Cladribine *(BAN, USAN, rINN)*

2-Chlorodeoxyadenosine; Cladribina; Cladribinum; Kladribiini; Kladribin; RWJ-26251; RWJ-26251-000. 2-Chloro-2′-deoxyadenosine.

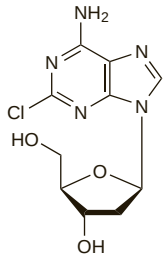
Кладрибин

$C_{10}H_{12}ClN_5O_3$ = 285.7.

CAS — 4291-63-8.

ATC — L01BB04.

ATC Vet — QL01BB04.



Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Cladribine). A white or almost white crystalline powder. It exhibits polymorphism. Slightly soluble in water and in methyl alcohol; soluble in dimethyl sulfoxide; practically insoluble in acetonitrile. Store at a temperature of 2° to 8°. Protect from light.

USP 31 (Cladribine). Store at a temperature of 2° to 8°. Protect from light.

Stability. Cladribine shows increased degradation in glucose 5%, therefore this diluent should not be used. Cladribine in sodium chloride 0.9% is stable for at least 24 hours at room temperature and ambient lighting in PVC infusion containers.

The manufacturers recommend that cladribine should be stored at 2° to 8° and protected from light.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p.635 and p.639.

Cladribine produces severe myelosuppression, including neutropenia, anaemia, and thrombocytopenia, especially at high doses. Transfusion of blood products may be required. Prolonged CD4 lymphopenia with a nadir at 4 to 6 months also develops. Prolonged bone-marrow hypocellularity may also occur, although it is not clear if this is due to the drug or underlying disease. Haemolytic anaemia has also been reported. Severe infections can occur, and may be fatal. Myelodysplastic syndrome has been reported rarely.

Other adverse effects include fever, chills, diaphoresis, fatigue, malaise, mild nausea and gastrointestinal disturbances, rashes, pruritus, purpura, headache, anxiety, dizziness, abnormal breath and/or chest sounds, cough, dyspnoea, oedema, tachycardia, hypotension, arthralgia, and myalgia. Reversible, mild increases in bilirubin and hepatic transaminases are common. Rare adverse events include hepatic, renal, or cardiac failure, atrial fibrillation, and hypereosinophilia; tumour lysis syndrome can occur, and may be fatal.

Very high doses of cladribine have been associated with severe renal and nervous system toxicity as well as myelosuppression. Severe neurotoxicity is rare at currently recommended doses, but confusion, neuropathy, ataxia, insomnia, and somnolence have occurred.

Carcinogenicity. As with some other antimetabolites (see p.635), Epstein-Barr virus-related lymphoma has been reported after cladribine therapy.[1] A study found that in patients with chronic lymphocytic leukaemia, treatment with cladribine did not increase the risk of secondary malignancies when compared with treatment with alkylating agents and combination therapy. However, lung cancers occurred more frequently with cladribine treatment.[2]

1. Niesvizky R, *et al.* Epstein-Barr virus-associated lymphoma after treatment of macroglobulinemia with cladribine. *N Engl J Med* 1999; **341:** 55.
2. Robak T, *et al.* Second malignancies and Richter's syndrome in patients with chronic lymphocytic leukaemia treated with cladribine. *Eur J Cancer* 2004; **40:** 383–9.

Precautions

For the precautions necessary with antineoplastics, see p.641. Careful haematological monitoring is recommended, especially during the first 4 to 8 weeks of therapy. Renal and hepatic function should also be monitored periodically.

Pharmacokinetics

Plasma-cladribine concentrations after intravenous infusion show either a biphasic or triphasic decline, with terminal half-lives ranging from 3 to 22 hours. A bi-exponential decline has been reported after subcutaneous injection, with an initial and terminal half-life of about 2 and 11 hours, respectively. Cladribine is extensively distributed and penetrates into the CNS. It is about 20% bound to plasma proteins. Cladribine is phosphorylated within cells by deoxycytidine kinase to form 2-chlorodeoxyadenosine-5′-monophosphate which is further phosphorylated to the diphosphate by nucleoside monophosphate kinase and to the active metabolite 2-chlorodeoxyadenosine-5′-triphosphate (CdATP) by nucleoside diphosphate kinase.

