fibrosis in the kidney were evident by Day 9. Blood urea nitrogen (BUN) showed mild to moderate elevation by Day 6 (Carson 2002).

Repeated s.c. administration of cladribine in mice was carried out to determine the  $\text{LD}_{10}$ , for subsequent pharmacokinetic comparisons between mouse and man. Doses of 12.6, 17, 42, 75 and 100 mg/kg/day were given for 5 days. The top dose was lethal to 40% of the animals during the first week of the 4-week observation period. No deaths occurred at 75 mg/kg/day and therefore the  $\text{LD}_{10}$  was somewhere between these figures (Reichelova, Juliusson et al., 1995).

The applicant reviewed the results of two studies using continuous i.v. infusion over 7 or 14 days in monkeys. At a dose of 1 mg/kg/day for 7 days, the animals became lethargic and developed diarrhoea, leukopenia and anaemia. This had recovered after a 1-week treatment-free period. At a dose of 2 mg/kg/day for 7 days, severe nausea and vomiting and seizures were observed. The animal became

ataxic on Day 9 and it was sacrificed on Day 10. Severe dehydration and electrolyte disturbances were attributed to the vomiting. Microscopic examination revealed marked suppression of rapidly dividing tissues such as bone marrow and testicular tissue, and accounts for the thinness of the skin and compromised integrity of the intestinal mucosa. In the 14-day study, lower doses (up to 0.6 mg/kg/day) were used. There were no deaths. The study included clinical observations, physical examinations (ECGs and ophthalmoscopy at pretest, end of treatment, end of recovery). Effects of treatment included weight loss (which may have been due in part to a reduction in food consumption caused by treatment-related lesions on the tongue), abnormal neurological functions, haematological effects (reduction of RBCs, haemoglobin, haematocrit, neutrophils and lymphocytes), changes in blood chemistry (decreased cholesterol, phosphate, potassium and albumin), and changes in the lymphocyte sub-sets (significant decreases of approximately 60% of total B and T cells). The target organs for lesions/necrosis were the bone marrow, skin, small intestine, lymphoid system, and salivary gland. Animals in the recovery group regained most of their body weight, and haematology and chemistry values had returned to or were approaching pre-dose values. Histopathological lesions had generally resolved by the end of the recovery period. The no toxic effect dose was 0.1 mg/kg in this study (Carson 2002).

#### Toxicokinetics

Toxicokinetics have not been reported.

#### Genotoxicity

An imbalance of deoxyribonucleoside triphosphate (dNTP) pools occurred within 3 h of treatment of mouse mammary tumour FM3A cells with 20  $\mu\text{M}$  cladribine. After a further 9 h, mature DNA strands broke and cells lost viability. Breaks in double- and single-strand DNA were observed after another 6 h. Double-strand breaks (DSB) are probably involved in cladribine-induced cell death, and may be triggered by dNTP imbalance. The percentage of cells in the S phase increased with time when these cells were incubated with cladribine, with the ratio of cells in the G1/S phases as well as cell viability decreasing throughout 24 h exposure (Hirota, Yoshioka et al., 1989).

Cladribine (0.3  $\mu\text{M}$ ) inhibited DNA synthesis in human lymphoblastic CCRF-CEM cells by 90% within 30 minutes. There was marked inhibition of intracellular conversion of cytidine to deoxycytidine, indicating inhibition of ribonucleotide reductase. Addition of deoxycytidine only restored DNA synthesis to 40% of its normal value, implying another mechanism apart from depletion of dNTP pools is involved (Griffing, Motyl et al., 1989).

Most DNA strand breaks induced in resting human peripheral blood lymphocytes by 500 rad  $\gamma$ -irradiation rejoined within 2h of exposure. Cladribine inhibited DNA repair, blocking unscheduled DNA synthesis with significant activity even at 100 nM (Seto, Carrera et al, 1986).

In resting human peripheral blood lymphocytes treated with 1 or 10  $\mu\text{M}$  cladribine, DNA strand breaks accumulated after 4h, intracellular NAD levels fell significantly after 8 h, ATP pools depleted after 24 h and cell death occurred after 48 h. NAD depletion and cladribine toxicity were prevented by incubation with the NAD precursor (and poly(ADP)-ribose synthetase inhibitor) nicotinamide (Seto, Carrera et al, 1985).

According to another published study, double-strand breaks were observed 2 h after incubation of Chinese hamster V79 cells with 5  $\mu\text{M}$  cladribine, but were almost rejoined by a subsequent 1 h incubation, despite the presence of drug in the medium. This repair was prevented by the addition of nicotinamide, but not by the addition of 9- $\beta$ -D-arabino-furanosyl-adenine (araA), which inhibits DNA polymerisation. The authors suggested that the repair of cladribine-induced DSB is achieved by ligation alone without DNA polymerisation (Tanabe, Hiraoka et al., 1989).

The repair of the potentially lethal damage to Chinese hamster V79 cells caused by X-irradiation was dose-dependently inhibited by cladribine (0.5 to 1.5 mM). The inhibition was prevented when deoxycytidine was added with the cladribine (Tanabe, Hiraoka et al., 1988).

In a further study, Chinese hamster V79 cells exposed to cladribine at 5 and 7.5  $\mu\text{M}$  for 3 h after X-irradiation enhanced the lethal effects of the X-rays dose-dependently. In the absence of cladribine, 90% of the DSB's were rejoined within 30 minutes of irradiation. Co-incubation with 5 to 10  $\mu\text{M}$  cladribine for 3 h after irradiation rejoined 15 to 40% of the DSB's. Almost all single-strand breaks

were rejoined within 15 minutes, regardless of the presence or absence of cladribine. The authors concluded that cladribine interfered exclusively with DSB repair, increasing the lethality in X-irradiated Chinese hamster V79 cells (Kuwabara, Tanabe et al. 1991).

### Carcinogenicity

The applicant, following the Note for Guidance on the Pre-clinical Evaluation of Anticancer Medicinal Products (CPMP/SWP/997/96), has not conducted carcinogenicity studies with cladribine.

### Reproductive and developmental toxicity

#### *Fertility and early embryonic development*

Fertility studies were not conducted, but marked testicular atrophy and the complete absence of spermatogenesis was noted in a monkey that had received cladribine by continuous i.v. infusion at 1 mg/kg/day for 7 days, then 2 mg/kg/day for 7 days after a one week rest.

#### *Embryo-foetal development*

Cladribine administered i.v. at 0.5, 1.5 and 3.0 mg/kg/day to Crl:CD-1(ICR)BR mice on days 6 to 15 of gestation produced foetal variations at the mid- and high-doses. At 3.0 mg/kg/day, foetal weight was significantly decreased and there were increased resorptions, reduced live litter sizes and increased malformations of the head, trunk and appendages. The NOEL was 0.5 mg/kg/day. There was no apparent maternal toxicity even at the high dose (Mitala, Hoberman et al. 1996).

At a dose of 4 mg/kg administered to mice (strain not specified) i.p. on day 7 of gestation, cladribine produced a foetal resorption rate of 83% (Skalko, Robbins et al., 1995).

Cladribine has been used as a teratogenic agent to investigate the relationship between p53-dependent apoptosis and teratogenesis in mouse embryos carrying different p53 genotypes. A single i.p. dose was administered on day 8 of gestation and embryos examined on day 11 or day 17. Cladribine stimulated nuclear p53 accumulation and triggered apoptosis in some (head-fold) but not all (primitive heart) developing structures. The induction of cell death was dependent on p53 gene dose, with the incidence of defects being 73.3% in p53 wild-type mice, 52.5% in heterozygous mutants and 2.2% in p53-null mutants. Abnormal development was manifested as eye defects by day 11, especially lens agenesis (Wubah, Ibrahim et al., 1996).

I.p. administration of cladribine (0.5 to 10 mg/kg) to CD-1 mice on day 8 of gestation produced a low incidence of microphthalmia at 5 mg/kg, but at 10 mg/kg, cladribine was embryo-lethal (Knudsen, Nguyen et al., 1997). This was further investigated in a later study, which suggested that microphthalmia was a critical malformation of cladribine in this model, with no effect at 1.5 mg/kg, teratogenicity at 5.0 mg/kg and embryo-lethality at 10.0 mg/kg, when administered on day 8 of gestation (Wubah, Setzer et al. 2001).

Cladribine administered i.v. at 0.3, 1.0 and 3.0 mg/kg/day to New Zealand White rabbits on days 7 to 19 of gestation produced reduced ossification of the phalangeal bones at 1.0 mg/kg/day. At 3.0 mg/kg/day, foetal weight was significantly decreased and there were increased malformations, mainly of the limbs. The NOEL was 0.3 mg/kg/day. There was no apparent maternal toxicity at any dose (Mitala, Hoberman et al. 1996).

In contrast to the effects in CD-1 mice (microphthalmia at 5 mg/kg i.p. on day 8), cladribine had little effect in Sprague-Dawley rats when administered i.p. at 15 mg/kg on day 10 of gestation (Knudsen, Nguyen et al. 1997).

### Local tolerance

Non-clinical studies using the subcutaneous route have not been conducted to investigate local tolerance specifically. However, studies in animals using this route did not reveal any irritation at the injection site. Clinical data is available using the subcutaneous route to provide information on the local tolerance of cladribine (Liliemark, Albertioni et al. 1992; Betticher, Zucca et al. 1996; Sperb, von Rohr et al. 1998).

### Ecotoxicity/environmental risk assessment

The applicant calculated crude predicted environmental concentration in the aquatic compartment. Based on worst-case conditions (maximum of usage, a removal rate of zero and a minimum of volume

of wastewater per capita and day), the calculated crude predicted environmental concentration of cladribine in the aquatic compartment was as low as 0.0008 mg/l.

### **Discussion on the non-clinical aspects**

The applicant has conducted an extensive review of the toxico-pharmacological studies for cladribine available in the literature. More than 80 studies have been found to be relevant for LITAK, and the bibliographical references have been provided and discussed by the applicant. Although GLP compliance was not systematically reported in the publications reviewed, consistent results have been shown across multiple studies, so that there is sufficient reassurance that the studies are reliable, and that the results are of general applicability. Furthermore, the current scientific knowledge on the toxico-pharmacological effects of cladribine has been confirmed through the vast clinical experience, as demonstrated by the clinical documentation presented by the applicant and the available experience in human. By choosing not to repeat certain animal studies, the applicant aimed to reduce the number of animals used for experimental purposes, and to limit animal testing to cases where there is a reasonable expectation that the result will extend the knowledge, with reference to Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes, and Council Decision 1999/575/EC of 23 March 1998 concerning the conclusion by the Community of the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes. This is in agreement with recital 10, and the general principles of Annex I of Directive 2001/83/EC, as amended. Although the studies described in the literature were conducted with cladribine from different sources, and mostly focussing on the intravenous route, no relevant differences with the LITAK formulation would reasonably be expected. Concerning the route of administration, the applicant claimed that the pharmacological and toxicological data published in the scientific literature are relevant for the proposed product LITAK, based mainly on the 100% bioavailability after subcutaneous administration. Thus, the relevance of studies which concern cladribine from different sources has been justified.

