Tinnitus, vertigo, deafness, headache, drowsiness, and other neurological symptoms have been reported, as have episodes of jaundice. Skin reactions to chlormethine hydrochloride include maculopapular rashes. Hypersensitivity is frequent when topical preparations are used.

Chlormethine hydrochloride has a powerful vesicant action on the skin and mucous membranes and great care must be taken to avoid contact with the eyes. Thrombophlebitis is a potential hazard of chlormethine particularly if it is not sufficiently diluted. Extravasation of the injection causes severe irritation and even sloughing. If extravasation occurs during injection, it has been suggested that the involved area should be infiltrated with an isotonic 4% solution of sodium thiosulfate, followed by the application of an ice compress intermittently for 6 to 12 hours, although the role of specific antidotes in antineoplastic extravasation is somewhat contentious (see p.640).

Chlormethine hydrochloride may produce temporary or permanent inhibition of fertility. There is some evidence of mutagenicity, teratogenicity, and carcinogenicity.

Effects on the nervous system. Severe immediate neurotoxicity developed[1] in 14 of 21 evaluable patients who underwent bone marrow transplantation after preparation with cytotoxic regimens including chlormethine 0.3 to 2 mg/kg. Symptoms developed a median of 4 days after treatment and included headache, hallucinations, confusion, convulsions, paraplegia, and tremor. Symptoms resolved in most, although in some they had not done so before their death. Six of the patients who recovered from acute toxicity developed a delayed neurotoxicity, beginning a median of 169 days after the first chlormethine injection and characterised by symptoms including confusion, somnolence, personality change, dementia, focal motor seizures, and hydrocephalus. Patients older than 21 years, those who had received CNS irradiation, and those treated concomitantly with other cytotoxic agents were at increased risk of neurotoxicity.

1. Sullivan KM, *et al.* Immediate and delayed neurotoxicity after mechlorethamine preparation for bone marrow transplantation. *Ann Intern Med* 1982; **97:** 182–9.

Handling and disposal. Chlormethine hydrochloride is a strong vesicant; avoid contact with skin and mucous membranes.

The manufacturers state that *unused injection* solutions of chlormethine hydrochloride may be neutralised by mixing with an equal volume of a solution containing sodium thiosulfate 5% and sodium bicarbonate 5% and allowing to stand for 45 minutes. Equipment used in the preparation and administration of such solutions may be treated similarly. Alternatively a solution containing sodium carbonate 2.5% or sodium hydroxide in a mixture of industrial methylated spirit and water has been suggested for the decontamination of equipment.

Urine produced for up to 48 hours after a dose of chlormethine should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Pharmacokinetics

On intravenous injection, chlormethine is rapidly converted to a reactive ethyleneimmonium ion. It usually disappears from the blood in a few minutes. A very small proportion is excreted unchanged in the urine.

Uses and Administration

Chlormethine belongs to the group of antineoplastic drugs described as alkylating agents. It also possesses weak immunosuppressant properties.

Chlormethine hydrochloride has been used in the treatment of advanced Hodgkin's disease (p.655), historically with a vinca alkaloid, procarbazine, and prednisone or prednisolone (the MOPP regimen). Chlormethine has also been tried in non-Hodgkin's lymphomas, notably mycosis fungoides (p.657), and some other malignancies including chronic leukaemias, tumours of the breast, ovary, and lung, and in polycythaemia vera. Chlormethine has been used in the management of malignant effusions but is not the agent of choice.

In the MOPP regimen chlormethine hydrochloride has been given in doses of 6 mg/m^2. However, when licensed for use as a single agent, the usual dose of chlormethine hydrochloride is 400 micrograms/kg, preferably as a single dose, although it may be divided into 2 or 4 equal doses on successive days. It is given by intravenous injection in a strength of 1 mg/mL in Water for Injections or sodium chloride 0.9%. Injection over 2 minutes into the tubing of a fast running intravenous infusion of sodium chloride 0.9% or glucose 5% may reduce the incidence of thrombophlebitis and the risk of extravasation.

The response should be assessed by the trend of the blood counts. Treatment with chlormethine may be repeated when the bone-marrow function has recovered.