◊ References.

1. Liliemark J. The clinical pharmacokinetics of cladribine. *Clin Pharmacokinet* 1997; **32:** 120–31.

Uses and Administration

Cladribine is a chlorinated purine nucleoside analogue that inhibits DNA synthesis and repair, particularly in lymphocytes and monocytes. It is used as an antimetabolite antineoplastic for the treatment of lymphoid malignancies including hairy-cell leukaemia (p.654) and chronic lymphocytic leukaemia (p.653). It has also been used in indolent low-grade non-Hodgkin's lymphomas (p.656), histiocytic syndromes (p.650), and in Waldenström's macroglobulinaemia (p.658).

The recommended intravenous dose of cladribine in hairy-cell leukaemia is a single course of 90 micrograms/kg (3.6 mg/m^2) daily for 7 days by continuous infusion. If the patient does not respond to the initial course, they are unlikely to respond to further doses. Cladribine is also given subcutaneously in a dose of 140 micrograms/kg (5.6 mg/m^2) daily for 5 consecutive days.

For the treatment of chronic lymphocytic leukaemia the recommended intravenous dose is 120 micrograms/kg (4.8 mg/m^2) daily for 5 consecutive days of a 28-day cycle; the infusion is given over 2 hours. Response should be determined every 2 cycles, and once maximum response has occurred a further 2 cycles of treatment are recommended, up to a maximum of 6 cycles. Patients who do not respond with a lymphocyte reduction of 50% or more after 2 cycles should not receive further therapy. Cladribine is also given subcutaneously in a dose of 100 micrograms/kg (4 mg/m^2) daily for 5 consecutive days. This dose of subcutaneous cladribine is also licensed in some countries for the treatment of indolent non-Hodgkin's lymphoma and Waldenström's macroglobulinaemia.

An oral formulation of cladribine is under investigation for the management of multiple sclerosis (see below); parenteral cladribine has also been used. Oral cladribine has also been investigated for chronic lymphocytic leukaemia.

◊ Reviews.

1. Robak T. Cladribine in the treatment of chronic lymphocytic leukemia. *Leuk Lymphoma* 2001; **40:** 551–64.
2. Goodman GR, *et al.* Cladribine in the treatment of hairy-cell leukaemia. *Best Pract Res Clin Haematol* 2003; **16:** 101–16.
3. Armitage JO, *et al.* Treatment of indolent non-Hodgkin's lymphoma with cladribine as single-agent therapy and in combination with mitoxantrone. *Int J Hematol* 2004; **79:** 311–21.
4. Robak T. The place of cladribine in the treatment of chronic lymphocytic leukemia: a 10-year experience in Poland. *Ann Hematol* 2005; **84:** 63–70.
5. Belani R, Saven A. Cladribine in hairy cell leukemia. *Hematol Oncol Clin North Am* 2006; **20:** 1109–23.
6. Sigal DS, Saven A. Cladribine in indolent non-Hodgkin's lymphoma. *Expert Rev Anticancer Ther* 2008; **8:** 535–45.

Multiple sclerosis. Parenteral cladribine has shown some evidence of benefit in multiple sclerosis (p.892) but it is not clear whether it improves attack rate or disease progression. An oral formulation is under investigation.

References.