### **Pharmacology**

A large number of pharmacodynamic studies that are relevant to the proposed indication for cladribine are available in the literature. Both *in vitro* and *in vivo* studies have been reported, and many included comparisons with other cytostatic agents. Cladribine is particularly active in cells that have high deoxycytidine kinase activity and relatively low deoxynucleotidase, such as lymphoma and leukaemia cell types. Solid tumours are much less sensitive to cladribine. The comparative pharmacodynamics of cladribine *versus* other cytotoxic agents is also known. In contrast to other cytotoxic agents tested, cladribine has been shown to be equally potent in resting cells and proliferating cells, which suggests it may have a role in indolent diseases. Primary pharmacodynamic studies were not repeated by the applicant and it is agreed that additional studies are not required, as they would be unlikely to add any significant new knowledge about the primary pharmacodynamics of cladribine.

The applicant has not conducted specific secondary pharmacodynamic or safety pharmacology studies. ECG measurements were included in the observations in a 2-week toxicity study in *Cynomolgus* monkeys, showing no adverse effect of treatment. The safety profile and the adverse effects observed in patients treated with cladribine have been extensively described in the literature and in the clinical study results submitted by the applicant. Although no specific secondary pharmacodynamic or safety pharmacology studies have been undertaken, this is acceptable in the specific case of LITAK because at the time when the development of LITAK started, clinical experience with cladribine was available already and therefore it would not have been useful to perform additional pharmacology studies in animals. This is in accordance with the CPMP Note for Guidance on the Pre-clinical Evaluation of Anticancer Medicinal Products (CPMP/SWP/997/96) which highlights the need of safety pharmacology studies for compounds with a *novel* mechanism of action.

The applicant did not carry out specific pharmacodynamic interaction studies with LITAK. Nevertheless, pharmacodynamic interactions have been reported between cladribine and interferon- $\alpha$ , with synergistic effects reported in granulocyte-macrophage progenitor cells and clonogenic blasts, and between cladribine and chlorambucil in CLL. Cross-reactions with other antineoplastic agents *in vitro* (e.g. doxorubicin, vincristine, cytarabine, cyclophosphamide) and *in vivo* have not been

observed. However, an *in vitro* study revealed cross-resistance between cladribine and nitrogen mustard (chlormethine) (Nagourney, Evans et al., 1993). For cytarabine, an *in vivo* cross-reaction without loss of activity has been reported. Due to the similar intracellular metabolism, cross-resistance with other nucleoside analogues, such as fludarabine or 2'-deoxycoformycin may occur. Therefore, simultaneous administration of nucleoside analogues with cladribine is not advisable. Corticosteroids have been shown to enhance the risk for severe infections when used in combination with cladribine and should not be given concomitantly with cladribine. Since interactions with drugs undergoing intracellular phosphorylation, such as antiviral agents, or with inhibitors of adenosine uptake may be expected, their concomitant use with cladribine is not recommended. The concomitant use of other myelosuppressive medicinal products is contraindicated (see section 4.3 of the Summary of Product Characteristics). No additional pharmacodynamic interaction studies with LITAK are prompted either on pharmacological grounds or based on the intended therapeutic use.

Overall, the knowledge about primary and secondary pharmacodynamics, safety pharmacology, and pharmacodynamic interactions of cladribine is considered sufficient, and therefore the requirements in terms of non-clinical pharmacology documentation as set out in Directive 2001/83/EC, as amended, are considered fulfilled.

### Pharmacokinetics

The pharmacokinetics of cladribine have been studied more extensively in clinical than in non-clinical studies. A series of articles and reviews are available in the published literature and have been submitted as bibliographic references. Sufficient details about the analytical methods are described in the publications of the individual investigations.

Bioavailability studies have only been performed in humans. Cladribine is 100% bioavailable following s.c. administration, although mean residence time was significantly shorter after s.c. as compared to i.v. administration. The pharmacokinetic parameters after continuous or intermittent i.v. infusion and after s.c. bolus injection are comparable, with a 100% bioavailability, similar AUC, half life, and clearance values. When the s.c. administration is compared with the 2-h i.v. infusion, even the differences in the peak plasma concentrations are minor.

The plasma concentration/time curve could be fitted to a 2-compartment model in both man and mouse following s.c. administration of half of the LD<sub>10</sub> and the MTD, respectively. The half-lives of drug disposition and elimination in mice were 11.4 and 150 minutes, respectively. The corresponding values in man were much longer, at 1.47 and 13.3 hours. The t<sub>max</sub> was similar (15 to 20 minutes), but a much higher C<sub>max</sub> occurred in mice.

Plasma protein binding was lower in mice (about 4%) than in patients (about 25%), but was variable, with values ranging from approximately 6 to 51%. In normal subjects it was slightly lower than in patients (10 to 33%, with a mean of 21%).

Cladribine is activated by intracellular conversion by deoxycytidine kinase to its monophosphate, which is phosphorylated by nucleoside monophosphate kinase to the diphosphate, and ultimately to the triphosphate 2-CdATP by nucleoside diphosphate kinase. In rats, cladribine is metabolised to 2-chloroadenine. High concentrations are found in patient plasma after oral administration, but also (lower) after i.v. administration. This metabolite seems to have some cytotoxic activity in itself (about 1/8 of that of 2-CdA). Thus, after oral administration the metabolite can be of some importance for the cytotoxic activity of 2-CdA while it is probably negligible when 2-CdA is administered i.v. or s.c.

Overall, the knowledge about the pharmacokinetics of cladribine as described in the literature is considered sufficient. The applicant did not carry out additional non-clinical pharmacokinetic studies with LITAK. Additional non-clinical pharmacokinetic studies are unlikely to add any significant new knowledge about the pharmacokinetic profile of cladribine, and are therefore not required. Thus, the requirements in terms of pharmacokinetic documentation as set out in Directive 2001/83/EC, as amended, are considered fulfilled.

### Toxicology

No acute toxicity studies were conducted using the proposed subcutaneous route. One of the primary aims of toxicity studies for this type of agent is to establish the MTD in rodents, which is used to define the starting dose in Phase I trials (Note for Guidance on the Pre-clinical Evaluation of

Anticancer Medicinal Products, CPMP/SWP/997/96). There was no mortality up to 90 mg/kg in the i.p. mouse study. However, the mouse is much less sensitive to cladribine than is man. Results from Phase I trials in man have been available since decades, supporting the currently approved regimen of 1 mg/ml solution administered by continuous i.v. infusion. It has been established that bioavailability was 100% in humans using the s.c. route, and that s.c. administration was well tolerated. Clinical Phase I trials have established the MTD of cladribine following i.v. administration, and the recommended dose in man has also been established for the i.v. route. Given the 100% bioavailability of the subcutaneous route, there is no requirement to conduct additional single-dose toxicity studies with LITAK.

The applicant submitted the results and study reports of two studies using continuous i.v. infusion over 7 days or 14 days in monkeys. Furthermore, repeat dose studies in mice using the intraperitoneal and subcutaneous route were submitted as bibliographic references. As stated in the Note for Guidance on the Pre-clinical Evaluation of Anticancer Medicinal Products (CPMP/SWP/997/96), a repeat dose study of limited duration in two rodent species should be performed prior to Phase I trials. Repeat dose toxicity studies should be conducted in a rodent and a non-rodent species. The duration of the studies should be at least as long as the duration of the clinical trials. In the case of LITAK, Phase I clinical trials have already been conducted, and the rodent species do not appear to be good predictors of human toxicity. Therefore, further studies in rodents would not be appropriate.

The repeat dose toxicity studies submitted were shorter than the duration of clinical trials, and used a different schedule compared to the proposed clinical schedule. Concerning the latter, the 100% bioavailability of cladribine after subcutaneous administrations justifies the relevance of the results of the intravenous toxicity study for the proposed clinical route of administration of LITAK. In addition, as the 14-day monkey study employed continuous treatment with cladribine, the toxicity is likely to be higher than with an intermittent regimen. The study is therefore considered relevant for LITAK. Concerning the limited duration, given the extensive clinical experience and submitted clinical safety data with cladribine, it is considered that additional long-term toxicity studies in animals would not yield any significant new information on the target organ toxicity and reversibility of effects.

The observed toxicity was typical for a drug of this type. Since toxicokinetics have not been reported, safety margins cannot be calculated. On a mg/kg basis, the no effect level in the 14-day monkey study is similar to that intended for patients.

The toxic signs observed in animal studies are dose-dependent and are generally slowly reversible. Haematotoxicity and neurotoxicity, (at  $\geq 4$  times the recommended dose), have also been reported in patients. The gastrointestinal effects observed in the toxicity studies are reported to be generally mild in patients. Toxicity associated with the recommended dosage in patients has been limited to myelosuppression (thrombocytopenia, neutropenia, anemia), fever, and infection.

In conclusion, given the repeated-dose toxicity studies submitted, the present state of scientific knowledge, and taking into account the extensive clinical experience with cladribine and safety documentation submitted, additional repeated-dose toxicity studies with LITAK are not required.

Conventional genotoxicity studies with cladribine have not been conducted by the applicant, but results from available studies in the literature have been submitted as bibliographical references. These studies have revealed the genotoxic effects of cladribine. Cladribine is a cytotoxic medicinal product, which is mutagenic to cultured mammalian cells. *In vitro* studies in various cell lines have shown that cladribine induces dNTP imbalance, DNA strand breaks, depletion of NAD and ATP, and cell death. It also inhibits DNA repair. These findings confirm the generally proposed mechanism of action and the therapeutic effect of cladribine. This is adequately reflected under "Carcinogenesis/mutagenesis" in section 5.3 of the Summary of Product Characteristics. Repetition of genotoxicity studies described in the bibliographic references is not considered necessary, as this is unlikely to yield any significant new knowledge about the mutagenic and clastogenic potential of cladribine. Similarly, in view of the present state of scientific knowledge, the conduct of additional genotoxicity studies is not considered necessary.

Carcinogenicity studies have not been conducted. Such studies with unequivocally genotoxic compounds are not required as they are presumed to be trans-species carcinogens, implying a hazard to humans. This is in accordance with the requirements of Directive 2001/83/EC, Annex I, Part I.4.2.3, and follows the recommendations of the ICH note for guidance on the need for carcinogenicity studies

of pharmaceuticals (ICH/S1A), and the Note for Guidance on the Pre-clinical Evaluation of Anticancer Medicinal Products (CPMP/SWP/997/96).

Specific studies on the effects of cladribine on fertility have not been conducted. According to the Note for Guidance on the Pre-clinical Evaluation of Anticancer Medicinal Products (CPMP/SWP/997/96), studies of toxicity to reproduction are not required because reproductive disturbances are expected. Indeed, it may be expected that cladribine, in common with other compounds of this type, may have an adverse effect on fertility. Testicular degeneration and aspermatogenesis was noted in a monkey given 2mg/kg/day for 7 days by continuous i.v. infusion. Adequate information has been included under "Impairment of fertility" in sections 4.4 and 5.3 of the Summary of Product Characteristics. Additional fertility and early embryonic development studies are therefore not required.

Embryo-foetal, prenatal and postnatal development studies have not been conducted. Based on published investigations, cladribine has produced embryotoxic and teratogenic effects in mice and rabbits, which is again not unexpected from a product of this type. LITAK is contraindicated in pregnancy and lactation, and section 4.6 of the Summary of Product Characteristics warns that women of child-bearing potential should use effective contraception during treatment with LITAK. According to the Note for Guidance on the Pre-clinical Evaluation of Anticancer Medicinal Products (CPMP/SWP/997/96), studies of toxicity to reproduction are not required because reproductive disturbances are expected. Additional animal studies of embryo-foetal, prenatal and postnatal development, or studies in which the offspring are dosed or further evaluated with LITAK are not required.

Local tolerance has not been investigated in specific non-clinical studies using the subcutaneous route. However those studies that have been conducted in animals using this route did not reveal any irritation at the injection site. The absence of further studies in animals is considered justified given that there is extensive clinical experience using this route. Additional non-clinical local toxicity studies are unlikely to add any significant new knowledge about the safety profile of cladribine, and are therefore not required.

An assessment of environmental risk has been undertaken, concentrating on the aquatic compartment. This seems reasonable given the water solubility, low vapour pressure and N-octanol/water partition coefficient of cladribine. The predicted environmental concentration of cladribine in the aquatic compartment is well below the limit of 0.1 µg/l, and consequently no further testing is considered necessary.

In conclusion, the knowledge about the toxicology of cladribine, based on available studies in the literature and the documentation submitted by the applicant, is considered sufficient. Given also the extensive clinical experience with cladribine, additional non-clinical toxicology studies are not expected to provide any significant new information about the safety profile of cladribine, and are therefore not required. The requirements in terms of toxicology documentation as set out in Directive 2001/83/EC, as amended, are considered fulfilled.

#### Conclusions on the non-clinical aspects

Overall, there is sufficient knowledge about the pharmacological and toxicological actions of cladribine, based on studies in the literature. The results of published pharmacological and toxicological tests have shown the potential toxicity of LITAK, undesirable toxic effects that might occur under the proposed conditions of use, and its pharmacological properties. The results of these tests are considered reliable and of general applicability. The format and critical assessment of the non-clinical evaluation of cladribine presented by the applicant is adequate. Adequate discussion and justifications for the non-clinical testing strategies have been provided. Given the present state of scientific knowledge, the bibliographical references provided by the applicant, and the extensive clinical documentation for LITAK, additional non-clinical pharmacology or toxicological studies are unlikely to add any significant new knowledge about the safety profile of cladribine, and are therefore not required. Thus, the requirements in terms of pharmacological and toxicological documentation as set out in Directive 2001/83/EC, as amended, are considered fulfilled.

#### 4: Clinical aspects

##### Clinical pharmacology

###### Pharmacokinetics

Available publications addressing pharmacokinetics of cladribine in humans have been submitted (Table 2). One study has been performed with LITAK (Sonderegger, Betticher et al 1996). All other pharmacokinetic studies have been performed using other cladribine products (own formulations, Leustatin/Leustat or Biodribin).

**Table 2: Pharmacokinetic studies with 2-CdA**

Author/ year	No pts.	Dose mg/kg/day x 5 days	Duration & Route	C <sub>max</sub> (nM)	t <sub>1/2</sub> β/ terminal (h)	AUC (nM.h)	Remarks
Liliemark et al. 1991	12	0.14	2h i.v. 24h i.v.	198 ± 87 23 ± 11	6.7 ± 2.5 N/A	588 ± 185 552 ± 258	
Liliemark et al. 1992	13	0.14	2h i.v. s.c. p.o. <sup>a</sup>	169 ± 90 318 ± 91 53 ± 6	9.9 ± 4.6 13.3 ± 7.1 13.1	761 ± 276 799 ± 212 400 ± 114	F=102%±28% F=48% ± 8%
		0.28	p.o. <sup>a</sup>	196±149	10.4 ± 3.4	667 ± 294	F=55% ± 17%
Albertioni et al. 1993	3	0.12 (2d)	s.c.	38-64	7.4-15.3	454-701	
Liliemark et al. 1995	38	0.12	2h i.v.	112 ± 46	10.0 ± 5.0	573 ± 244	CLL pts.
	11	0.09 (7d)	s.c.	N/A	10.3 ± 7.0	611 ± 181	HCL pts.
	8	0.12	2h i.v.	N/A	5.3 ± 2.6	453 ± 309	AML pts.
Saven et al. 1996	10	0.14 0.28	2h i.v. p.o.	54 ± 20 42 ± 19	16.4 ± 7.1 N/A	199 ± 70 146 ± 56	F= 37% ± 10%
Tobinai et al. 1997	9	3: 0.06 6: 0.09 (7d)	24h i.v. 24h i.v.	18.5±1.7 21.0±3.7	22.5 ± 7.4 30.3 ± 9.5	2661±300 3128±538	AUC of 7 days AUC of 7 days
Albertioni et al. 1998	17	10mg/m <sup>2</sup>	p.o.	107	21.1	541	
Sonderegger et al. 1998/2000	9	0.10	24h i.v. s.c.	18 ± 2 179 ± 56	6.1 11.0	571 ± 50 608 ± 65	Identical bioavailability

N/A, not analysed; a, in phosphate buffered solution (PBS) with omeprazole; F = bioavailability

###### Absorption

Cladribine shows complete bioavailability after parenteral administration; the mean area under the concentration versus time curve (AUC) in plasma is comparable after continuous or intermittent 2-hour intravenous infusion and after subcutaneous injection. In a study in patients with low-grade non-Hodgkin's lymphoma or chronic lymphocytic leukaemia, patients received a 2 h i.v. infusion (0.14 mg/kg), a subcutaneous dose (0.14 mg/kg) and an oral dose (as either a solution or in capsules at 0.14 mg/kg or a solution at 0.28 mg/kg) on consecutive days, although in different orders. The subcutaneous administration produced a high peak concentration (318 pmol/ml) of short duration, but the AUC (799 pmol.h/ml) was almost the same as that following i.v. infusion (761 pmol.h/ml; bioavailability 102%). The t<sub>max</sub> following s.c. administration was 0.34 h (Liliemark, Albertioni et al. 1992).

In patients with low grade lymphoproliferative disorders, a single dose of 0.1 mg/kg was administered by the i.v. or s.c. routes. The AUC's were 548 and 570 pmol.h/ml following i.v. and s.c. administration, respectively. In the latter group, C<sub>max</sub> was 180 pmol/ml and occurred at 30 minutes post-dose (Sonderegger, Betticher et al. 1996).

###### Distribution

The steady-state plasma concentration of cladribine amounts to about 7 ng/ml and is reached within 5 to 8 hours after the start of a 2-hour infusion. A maximum plasma concentration C<sub>max</sub> of 48 ng/ml is

measured on average 112 minutes after the infusion. After subcutaneous bolus injection a maximum plasma concentration  $C_{max}$  of 91 ng/ml is reached on average after 20 minutes only (dose: 0.14 mg/kg body weight/day). In another study using a dose of 0.10 mg/kg body weight/day, the maximum plasma concentration  $C_{max}$  after continuous intravenous infusion was 5.1 ng/ml ( $t_{max}$ : 12 hours) compared to 51 ng/ml after subcutaneous bolus injection ( $t_{max}$ : 25 minutes). The clinical relevance of the different peak plasma concentrations after intravenous and subcutaneous administration of cladribine has not been examined.

The mean volume of distribution in man is reported to be 9.2 l/kg (Liliemark and Juliusson, 1991). Plasma protein binding of cladribine is 25% on average with a wide interindividual variation (5 - 50%) (Albertioni, Herngren et al. 1994). Cladribine crosses the blood-brain barrier and has been measured in CSF at levels about 25% of those in plasma. Intrathecal concentrations of cladribine average 18 - 25% of the plasma concentrations in studies with intravenous administration. Peak cerebrospinal fluid concentrations of 6 and 2 ng/ml, respectively, could be measured after intermittent 2-hour infusion or continuous intravenous infusion (dose: 0.12 mg/kg body weight/day). In one single patient administered LITAK by subcutaneous bolus, intrathecal concentration after 2 hours reached 8.75% of the plasma concentration, but further experience is needed (Liliemark and Juliusson, 1992; Saven, Kawasaki et al., 1993).

Intracellular concentrations are reportedly much greater than those in plasma and that the intracellular half-life is longer. (Liliemark and Juliusson 1995). Intracellular concentration of cladribine exceeds plasma drug concentration by 128 to 375 times.

#### Metabolism

Intracellular cladribine is metabolised predominantly by deoxycytidine kinase to 2-chlorodeoxyadenosine-5'-monophosphate that is further phosphorylated to the diphosphate by nucleoside monophosphate kinase and to the active metabolite 2-chloro-deoxy-adenosinetriphosphate (2-CdATP) by nucleoside diphosphate kinase. Cladribine is concentrated intracellularly due to rapid metabolic activation to this pharmacologically active metabolite (2-CdATP). No other metabolic pathways have been described and plasma concentrations of 2-CdATP have not been reported.

#### Elimination

In man, elimination occurs via a 2- or 3-compartment model, with  $\alpha$ - and  $\beta$ -half-lives of about 35 minutes and 6.7 hours, respectively.

Terminal half-life is reported to be 7 to 10 hours after continuous i.v. administration (0.1 mg/kg/day for 7 days) and 19.5 hours after intermittent i.v. infusion (0.14 mg/kg/day for 2 h/day on 5 consecutive days). The biexponential decline of the serum concentration of cladribine after subcutaneous bolus injection is comparable to elimination parameters after 2-hour intravenous infusion with an initial and terminal half-life of approximately 2 hours and 11 hours, respectively (Liliemark and Juliusson 1991).

The intracellular retention time of cladribine nucleotides *in vivo* is clearly prolonged as compared to the retention time in the plasma: Half-lives  $t_{1/2}$  of initially 15 hours and subsequently more than 30 hours were measured in leukaemic cells.

Cladribine is eliminated mainly by the kidneys. The renal excretion of unmetabolised cladribine occurs within 24 hours and accounts for 15% and 18% of the dose after 2-hour intravenous and subcutaneous administration, respectively. The remaining 82-85% is apparently excreted as metabolites, but this has not been studied further. The mean plasma clearance amounts to 794 ml/min after intravenous infusion and to 814 ml/min after subcutaneous bolus injection at a dose of 0.10 mg/kg body weight/day (Sonderregger, Betticher et al. 1996).

#### Bioavailability/Bioequivalence

The available published studies about the bioavailability of subcutaneous cladribine were presented by the applicant. The bioavailability of the subcutaneous administration, compared to 2-hour i.v. infusion in 13 patients, was  $102 \pm 28 \%$  with no difference in the AUC (Liliemark, Albertioni et al., 1992). These patients had malignant haematologic disease (B-cell chronic lymphocytic leukaemia (CLL) and low-grade non-Hodgkin's lymphoma). One study compared the pharmacokinetics of LITAK administered as a 24-hour intravenous infusion versus subcutaneous administration at a dose 0.1 mg/kg/day for 5 days (Sonderregger, Betticher et al., 1996). This study was conducted in 9 patients

with low-grade lymphoproliferative disorders (non-Hodgkin's lymphoma or chronic lymphocytic leukaemia). The volume of distribution was 1.58 l/kg for i.v. and 1.67 l/kg for s.c. cladribine. The applicant did not carry out additional bioavailability studies with LITAK. Although a different cladribine formulation than LITAK was used in the studies published by Liliemark and colleagues, the applicant claimed that results are considered valuable and relevant since they have established a 100% bioavailability of cladribine following subcutaneous administration as seen with LITAK.