1. Sipe JC, *et al.* Cladribine in treatment of chronic progressive multiple sclerosis. *Lancet* 1994; **344:** 9–13.
2. Romine JS, *et al.* A double-blind, placebo-controlled, randomized trial of cladribine in relapsing-remitting multiple sclerosis. *Proc Assoc Am Physicians* 1999; **111:** 35–44.
3. Rice GPA, *et al.* Cladribine and progressive MS: clinical and MRI outcomes of a multicenter controlled trial. *Neurology* 2000; **54:** 1145–55.
4. Janiec K, *et al.* Effect of immunosuppressive cladribine treatment on serum leucocytes system in two-year clinical trial in patients with chronic progressive multiple sclerosis. *Med Sci Monit* 2001; **7:** 93–8.
5. Sipe JC. Cladribine for multiple sclerosis: review and current status. *Expert Rev Neurother* 2005; **5:** 721–7.
6. Brousil JA, *et al.* Cladribine: an investigational immunomodulatory agent for multiple sclerosis. *Ann Pharmacother* 2006; **40:** 1814–21.
7. Leist TP, Vermersch P. The potential role for cladribine in the treatment of multiple sclerosis: clinical experience and development of an oral tablet formulation. *Curr Med Res Opin* 2007; **23:** 2667–76.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Intocel; Leustat; ***Austral.:*** Leustatin; Litak; ***Austria:*** Leustatin; ***Belg.:*** Leustatin; ***Braz.:*** Leustatin; ***Canad.:*** Leustatin; ***Cz.:*** Leustatin; Litak; ***Denm.:*** Leustatin; Litak; ***Fin.:*** Leustatin; Litak; ***Fr.:*** Leustatine; Litak; ***Ger.:*** Leustatin; Litak; ***Gr.:*** Leustatin; ***Hong Kong:*** Leustatin; ***Israel:*** Leustatin; Litak; ***Ital.:*** Leustatin; ***Neth.:*** Leustatin; Litak; ***Norw.:*** Leustatin; ***NZ:*** Leustatin; ***Philipp.:*** Leustatin; ***Pol.:*** Biodribin; ***Port.:*** Litak; ***S.Afr.:*** Leustatin; ***Spain:*** Leustatin; ***Swed.:*** Leustatin; ***Switz.:*** Leustatin; Litak; ***Thai.:*** Leustatin†; ***UK:*** Leustat; Litak; ***USA:*** Leustatin; ***Venez.:*** Leustatin.

Clofarabine *(BAN, USAN, rINN)*

Cl-F-Ara-A; Clofarabina; Clofarabinum. 2-Chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9*H*-purin-6-amine.

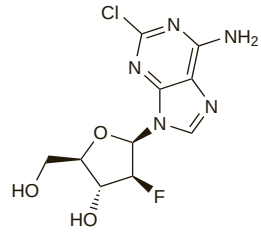
Кльофарабин

$C_{10}H_{11}ClFN_5O_3$ = 303.7.

CAS — 123318-82-1.

ATC — L01BB06.

ATC Vet — QL01BB06.



Adverse Effects, Treatment, and Precautions

As for Fludarabine Phosphate, p.721, although neurotoxicity is less severe. Capillary leak syndrome resulting from cytokine release has occurred with clofarabine, causing respiratory distress, hypotension, pleural and pericardial effusions, and multi-organ failure. Prophylactic corticosteroids may be useful, but clofarabine must be stopped immediately if signs or symptoms of capillary leak syndrome develop (respiratory status and blood pressure should be monitored during infusion). Other adverse effects include anxiety, flushing, tachycardia, hypotension, hepatotoxicity, haematuria, myalgia, arthralgia, and headache.

Renal and hepatic function, and complete blood counts, should be monitored during clofarabine therapy. Hydration should be maintained during treatment to minimise the risk of tumour lysis syndrome and other adverse effects.

Pharmacokinetics

Clofarabine is about 47% bound to plasma proteins. About 50 to 60% of a dose is excreted unchanged in the urine and it has a terminal half-life of about 5 hours.

Uses and Administration

Clofarabine, a purine nucleoside analogue, is used as an antimetabolite antineoplastic in the treatment of relapsed or refractory acute lymphoblastic leukaemia (p.651) in patients aged 1 to 21 years. A dose of 52 mg/m^2 is given daily for 5 days, by intravenous in-