#### Pharmacokinetics in special populations

There are no formal studies available using cladribine in patients with renal or hepatic impairment. Clinical experience is very limited and safety of LITAK in these patients is not well established. LITAK is therefore contraindicated in patients with moderate to severe renal impairment (creatinine clearance  $\leq 50$  ml/min) or with moderate to severe hepatic impairment (Child-Pugh score  $\geq 4$ ). The use of LITAK in children has not been investigated. Experience with patients older than 75 years is also limited. Elderly patients should be treated by individual assessment and careful monitoring of the blood counts and of the renal and hepatic function. The effects of gender, race, weight have not been studied.

Possible drug-drug interactions have not been studied.

#### **Pharmacodynamics**

##### Mechanism of action

Cladribine (2-chloro-2'-deoxy-adenosine) is an antimetabolite especially active for the treatment of lymphoproliferative disorders with a low proliferation fraction. It is a prodrug that is activated by intracellular phosphorylation through deoxycytidine kinase (dCK).

The single substitution of chlorine for hydrogen distinguishes cladribine from its natural counterpart 2'-deoxyadenosine and renders the molecule resistant to deamination by adenosine deaminase.

Cladribine is a prodrug which is converted intracellularly by phosphorylation into the active metabolite 2-chlorodeoxyadenosine-5'-triphosphate (2-CdATP) by deoxycytidine kinase (dCK). Administration of cladribine leads to a rapid accumulation of the active nucleotide, 2-chlorodeoxyadenosine-5'-triphosphate (2-CdATP), predominantly in cells with a high dCK activity and a low level of deoxynucleotidases. This feature is a characteristic of lymphoid cells and various malignant cells derived from the haematopoietic system.

Normal haematopoietic precursor cells are sensitive to cladribine causing a dose-dependent suppression of all haematopoietic cell lines. Non-haematologic tissues seem to be unaffected, explaining the low incidence of non-haematopoietic toxicity

##### Primary pharmacology

The applicant has submitted four published phase I trials with cladribine including patients with T-cell and B-cell neoplasms (Table 3).

Patients with far-advanced intractable haematologic malignancies who had exhausted all conventional modes of therapy were treated in an open-label phase I single centre study (Carson, Wasson et al. 1984). 9 patients were treated with cladribine 0.1 – 1.0 mg/kg/day by continuous intravenous infusion for 4-14 days. In all patients with leukaemia, cladribine lowered the peripheral blast cell count by at least 50%. Responses were observed at all dosages (0.1 - 1.0 mg/kg/day). One patient with a severe autoimmune haemolytic anaemia refractory to conventional chemotherapy responded to 2-CdA and the haemolytic process was terminated. Bone marrow suppression was the dose-limiting toxicity. Leukopenia and thrombocytopenia were observed in all patients receiving a dose of 0.2 mg/kg/day for at least 5 days.

Another open-label phase I single centre study included patients with residual or recurrent malignant astrocytomas after definitive surgery and irradiation with measurable or assessable disease as evident on computerised axial tomographic (CAT) scans or magnetic resonance imaging (MRI) scans of the brain and patients with measurable or assessable metastatic malignant melanoma and metastatic renal cell carcinoma (Saven, Kawasaki et al. 1993). For melanoma and renal cell carcinoma patients the presence of untreated cranial metastasis was an exclusion criteria. Cladribine was administered as a 7-day course, up to 4 courses every 28 days (exact study period unknown) - 0.10, 0.15 or 0.20

mg/kg/day by continuous intravenous infusion for 7 days. Two of 21 patients (9.5%) with malignant astrocytomas achieved a partial response of 7 and 9 months of duration, respectively. No patients with metastatic malignant or metastatic renal cell carcinoma responded. One of the 7 patients receiving a dose of 0.10 mg/kg/day experienced a grade 4 thrombocytopenia during the 2nd course of cladribine. Four of 11 patients receiving a dose of 0.15 mg/kg/day experienced severe myelotoxicity (2 with a grade 3 neutropenia, 1 with a grade 3 neutropenia and grade 4 thrombocytopenia, 1 with a grade 4 neutropenia and grade 4 thrombocytopenia). All three patients receiving a dose of 0.20 mg/kg/day developed myelosuppression (1 with grade 3 neutropenia, 1 with grade 4 neutropenia and 1 with grade 4 neutropenia and grade 4 thrombocytopenia). There seemed to be a trend towards cumulative myelotoxicity after repeated dose of cladribine. Two patients experienced neurological complications.

A phase I study of intermittent infusion cladribine was conducted in patients with solid tumours (Kobayashi, Vogelzang et al. 1994). Patients with solid tumours refractory to standard therapy or lacking a suitable standard therapy (predominantly non-small cell lung cancer and colorectal cancer). Cladribine was given as 5-day course, up to 6 courses every 28 days (exact study period unknown) 4, 6 or 8 mg/m<sup>2</sup>/day by intermittent 1-hour intravenous infusion for 5 days; first cycle: 20 mg/m<sup>2</sup> corresponding to the commonly used dosage of 0.1mg/kg/day for 7 days. No objective responses were noted, although one patient with colon cancer had stable disease for six cycles before experiencing disease progression. Myelosuppression was dose-limiting. Grade 4 leucopenia and neutropenia occurred in 2/4 patients receiving the dose level of 8 mg/m<sup>2</sup>/day. Minimal thrombocytopenia was seen and there was no evidence for cumulative myelosuppression with time. Two patients receiving a dose of 6 mg/m<sup>2</sup>/day were hospitalised for fever following neutropenia.

Another trial was a dose escalation trial of cladribine using five daily intravenous infusions in patients with advanced haematologic malignancies, predominantly non-Hodgkin's lymphoma and acute myeloid leukaemia and myelodysplasia (Larson, Mick et al. 1996). Cladribine 2.5, 4, 6, 8, 10, 12.5, 15, 18, or 21.5 mg/m<sup>2</sup>/day was administered by intermittent 1-hour intravenous infusion for 5 days. There were three complete responses (1 case at 8 mg/m<sup>2</sup>/day lasting for 7 months and 2 cases at 15 mg/m<sup>2</sup>/day lasting for more than 2 years). Partial remissions were observed in 5 patients: 1 patient with NHL treated at 6 mg/m<sup>2</sup>/day, 1 patient with CLL and 1 patient with PLL treated at 12.5 mg/m<sup>2</sup>/day, and 1 patient with CML and 1 patient with low-grade NHL treated at 18 mg/m<sup>2</sup>/day. Minor responses were seen in 10 patients. Myelosuppression was observed in the majority of patients, which was partly prolonged. Cumulative thrombocytopenia was particularly pronounced in heavily pretreated patients. Several patients required prophylactic platelet transfusions since thrombocytopenia did not resolve and was prolonged. Dose-limiting non-haematological toxicity, especially neurotoxicity, was not observed at doses including 21.5 mg/m<sup>2</sup>/day. The maximally tolerated dose (MTD) could not be defined.

**Table 3: Summary of phase I studies presented**

Reference	N	Maximally tolerated doses	Dose limiting toxicity
Carson 1984	9	0.1 mg/kg/day x 7 continuous i.v.	Myelosuppression and at higher doses renal and neurotoxicity
Saven 1993	21 *	0.1 mg/kg/day x 7 continuous i.v.	Myelosuppression
Kobayashi 1994	18 *	6 mg/m <sup>2</sup> /day x 5 i.v. over 1 hour	Myelosuppression
Larson 1996	42 **	21.5 mg/m <sup>2</sup> /day x 5 i.v. over 1 hour	Not reached

\* non-haematopoietic malignancies

\*\* advanced haematological malignancies

### **Discussion on clinical pharmacology**

The cladribine product currently approved and marketed (Leustatin/Leustat) in the Community is a 1 mg/ml solution administered by continuous intravenous infusion. The proposed product LITAK is a more concentrated solution (2 mg/ml), which can be injected subcutaneously.

### **Biopharmaceutic studies**

The applicant did not carry out specific biopharmaceutics studies with LITAK. The results of two studies available in the literature were submitted in the form of bibliographic references, investigating the bioavailability of cladribine following subcutaneous injection. The applicant did not submit individual reports of bioanalytical and analytical methods for the clinical biopharmaceutics documentation provided. Sufficient details about these methods are available in the bibliographical references submitted. These studies show that subcutaneous administration has 100% bioavailability, the AUC being identical to that after intravenous infusion. No direct relationship has been found between plasma systemic exposure of cladribine and intracellular exposure to cladribine nucleotides, the active metabolites. The terminal elimination half-lives of 2-CdA in plasma are long and the retention time of intracellular nucleotide metabolites is prolonged, which supports the intermittent dosing of cladribine, e.g. by subcutaneous bolus injection. The pharmacokinetics of intracellular nucleotides after intravenous and subcutaneous administration of cladribine was shown to be similar. Therefore, no relationship between plasma drug disposition, the route of administration and response is expected, which is also confirmed by clinical results showing no difference in efficacy after intravenous and subcutaneous administration of cladribine. The studies are of high quality and taken together with all the clinical documentation submitted, enable a well-founded and scientifically valid characterisation of the bioavailability of subcutaneous cladribine. No significant new information would be expected from repeating biopharmaceutic studies, and repeating such studies would be considered to be contrary to generally accepted principles of medical ethics. Thus, in this case the proposed format presented by the applicant is acceptable. Although bibliographical data were generated using different formulations of cladribine, and although a different cladribine formulation than LITAK was used in the studies published by Liliemark et al., clinical results have confirmed that there are no significant clinical differences between the different formulations of cladribine including intravenous and subcutaneous administration, and LITAK. Given the present state of scientific knowledge, the bibliographical references provided by the applicant, and the extensive clinical efficacy documentation for LITAK, additional bioavailability/bioequivalence studies are not required.

#### Studies pertinent to pharmacokinetics using human biomaterials

The applicant did not carry out specific plasma protein binding studies with LITAK. The applicant submitted the results of a relevant published plasma protein binding study with cladribine in the format of a bibliographic reference (Albertioni, Hengren et al. 1994). The study is of high quality, and enables a well-founded and scientifically valid characterisation of the protein binding of cladribine in healthy subjects and in patients with leukaemia. Sufficient documentation has been provided on the plasma protein binding of cladribine and adequate information has been included in the SPC. No significant new information would be expected from repeating such study, and repeating such study would be considered to be contrary to generally accepted principles of medical ethics. Thus, in this case the proposed format presented by the applicant is acceptable. Given the present state of scientific knowledge, the bibliographical references provided by the applicant, and the extensive clinical documentation for LITAK, additional plasma protein binding studies are not required.

The applicant has not performed hepatic metabolism studies and interaction studies using human biomaterials. Cladribine is a pro-drug that is metabolised intracellularly following parenteral administration, and subcutaneously administered cladribine is not likely to be primarily affected by a hepatic first pass effect. Furthermore, LITAK should not be used concomitantly with other myelosuppressive medicinal products. Given the present state of scientific knowledge, the conditions of normal use and the contraindication in case of patients with moderate to severe hepatic impairment (Child-Pugh score  $\geq 4$ ) as reflected in the SPC, additional hepatic metabolism studies and interaction studies using human bio-materials, or additional studies using other human biomaterials are not required.

### Human pharmacokinetic studies

The applicant has not conducted pharmacokinetic studies in healthy subjects and initial tolerability studies. This is in agreement with the CPMP Note for Guidance on Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95 rev. 2). Therefore, additional human healthy subjects pharmacokinetic and initial tolerability studies are not required.

The applicant did not carry out specific studies with regard to patient pharmacokinetics or initial tolerability. The applicant submitted the results of patient pharmacokinetics or initial tolerability studies available in the literature in the format of bibliographic references. These studies were of high quality and allowed a well-founded and scientifically valid characterisation of the pharmacokinetics and initial tolerability of cladribine in patients with various haematological malignancies, as well as the provision of adequate information in the SPC. No significant new information would be expected from repeating pharmacokinetics or initial tolerability, and repeating such studies would be considered to be contrary to generally accepted principles of medical ethics. Thus, in this case the proposed format presented by the applicant is acceptable. Given the present state of scientific knowledge, the clinical documentation provided by the applicant, additional pharmacokinetic and initial tolerability studies are not required.

There are no studies investigating the pharmacokinetics of cladribine in special populations. However, 15-18% of a subcutaneous dose of cladribine is eliminated unchanged in the urine, and the fate of the remaining 82-85% (assumed metabolised) has not been described. Since no guidance is available with respect to dose-adjustment, LITAK should be contraindicated in patients with moderate to severe renal impairment (creatinine clearance  $\leq 50$  ml/min) and with moderate to severe hepatic impairment (Child-Pugh score  $\geq 4$ ) (see also Discussion on clinical safety). The contraindications and the lack of information on the pharmacokinetics of cladribine in special populations have been adequately reflected in the SPC.

The applicant has not performed specific studies in patients with hepatic dysfunction and interaction studies in humans. Because cladribine is a pro-drug that is metabolised intracellularly following parenteral administration, subcutaneously administered cladribine is not likely to be primarily affected by a hepatic first pass effect. Given the conditions of normal use reflected in the SPC, namely a contraindication in case of patients with moderate to severe hepatic impairment (Child-Pugh score  $\geq 4$ ), additional studies on intrinsic and extrinsic factors are not required.

### Human pharmacodynamic studies

The applicant has not conducted pharmacodynamic and pharmacokinetic/pharmacodynamic studies in healthy subjects. This is in agreement with the CPMP Note for Guidance on Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95 rev. 2), and additional human healthy subjects pharmacokinetic and initial tolerability studies are not required. The applicant did not carry out specific patient pharmacodynamic and pharmacokinetic/pharmacodynamic studies with LITAK. Several studies available in the literature have demonstrated the pharmacodynamic action correlated to the efficacy of cladribine following subcutaneous injection. The results are reported in sufficient detail to enable a well-founded and scientifically valid characterisation of the pharmacodynamic action of cladribine, of the dose-response and provide valid justification for the dosage and conditions of administration, and allow the provision of adequate information in the SPC. No significant new information would be expected from repeating clinical pharmacodynamic studies, and repeating such studies would be considered to be contrary to generally accepted principles of medical ethics. Given the present state of scientific knowledge, the bibliographical references provided by the applicant, and the intended condition of use as described in the SPC, additional pharmacodynamic studies are not considered necessary.

A change in schedule to 5 days for subcutaneous formulation (as opposed to 7 days for the intravenous formulation) has been introduced. The argument for the change is that a subcutaneous treatment daily for 5 days (on working days) will allow out-patient treatment and thus be more convenient both for patients and the treating team. The dosage regimen for subcutaneous administration of LITAK in HCL is 0.14 mg/kg body weight/day given on 5 consecutive days (total dosage per cycle 0.7 mg/kg). This is essentially the same exposure as that achieved following 7-days administration by intravenous route (administered at a dose of 0.09 mg/kg/day).

No pharmacodynamic interaction studies have been conducted by the applicant and this is acceptable because LITAK is indicated as monotherapy. Nevertheless, the applicant has submitted available experience from the literature with cladribine in combination with other cytotoxic agents in the form of bibliographic references. These studies have shown that haematotoxicity is higher when cladribine is combined with other anti-neoplastic drugs such as anthracyclines, alkylating agents, platinum compounds or immunomodulatory drugs. Concomitant use with other myelosuppressive medicinal products is therefore contraindicated and this is adequately reflected in sections 4.3 and 4.5 of the Summary of Product Characteristics. Therefore, no pharmacodynamic interaction studies with LITAK are considered necessary either on pharmacological grounds or on grounds of the therapeutic use as a monotherapy.

#### Conclusion on the clinical pharmacology

Overall, there is adequate information available on the clinical pharmacology of cladribine. The available published studies submitted as bibliographic references adequately describe the results of bioavailability, pharmacokinetic and the pharmacodynamic studies that are relevant for LITAK. Additional clinical pharmacology studies are unlikely to add any significant new knowledge about the clinical pharmacology of LITAK, and are therefore not considered necessary. Therefore, the requirements in terms of clinical pharmacology documentation as set out in Directive 2001/83/EC, as amended, are considered fulfilled.

#### **Clinical Efficacy**

The first studies with LITAK were initiated by investigators at the University Hospital Insel, Berne in 1992/3 and from 1994 onward co-ordinated by the Swiss Group for Clinical Cancer Research (SAKK).

#### *Main studies in hairy cell leukaemia*

There were two trials of LITAK that included a significant number of patients with HCL. SAKK 32/93 is the main study for the purpose of this application. SAKK 32/95 investigated the use of cladribine administered as a subcutaneous bolus injection. A third study is still ongoing (SAKK 32/98). A summary of the clinical documentation for efficacy submitted is presented in Table 4.

**Table 4: Summary of the clinical trials**

Trial	Treatment	Days	Enrolled	Evaluated	Aggressive lymphoma	Indolent lymphoma			
						HCL	NHL	CLL	LL
PS 1	0.1 mg/kg/day i.v.	7	148	129	37	22	45	22	3
PS 2	0.1 mg/kg/day s.c.	5	165	150	22	-	68	38	22
SAKK 32/93	0.14 mg/kg/day s.c.	5	63	62	-	62	-	-	-
SAKK 39/93	0.1 mg/kg/day i.v. or s.c.	7	40	37	3 §	-	34	-	-
Pilot to 32/95	0.25 mg/kg s.c.	1	15	15	-	15	-	-	-
SAKK 32/95	0.25 mg/kg s.c.	1	59	59	-	59	-	-	-
Pilot to 37/95	0.1 mg/kg/day s.c.¶	3 to 5	19	19 *	-	-	7	9	3
SAKK 37/95	0.1 mg/kg/d s.c.¶	3 or 5	23	21 **	-	-	5	16	-
Pilot Study 3	0.14 mg/kg/day s.c. + interleukin-2	4 or 5	31	31	2 §§	1	18	4	6
	<b>TOTAL</b>		<b>563</b>	<b>523</b>	<b>64</b>	<b>159</b>	<b>177</b>	<b>89</b>	<b>34</b>
SAKK 32/98	0.14 mg/kg/wk s.c. vs. 0.14 mg/kg/day s.c.	5 wks vs. 5 days	ongoing			65 °			

¶, cladribine in combination with cyclophosphamide and prednisone (CCP), pilot study: 3 days (cycles 1 & 2), 4 days (cycles 3 & 4), 5 days (cycles 5 & 6), SAKK study: 5 days for previously untreated patients, 3 days for previously treated patients

\*, only 18/19 patients evaluable for analysis due to 1 early therapy withdrawal

\*\* , only 20/21 patients evaluable for analysis: 1 early therapy withdrawal

°, status of patient enrolment end of May 2002

§, 3/37 patients were classified for IWF D, which is graded as aggressive lymphoma (histological subtype: follicular grade III) according to the R.E.A.L. classification; §§, 2/31 patients with aggressive lymphoma; 1 follicular grade III (IWF D), 1 mantle cell lymphoma IWF F

wk = week, d = day, HCL = hairy cell leukaemia, NHL = indolent non-Hodgkin's lymphoma, CLL = chronic lymphocytic leukaemia, LL = lymphoplasmacytic lymphoma.

#### *Description of the studies*

The response criteria for HCL patients were defined according to the Consensus Resolution (1987). Complete remission (CR) was defined as disappearance of all evidence of disease, i.e. normal peripheral blood counts, absence of hairy cells in the peripheral blood and the bone marrow (TRAP negative), regression to normal of disease-related organomegaly. For partial remission (PR), all of the following criteria had to be met: > 50% improvement or normal peripheral blood counts, circulating hairy cells ≤ 5% of lymphocytes, > 50% reduction of bone marrow infiltration by hairy cells, > 50% reduction of palpable disease-related organomegaly. Time to treatment failure (TTF) was defined as the time between treatment start and progression, relapse, second tumour or death, whichever occurred first.

#### SAKK 32/93

SAKK 32/93 was an open-label, prospective, phase II, multicentre study and involved 14 centres in Switzerland, 3 centres in Germany and one in Austria (von Rohr, Schmitz et al., 2002). Patients with HCL, including the prolymphocytic variant, either newly diagnosed or in progression following

previous treatment (splenectomy, IFN, DCF) were included. No upper age limit was defined as selection criterion. Renal and hepatic impairment were exclusion criteria. *Dose and treatment regimen*: Cladribine was administered as a subcutaneous bolus injection daily for 5 days at a dose of 0.14 mg/kg/day (one treatment cycle). An evaluation followed on day 29. If the patient had progressive disease he/she went directly to a new cycle, but now with i.v. treatment. All others were re-evaluated at day 71. If they at that time were in CR or PR they were observed without further treatment. If the day 71 evaluation showed no response they went on to a “salvage” second cycle which would be with continuous i.v. infusion 0.1 mg/kg/d for 7 days. The cycle could be repeated once after 28 days. Cladribine was supplied by Lipomed and the dosage form was manufactured by the pharmacy at the University Hospital of Berne as a solution of 2 mg cladribine/ml 0.9% sodium chloride. All patients received prophylactic allopurinol for the first 14 days of the study. *Objectives* were evaluation of efficacy after one treatment cycle as measured by remission rate, remission duration and time to treatment failure. Other objectives were safety, changes in the lymphocyte populations, response rate to i.v. salvage therapy (not studied due to low number of patients) and changes in TNF and sIL2R (not done due to economical problems). CR was defined as disappearance of all evidence of disease, normalisation of peripheral counts, absence of hairy cells and reversion of TRAP stain to negative. PR status required normalisation of peripheral blood, reduction of hairy cells to less than 5% of lymphocytes and more than 50% reduction of bone marrow infiltration and of palpable, disease related organomegaly. Duration of CR was measured from the moment CR was first recorded. Duration of PR was measured from start of treatment and both until disease progression. TTF was measured from start of treatment to progression, relapse, second tumour, discontinuation for toxicity or treatment-related death.

#### SAKK 32/95

SAKK 32/95 and its pilot study was an open-label, prospective, phase II, multicentre study and involved 8 centres in Switzerland (Franscini, Tobler et al., 1997). Cladribine was administered as a subcutaneous bolus injection given once only at a dose of 0.25 mg/kg/day (one treatment cycle) to patients with HCL, including the prolymphocytic variant, either newly diagnosed or in progression following previous treatment (splenectomy, IFN, DCF). *Dose and treatment regimen*: Cladribine was administered as a subcutaneous bolus injection given once only at a dose of 0.25 mg/kg/day (one treatment cycle). An evaluation followed on day 71. If the day 71 evaluation showed no response the patient went on to the second cycle which would be with s.c. injection of 0.14 mg/kg/d for 5 days. The cycle could be repeated once after 28 days. Cladribine was supplied by Lipomed and the dosage form was manufactured by the pharmacy at the University hospital of Berne as a solution of 2 mg cladribine/ml 0.9% sodium chloride. *Objectives* were evaluation of efficacy after one treatment cycle as measured by remission rate and remission duration. Other objectives were safety, changes in the lymphocyte populations, response rate to second cycle therapy. CR was defined as disappearance of all evidence of disease, normalisation of peripheral counts, absence of hairy cells and reversion of TRAP stain to negative. PR status required normalisation of peripheral blood, reduction of hairy cells to less than 5% of lymphocytes and more than 50% reduction of bone marrow infiltration and of palpable, disease related organomegaly. Duration of CR was measured from the moment CR was first recorded. Duration of PR was measured from start of treatment and both until disease progression.

#### SAKK 32/98

SAKK 32/98 is an ongoing open-label, prospective, phase III, multicentre study comparing cladribine given daily SC for 5 days with cladribine once weekly for 5 weeks in patients with newly diagnosed HCL including the prolymphocytic variant.

The only phase III study is SAKK study 32/98. This study compares daily versus weekly administration of cladribine in patients with HCL. Patients enrolled are those with HCL (classic and prolymphocytic variant), newly diagnosed or progressive disease after previous treatment. They are randomised to one of the two arms:

Arm A: 0.14 mg/kg/day x 5 days, bolus subcutaneously (1 cycle)  
Arm B: 0.14 mg/kg/week x 5 weeks, bolus subcutaneously (1 cycle)  
If no response 2<sup>nd</sup> cycle: 0.14 mg/kg/day x 5 days, bolus subcutaneously

*Dose and treatment regimen:* Cladribine is administered as a subcutaneous bolus injection at a dose of 0.14 mg/kg/day and by randomisation given either daily for 5 days only or once weekly for 5 weeks. An evaluation follows on day 71. If the day 71 evaluation shows no CR or PR the patient goes on to the second cycle with s.c. injection of 0.14 mg/kg/d for 5 days. In an amendment to the protocol of April 2001 the recommendation for the second cycle treatment has been changed from cladribine to rituximab (in a SAKK protocol). Cladribine is supplied by Lipomed and the dosage form is a solution of 2 mg cladribine/ml 0.9% sodium chloride. *Objectives:* Initially, the primary objective of this study was to compare the acute haematotoxicity of the two regimens using white blood cell (WBC) and neutrophil counts as endpoints. Secondary endpoints included acute infection rate, response rate, remission duration, relapse-free survival. In an amendment of April 2000 the only primary objective was defined as changes in the WBC count. CR was defined as disappearance of all evidence of disease, normalisation of peripheral counts, absence of hairy cells and reversion of TRAP stain to negative. PR status requires normalisation of peripheral blood, reduction of hairy cells to less than 5% of lymphocytes and more than 50% reduction of bone marrow infiltration and of palpable, disease related organomegaly. Duration of CR is measured from the moment CR was first recorded. Duration of PR is measured from start of treatment and both until disease progression. With the amendment of April 2000 making WBC changes the only primary objective a total of 100 patients will be needed to detect a 50% reduction in the toxicity. The accrual rate is expected to be 30 patients/year.

## Results

### SAKK 32/93

The study accrual period was 1993-1995. The number of patients included was 63. One patient was not eligible due to a concomitant cancer and one was not evaluable due to start of IFN two weeks after therapy with 2-CdA. 61 patients were therefore eligible and evaluable. The median age was 54 years (range: 28-85, with 10 and 4 patients  $\geq$  68 and 75, respectively). 33 patients were newly diagnosed, 15 had relapse after a previous treatment and 14 had progressive disease under a previous treatment other than 2-CdA. Only 2 patients had the prolymphocytic variant of the disease.

None of the patients actually received the salvage i.v. therapy; in one patient who did not achieve a primary CR or PR no further therapy was given due to medical problems unrelated to 2-CdA. One other patient who needed more than one treatment cycle received the sc. bolus by mistake.

A summary of the clinical efficacy results is shown in Table 5. The efficacy in patients who were newly diagnosed (n=33) was comparable to that in patients who had relapsed or were refractory (n=30) to previous therapy. Most responses in the form of PR's occurred early (i.e. within the first 10 weeks), but the response quality slowly improved and the PR's converted to CR's in the follow-up period. Only 3 patients received more than one treatment cycle. As seen below 60/62 patients or 97% achieved CR or PR, only 2 patients did not reach this status.

Possible associations between patient characteristics/ baseline parameters and the achievement of CR were examined by univariate and multivariate analyses. Only normal haemoglobin was associated with a higher remission and among patients with prior therapy females had a lower probability to achieve CR. Pretreatment with splenectomy or interferon did not affect the response rate or TTF but patients receiving chemotherapy pretreatment only had a lower response rate and a shorter TTF.

Median time to treatment failure was 38 months. The failure-free proportion was 0.90 at one year, 0.76 at 2 years and 0.65 at 3 years. The reasons for treatment failure in the 20 patients were: relapse after CR 8 patients, progression after PR 7, secondary tumours 3, deaths from other causes 2. At 3 years, 66% were still in remission. Median survival has not been reached. At one year, 97% were alive and 93% at two years.

**Table 5: Summary of clinical efficacy results for SAKK 32/93 (HCL)**

	Best response at any time	At 4 weeks	At 10 weeks	At any follow-up
CR	47/62 (76%)	7/62 (11%)	11/62 (18%)	46/62 (74%)
PR	13/62 (21%)	41/62 (66%)	38/62 (61%)	7/62 (11%)
CR+PR	60/62 (97%)	48/62 (77%)	49/62 (79%)	53/62 (86%)
TTF (median)	38 months			

### SAKK 32/95

The results are based on a report on the preliminary results of the final analysis for all 59 patients (report dated June 19, 2001). The study period was 1996 to 1998. The number of patients entered was 59. The median age was 56 years. Forty-three patients were newly diagnosed, 11 had relapse after a previous treatment and 5 had progressive disease under a previous treatment other than 2-CDA. Five patients had the prolymphocytic variant of the disease. Thirty-one of 59 patients received the second cycle, 3 patients received 3 cycles. Only 11/59 (19%) of the patients achieved CR or PR at day 71 (the corresponding value for the 15 patients in the pilot study 32/95 was 27%). Most of the patients not responding to the first bolus injection responded to the second cycle of therapy and the final CR+PR for the interim population of the SAKK study (n=46, June 1998) was 72%. There is no report of remission duration or of survival.

### SAKK 32/98

The study started in September 1998. As of March 2002, 50 patients had entered the study. No efficacy results are available.

#### *Historical control*

In published series mainly using 0.1 mg/kg/d cont. i.v. cladribine, for 7 days, totalling 1754 patients, the pooled response rate was 92%, with 68% achieving a complete remission, and a median TTF above 36 months (Cheson, Sorensen et al. 1998; Estey, Kurzrock et al. 1992; Seymour, Kurzrock et al. 1994; Dann, Gillis et al. 1994; Piro, Ellison et al. 1994; Tallman, Hakimian et al. 1996; Hoffman, Janson et al. 1997; Lauria, Rondelli et al. 1997; Saven, Burian et al. 1998; Bastie, Cazals-Hatem et al. 1999; Jehn, Bartl et al. 1999; Robak, Blasinska-Morawiec et al. 1999; Zinzani, Magagnoli et al. 2000). In a larger review of 54 published series, totalling 3294 (55% pre-treated) patients, the response rate was 93% with 72% complete remission after i.v. cladribine.

In comparison to cladribine, deoxycoformycin (Pentostatin) has a response rate of 63% - 97%, with 33% - 92% of CR (Jaiyesimi, Kantarjian et al. 1993, Annino, Ferrari et al. 1994; Brogden and Sorkin 1993). IFN- $\alpha$  is also effective in the induction of remission in HCL, with a remission rate of 78% to 100%, although complete remissions are only observed in 0 - 40% of the patients (Damasio, Bernasconi et al. 1987; Federico, Frassoldati et al. 1994; Jaiyesimi, Kantarjian et al. 1993).

#### *Clinical studies in special populations*

##### Elderly patients

LITAK has not been specifically investigated in the elderly patients. 7 - 10% of the patients were older than 75 years of age in studies PS1, PS2 and SAKK 32/93. The age distribution of patients in studies PS1, PS2 and SAKK 32/93 was similar to that in a large cohort study of 979 patients studied by Cheson et al (1999), which reported a lower response rate and survival were in patients  $\geq$  68 years of age. In the LITAK studies the efficacy was comparable in all age groups but numbers in the high age groups were small: in the 32/93 HCL study there were 3 /4 responders among patients 75 years or older. In PS1 5/9 were responders and in PS2 5/12. Thus 13/25 (52%) patients aged 75 years or more had complete or partial response.

##### Discussion on clinical efficacy

Cladribine is reported to be highly effective as primary and secondary treatment of HCL showing a significant benefit with regard to response rate and response duration if compared to alternative treatments, such as interferon- $\alpha$ . Although deoxycoformycin is also an effective drug for the treatment

of HCL, cladribine has been shown to be less toxic. In HCL a single cycle of 5 days with a total dose of 0.7 mg/kg body weight is sufficient to induce a durable and in the majority of cases complete remission with tolerable toxicity. In twelve reported series totalling 1754 patients, the response rate was 92%, with 68% achieving a complete remission. Relapsing patients usually respond to a second or third cycle of cladribine. Most clinicians consider cladribine as the standard for first and second line therapy.

The applicant did not carry out randomised controlled trials in the target population. However, the results of the uncontrolled submitted by the applicant using LITAK have shown a high level of efficacy following subcutaneous administration of cladribine in the treatment of patients with HCL, and the efficacy of LITAK is similar to that reported in the literature following intravenous cladribine. Source data verifications of SAKK 32/93 and SAKK 32/95 revealed some minor protocol deviations with respect to entry criteria, some discrepancies between the hospital file and the CRF, some missing data, misinterpretations and adjustment of dates, all typical of non-monitored trials but not affecting the main conclusions from the study.

In conclusion, SAKK 32/93 showed that cladribine at the recommended subcutaneous dose of 0.14 mg/kg body weight/day for 5 consecutive days has the same level of efficacy in patients with HCL as 0.1 mg/kg/day administered by continuous intravenous infusion for 7 days. For HCL, the response rate of 97% with 76% CR and a long-lasting remission duration (73% at 4 years) observed for LITAK was comparable to that reported for i.v. cladribine, and superior to that reported for interferon-alpha and pentostatin, which also shorter remission durations. In comparison to these agents, the efficacy results with cladribine are clearly outstanding. SAKK 32/95 showed that low-dose single-shot cladribine leads to a significantly lower response-rate than standard 5-day schedules.

#### Conclusion on the clinical efficacy

The results of the uncontrolled clinical trials submitted by the applicant are sufficient to establish the clinical efficacy of LITAK in the proposed indication. Given the present state of scientific knowledge and the uncontrolled clinical documentation provided, additional randomised controlled studies to compare subcutaneous versus intravenous cladribine or other anticancer agents are unlikely to add any significant new knowledge about the clinical efficacy profile of subcutaneous cladribine in the treatment of hairy cell leukaemia, and are therefore considered unnecessary, and the requirements in terms of demonstration of clinical efficacy as set out in Directive 2001/83/EC, as amended, are considered fulfilled.

#### **Clinical safety**

##### *Patient exposure*

##### *Adverse events and serious adverse event/deaths*

The most important severe toxicity with cladribine was infection and haematological toxicity (Table 6). All other toxicity was mild or absent and generally less pronounced than following treatment with other types of chemotherapy. The haematological changes were especially neutropenia during the treatment and a very prolonged lymphocytopenia during and following the treatment, factors which both contribute to the high infection rate, which for the diseases treated, especially HCL and CLL, is an inherent characteristic of the disease. Late complications were seen in all studies. In the 341 patients in PS 1, PS 2 and 32/93 12 late severe AEs occurred, 4 pneumonias, 6 sepsis cases, one *Nocardia* abscess and one *Salmonella* infection.

Very common adverse reactions observed during the three most relevant clinical trials with LITAK in 279 patients treated for various indications and in 62 patients with HCL were myelosuppression, especially severe neutropenia (41% (113/279), 98% (HCL, 61/62)), severe thrombocytopenia (21% (58/279), 50% (HCL, 31/62)), severe anaemia (14% (21/150), 55% (HCL, 34/62)), severe immunosuppression/lymphopenia (63% (176/279), 95% (HCL, 59/62)), infections (39% (110/279), 58% (HCL, 36/62)), and fever (up to 64%).

Culture-negative fever following treatment with cladribine occurs in 10-40% of patients with HCL and is rarely observed in patients with other neoplastic disorders. Skin rashes (2 - 31%) are mainly described in patients with other concomitant medications known to cause rash (antibiotics and/or

allopurinol). Gastrointestinal adverse events like nausea (5 - 28%), vomiting (1 - 13%), and diarrhoea (3 - 12%) as well as fatigue (2 - 48%), headache (1 - 23%), and decreased appetite (1 - 22%) have been reported during treatment with cladribine. LITAK is unlikely to cause alopecia; mild and transient alopecia for a few days was observed in 4/523 patients during the treatment with LITAK, but could not clearly be associated with cladribine.

**Table 6: Infections and myelotoxicity in all studies with LITAK**

Trial	Treatment	Days	No. pts.	AE (% pts.)	Infections	Lympho- cytopenia <sup>°</sup>	Neutropenia <sup>°</sup>	Thrombo- cytopenia <sup>°</sup>	Deaths
				%	%	%	%	%	No.
PS 1	0.1 mg/kg/day i.v.	7	129	81	50	65	53	26	71
PS 2	0.1 mg/kg/day s.c.	5	150	39	30	61	30	16	48
SAKK 32/93	0.14 mg/kg/day s.c.	5	62	64	58	95	98	50	5
SAKK 39/93	0.1 mg/kg/day i.v. or s.c.	7	37	78	49	97	22	11	7
Pilot 32/95 to	0.25 mg/kg s.c.	1	15	53	40	100	80	13	2
SAKK 32/95	0.25 mg/kg s.c.	1	59	47	22	70	71	17	3
Pilot 37/95 to	0.1 mg/kg/day s.c. CCP ¶	3 to 5	19	N/A	58	53*	42	5	6
SAKK 37/95	0.1 mg/kg/day s.c. CCP ¶	3 or 5	21	87	80	65	80	25	8
Pilot Study 3	0.14 mg/kg/day s.c. + IL-2	4 or 5	31	N/A	26	55*	N/A	6	7
	<b>TOTAL</b>	<b>1-7</b>	<b>523</b>	<b>39-87</b>	<b>22-80</b>	<b>44-100</b>	<b>22-98</b>	<b>5-50</b>	<b>157</b>

AE, adverse event; ¶ cladribine in combination with cyclophosphamide and prednisone (CCP), pilot study: 3 days (cycles 1 & 2), 4 days (cycles 3 & 4), 5 days (cycles 5 & 6), SAKK study: 5 days for previously untreated patients, 3 days for previously treated patients; N/A, not assessed  
\*, only value for leukopenia available; °, WHO grade ≥ 3

Adverse reactions that have been reported including information on frequency are listed in the table 7. The frequencies are defined as follows: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), very rare (<1/10,000) including isolated reports.

**Table 7: Adverse reactions that have been reported for LITAK**

Infections and infestations	Very common: infections (e.g. pneumonia, septicaemia)
Neoplasms benign, malignant and unspecified	Common: second malignancies
Vascular disorders	Very common: pancytopenia/myelosuppression, purpura Common: petechiae, haemorrhages
Immune system disorders	Very common: immunosuppression Uncommon: haemolytic anaemia Very rare: graft-versus-host disease, tumour lysis syndrome
Metabolism and nutrition disorders	Very common: decreased appetite
Nervous system disorders	Very common: headache, dizziness Common: insomnia, anxiety Uncommon: somnolence, paraesthesia, weakness, lethargy, polyneuropathy, confusion, ataxia Very rare: depression, epileptic seizure
Eye disorders	Uncommon: conjunctivitis Very rare: blepharitis
Cardiac disorders	Common: tachycardia, heart murmur, hypotension, epistaxis, myocardial ischaemia *
Respiratory, thoracic and mediastinal disorders	Very common: abnormal breath sounds, abnormal chest sounds, cough Common: shortness of breath, pulmonary interstitial infiltrates mostly due to infectious aetiology, mucositis Uncommon: pharyngitis Very rare: lung embolism
Gastrointestinal disorders	Very common: nausea, vomiting, constipation, diarrhoea Common: gastrointestinal pain, flatulence
Hepato-biliary disorders	Common: reversible, mostly mild increases in bilirubin and transaminases Very rare: cholecystitis
Skin and subcutaneous tissue disorders	Very common: rash, localised exanthema, diaphoresis Common: pruritus, skin pain, erythema, urticaria Uncommon: phlebitis
Musculoskeletal and connective tissue disorders	Common: myalgia, arthralgia, arthritis, bone pain
General disorders and administration site conditions	Very common: injection site reactions, fever, fatigue, chills, asthenia Common: oedema, malaise, pain Uncommon: cachexia Very rare: amyloidosis

Non-haematological adverse reactions were generally mild to moderate in severity.

A total of 265 patients received s.c. bolus injections in studies PS 2, 32/93 and 32/95. 16 reactions were reported in 591 cycles of therapy, 12 were mild, 3 moderate and 1 severe. The reactions were induration of the skin, rash, inflammation. Skin rash is also frequently observed after i.v. cladribine, in about 31%. Adverse reactions related to skin and subcutaneous tissue are mostly mild or moderate and transient, usually resolving within a cycle interval of 30 days.

Serious adverse events like ileus, severe hepatic failure, renal failure, cardiac failure, atrial fibrillation, cardiac decompensation, apoplexy, neurological disturbances in speech and swallowing, tumour lysis syndrome with acute renal failure, transfusion-related graft-versus-host disease, Stevens-Johnson syndrome / Lyell syndrome (toxic epidermal necrolysis), haemolytic anaemia, hypereosinophilia (with erythematous skin rash, pruritus, and facial oedema) are rare.

Long-term immunosuppression is a concern associated with the use of cladribine. A detailed analysis of three clinical trials (PS1, PS2 and SAKK 32/93) has shown that there is no clear evidence that long-lasting lymphocytopenia induced by LITAK is associated with any serious complications. Despite a recovery time of up to 2 years of T cells, only 2 (3.2%) patients in SAKK 32/93 experienced late infection.

A total of 157 deaths in 523 patients were reported. The majority of deaths related to the medicinal product are due to infectious complications. Further rare cases with fatal outcome, reported in association with LITAK chemotherapy, were second malignancy, cerebro- and cardiovascular infarctions, graft-versus-host disease caused by multiple transfusions of non-irradiated blood, as well as tumour lysis syndrome with hyperuricaemia, metabolic acidosis, and acute renal failure. The most frequent causes of death were: disease progression (13%), pneumonia/sepsis (5.7%), progression and pneumonia/sepsis (2.7%), unknown / lost to follow-up (2.1%), second malignancy (1.0%) and other causes (< 1%).

Secondary malignancies or transformations to higher malignancy grades were diagnosed in 17 patients (3%). All except 4 had received prior treatment. In 8 of the cases the time from cladribine treatment to the diagnosis of the second neoplasm was 6 months. The frequency of secondary malignancy following treatment with LITAK was 3.4% in all 232 HCL patients treated during the past decade in one of the Swiss clinical trials. A review of the incidence of second malignancy in various HCL studies from 1970 onwards has been presented. In 9 studies with cladribine, secondary malignancies were observed ranging from 0% (N=23) (Zinzani, Magagnoli et al. 2003) to 9.5% (N=379) (Goodman, Burian et al. 2003), after a median follow up time of 8.5 and 7.0 years, respectively. In the four larger studies, observed/expected ratios (based on the U.S. National Cancer Institute SEER data) varied from 1.22 (N=126, 95% CI: 0.4 to 2.7) (Kurzrock, Strom et al. 1997) to 1.50 (N=882, 95% CI: 1.14 to 1.93) (Cheson, Vena et al. 1999), 1.88 (N=358, 95% CI: 1.2 to 2.7) (Saven, Burian et al. 1988) and 2.03 (N=379, 95% CI: 1.5 to 2.7) (Goodman, Burian et al. 2003).

In comparison, the frequency of secondary malignancies following deoxycoformycin in one study was 6.9% with an observed/expected ratio of 1.43 (N=337, 95% CI: 0.93 to 2.10) (Cheson, Vena et al. 1999), in another 4.2% (N=24) (Kraut, Grever et al. 1994) and in a third 17.9% (N=28) (Johnston, Eisenhauer et al. 2000). Interferon alpha treatment in 4 studies led to frequencies of 8.2% (N=97) (Troussard, Henry-Amar et al. 1994), 5.7% (N=53) (Smith, Longo et al. 1991), 3% (N=200) (Pawson, A'Hern et al. 1996) and 2.9% (N=35) (Berman, Heller et al. 1990), while in one study as many as 18.8% (N=69) patients developed secondary malignancies with an observed/expected ratio of 4.33 (Kampmeier, Spielberger et al. 1994; Spielberger, Mick et al. 1994).

#### *Laboratory findings*

The number of patients analysed for laboratory safety was low. Mild increase in creatinine, transaminases, alkaline phosphatase and bilirubin have been observed in a minority of patients. A summary of biochemistry data in HCL has been provided. In study SAKK 32/93, three patients had a mild or moderate increase of creatinine levels. Mild transaminase elevation was observed in 5 patients. A mild elevation of alkaline phosphatase was observed in 5 patients, and a moderate elevation in one patient. Mild elevation of bilirubin was observed in 14 patients and moderate elevation in 1 patient. Similar results were observed for LDH.

#### *Safety in special populations*

The experience with LITAK in patients above 75 years of age is limited. Apart from asymptomatic transient and mild elevation of creatinine or liver enzymes, no specific age-related complications were observed. Among 11 deaths in this population 3 were possibly related to treatment (one cardiac, 2 infectious episodes).

## **Discussion on clinical safety**

The safety issues are dominated by infections and haematologic toxicity and a long-standing immune suppression, which is only accompanied by relatively few delayed infections and a rate of secondary neoplasias which does not seem increased compared to deoxycoformycin and interferon-alpha. Apart from myelosuppression, the clinical safety profile of cladribine is unremarkable. Like a number of other anticancer drugs, it has a potential for neurotoxicity and possibly cardiac and renal toxicity.

During the first month following treatment, myelosuppression is most notable and red blood cell or platelet transfusions may be required. Cladribine also induces marked and prolonged yet transient reduction in the number of normal peripheral lymphocytes including T cells, B cells and natural killer (NK) cells. No differences in lymphocyte subpopulations after administration of LITAK subcutaneously and by intravenous route were observed (data not shown). NK cells recover during the first 3-12 months, while B-cells and CD4 cells recover as late as 1-2 years or longer after treatment. An increased incidence of opportunistic infections is expected during, and for 6 months following, therapy with cladribine. The association between a prolonged immune suppression and late occurring opportunistic infections remains an issue of debate. Several studies do not show a correlation, and this might be explained by the relatively rapid recovery of NK cells. Other studies showed that pre-existing immune suppression due to heavy prior treatment and concurrent therapy with corticosteroids may be important factors associated with late occurring opportunistic infections. Patients with symptoms of bone marrow depression should be treated with caution since further suppression of bone marrow function should be anticipated.

Therapeutic risks and benefits should be carefully evaluated in patients with active or suspected infections. The risk of severe myelotoxicity and long-lasting immunosuppression is increased in patients with a disease-related bone marrow infiltration or a previous myelosuppressive treatment. Dose reduction and regular monitoring of the patient is required in such cases. Pancytopenia is normally reversible and the intensity of bone marrow aplasia is dose-dependent. Careful and regular monitoring of peripheral blood counts is essential during, and for 2 to 4 months following, treatment with cladribine to detect potential adverse reactions and consequent complications (anaemia, neutropenia, thrombocytopenia, infections, haemolysis or bleedings), and to survey haematologic recovery. Fever of unknown origin frequently occurs in patients treated for hairy cell leukaemia, and is manifested predominantly during the first 4 weeks of therapy. The origin of febrile events should be investigated by appropriate laboratory and radiologic tests. Less than a third of febrile events are associated with a documented infection. In case of fever related to infections or agranulocytosis, an antibiotic treatment is indicated. Although anti-infective prophylaxis is not generally recommended, it may be beneficial for patients immunocompromised prior to therapy with cladribine or for patients with a pre-existing agranulocytosis. These warnings and special precautions for use are adequately reflected in the SPC (4.4). The immunosuppression, the risk of long-term lymphocytopenias, and the risk of opportunistic infections with LITAK are adequately reflected in the SPC (4.8).

Treatment with nucleoside analogues is associated with the occurrence of second malignancies. Secondary malignancies are expected to occur in patients with hairy cell leukaemia. Their frequency varies widely, ranging from 2% to 21%. The peak risk is at 2 years after diagnosis with a median between 40 and 66 months. The cumulative frequencies of second malignancy are 5%, 10-12% and 13-14% following 5, 10 and 15 years respectively after diagnosis of hairy cell leukaemia. Following cladribine, the incidence of second malignancies ranges from 0% to 9.5% after a median observation period of 2.8 to 8.5 years. The frequency of second malignancy following treatment with LITAK was 3.4% in all 232 hairy cell leukaemia patients treated during a 10-year period. The highest incidence of second malignancy with LITAK was 6.5% after a median follow up of time of 8.4 years. There was no evidence that cladribine-treated patients have a higher frequency of secondary malignancies than patients treated with alpha-interferon or deoxycoformycin. However, the incidence of secondary malignancies was significantly higher compared to the general population. Therefore, patients treated with cladribine should be regularly monitored. Warnings about secondary malignancies and regular monitoring as a precaution are adequately reflected in the SPC (4.4). The applicant has also committed to provide the CPMP with an annual follow-up report on second malignancies in SAKK studies pilot 1, 32/93, 32/95 and 32/98.

In patients with a high tumour burden, prophylactic allopurinol therapy to control serum levels of uric acid, together with adequate or increased hydration, should be commenced 24 hours before the start of

chemotherapy. A daily oral dose of 100 mg of allopurinol is recommended for a period of 2 weeks. In case of an accumulation of the serum uric acid above the normal range, the dose of allopurinol may be increased to 300 mg/day. These precautions are adequately reflected in the SPC (4.4).

LITAK has not been specifically investigated in the elderly patients. Since the experience with LITAK in those above 75 years is limited, caution and regular monitoring of blood counts and hepatic and renal function are recommended when treating patients who are more than 75 years old. This is adequately reflected in the SPC (4.2).

There is concern on the safety of LITAK in patients with renal or hepatic dysfunctions (see also Discussion on human pharmacokinetic studies). There were 3 cases of renal failure, 5 of severe liver injury, 3 of mild elevation in serum creatinine and 12 with increases in serum transaminases. Although there are other explanations for some of these such as pre-existing disorders or tumour lysis syndrome, there still remains concern on the safety of LITAK in patients with renal or hepatic dysfunctions. Since no guidance is provided with respect to dose-adjustment, LITAK is contraindicated in patients with moderate to severe renal impairment (creatinine clearance  $\leq$  50 ml/min) and with moderate to severe hepatic impairment (Child-Pugh score  $\geq$  4). Adequate information has been included in the SPC (4.2, 4.3, 4.4 and 5.2).

No interaction studies have been carried out and since the haematotoxicity is higher when cladribine is combined with other anti-neoplastic drugs such as anthracyclines, alkylating agents, platinum compounds or immunomodulatory drugs, LITAK should not be used concomitantly with other myelosuppressive medicinal products. LITAK has therefore been contraindicated for concomitant use with other myelosuppressive medicinal products, and the information is adequately reflected in the SPC (4.3, 4.5).

#### Conclusion on the clinical safety

The documentation submitted by the applicant is considered sufficient to establish the safety of LITAK in the proposed indication, and the implications of the toxicity profile of LITAK are adequately reflected in the Summary of Product Characteristics. The applicant has committed to conduct a prospective long-term screening for secondary malignancies. Besides the screening for secondary malignancies, additional studies to further characterise the safety profile of cladribine are not considered necessary. Overall, the requirements in terms of demonstration of clinical safety as set out in Directive 2001/83/EC, as amended, are considered fulfilled.

### **5 Overall conclusions, benefit/risk assessment and recommendation**

#### **Quality**

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the benefit/risk balance of the product. Preclinical pharmacology and toxicology

Cladribine is preferentially concentrated in lymphocytes by conversion to its active metabolite 2-CdATP. Cladribine is toxic to hematopoietic cells, especially to lymphoid and various malignant cells. It acts in similar doses on proliferating and resting cells and has no effect on non-haematopoietic tissues and limited activity in solid tumours. The results of published pharmacological and toxicological tests have shown the potential toxicity of LITAK, undesirable toxic effects that might occur under the proposed conditions of use, and its pharmacological properties. Overall, it can be concluded that the information on the pharmacology and toxicology of cladribine is comprehensive, that the level of safety is well documented and is acceptable for its proposed use. Based on the similar bioavailability after intravenous and subcutaneous administration, the pharmacological and toxicological data published in the scientific literature are relevant for the proposed product LITAK, and cover all aspects of the safety assessment. The essential data derived from pre-clinical studies, which pertain to human risk, have been incorporated into the Summary of Product Characteristics. Additional non-clinical pharmacology or toxicological studies are not necessary, and the requirements in terms of pharmacological and toxicological documentation as set out in Directive 2001/83/EC, as amended, are considered fulfilled.

### **Efficacy**

The formulation of LITAK, 10 mg cladribine in 5 ml physiological sodium chloride solution, enables a 5-day regimen of subcutaneous bolus injection that is therapeutically similar to the standard 7-day continuous intravenous infusion regimen. Concerning the clinical pharmacology, there is adequate and comprehensive information available, and this is based largely on the published results of relevant studies available as bibliographical references, rather than studies conducted by the applicant. It is acknowledged, however, that it would be contrary to generally accepted principles of medical ethics to repeat such clinical trials in patients. Additional clinical pharmacology studies are therefore not considered necessary.

The results of the uncontrolled clinical trials submitted by the applicant are sufficient to establish the clinical efficacy of LITAK in the proposed indication. The SAKK studies using LITAK have shown a high efficacy of subcutaneous administration of cladribine in the treatment of patients with HCL, and the efficacy of LITAK is similar to that reported in the literature for intravenous cladribine. Based on the clinical documentation submitted, and the extensive clinical experience with cladribine, further clinical studies to demonstrate the efficacy of subcutaneous cladribine in the proposed indication are not considered necessary. The requirements in terms of demonstration of clinical efficacy as set out in Directive 2001/83/EC, as amended, are considered fulfilled.

### **Safety**

The main toxicity with cladribine is a high frequency of myelosuppression, prolonged lymphocytopenia and immune suppression and an increased infection rate including late occurring and opportunistic infections. Other toxicity has generally been mild. The subcutaneous administration by bolus injection was well tolerated and local reactions to the s.c. injection was reported in less than 3% of the cycles. The incidence of secondary neoplasias with cladribine was not higher than that observed for other agents, yet it is higher than expected in the general population, so that monitoring and annual reporting of secondary neoplasias as a follow-up measure are required. Otherwise, additional clinical studies to further characterise the safety profile of cladribine are not considered necessary. Overall, the requirements in terms of demonstration of clinical safety as set out in Directive 2001/83/EC, as amended, are considered fulfilled.

### **Benefit/risk assessment**

The overall response rates and remission duration observed in the clinical trials using LITAK in newly diagnosed and in pre-treated patients with HCL are comparable with the results described in the literature for intravenous cladribine. Further, the data show that LITAK at the recommended subcutaneous dose of 0.14 mg/kg body weight/day for 5 consecutive days has a similar level of efficacy in patients with HCL as 0.1 mg/kg/day administered by continuous intravenous infusion for 7 days. The 5-day subcutaneous schedule that is proposed for LITAK may be more convenient than the 7-day intravenous regimen. The main toxicity of cladribine is haematological whilst other types of toxicities have generally been mild. In conclusion LITAK administered s.c. has a positive benefit/risk ratio in the treatment of patients with HCL.

**Recommendation**

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of LITAK in the treatment of hairy cell leukaemia was favourable and therefore recommended the granting of the marketing authorisation.

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