Intracavitary injections of 200 to 400 micrograms/kg have been given in the treatment of malignant, especially pleural, effusions. In mycosis fungoides with extensive skin involvement, very dilute solutions of chlormethine (e.g. 200 micrograms/mL) have been applied topically.

Histiocytic syndromes. Dilute solutions of chlormethine (200 micrograms/mL) have been applied topically for the cutaneous symptoms of Langerhans-cell histiocytosis (p.650).[1,2] Such therapy was reported to effectively clear skin lesions in most patients, and be well tolerated. However, although no malignant skin disease developed during the follow-up of one group of children, the long-term effects of topical chlormethine are of concern in young patients.[2]

1. Sheehan MP, *et al.* Topical nitrogen mustard: an effective treatment for cutaneous Langerhans cell histiocytosis. *J Pediatr* 1991; **119:** 317–21.
2. Hoeger PH, *et al.* Long term follow up of topical mustine treatment for cutaneous Langerhans cell histiocytosis. *Arch Dis Child* 2000; **82:** 483–7.

Mycosis fungoides. Chlormethine is used topically in the management of mycosis fungoides (p.657). A retrospective cohort analysis[1] of 203 patients treated with chlormethine found a partial response rate of 33% and a complete response rate of 50%. The median time to achieve complete response was 12 months and the time to relapse was also 12 months. Mild disease of limited skin involvement responded better than generalised patch/plaque disease, and more patients with mild disease obtained long-term remission. Maintenance therapy was used in some patients, but on cessation the relapse rate was similar to patients who did not receive maintenance therapy. Treatment had usually been applied as either an aqueous solution or an ointment containing chlormethine 100 to 200 micrograms/mL.

1. Kim YH, *et al.* Topical nitrogen mustard in the management of mycosis fungoides: update of the Stanford experience. *Arch Dermatol* 2003; **139:** 165–73.

Preparations

BP 2008: Chlormethine Injection;
USP 31: Mechlorethamine Hydrochloride for Injection.

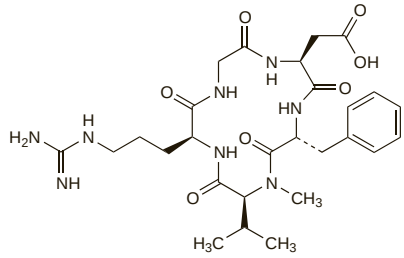
Proprietary Preparations (details are given in Part 3)
Canad.: Mustargen; ***Fr.:*** Caryolysine; ***Gr.:*** Caryolysine; ***Israel:*** Mustargen; ***Switz.:*** Mustargen; ***USA:*** Mustargen.

Cilengitide *(USAN, rINN)*

Cilengitida; Cilengitidum; EMD-121974. Cyclo(L-arginylglycyl-L-α-aspartyl-D-phenylalanyl-*N*-methyl-L-valyl).

Циленгитид

$C_{27}H_{40}N_8O_7$ = 588.7.
CAS — 188968-51-6.



Profile

Cilengitide is an angiogenesis inhibitor under investigation in the treatment of glioma, pancreatic cancer, and non-small cell lung cancer.

◊ References.

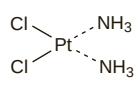
1. Friess H, *et al.* A randomized multi-center phase II trial of the angiogenesis inhibitor cilengitide (EMD 121974) and gemcitabine compared with gemcitabine alone in advanced unresectable pancreatic cancer. *BMC Cancer* 2006; **6:** 285.
2. Hariharan S, *et al.* Assessment of the biological and pharmacological effects of the αvβ and αvβ integrin receptor antagonist, cilengitide (EMD 121974), in patients with advanced solid tumors. *Ann Oncol* 2007; **18:** 1400–7.
3. MacDonald TJ, *et al.* Phase I clinical trial of cilengitide in children with refractory brain tumors: Pediatric Brain Tumor Consortium Study PBTC-012. *J Clin Oncol* 2008; **26:** 919–24.
4. Reardon DA, *et al.* Cilengitide: an integrin-targeting arginine-glycine-aspartic acid peptide with promising activity for glioblastoma multiforme. *Expert Opin Invest Drugs* 2008; **17:** 1225–35.

Cisplatin *(BAN, USAN, rINN)*

CDDP; Cisplatina; Cisplatine; Cisplatino; Cisplatinum; Cis-platinum; Ciszplatin; DDP; *cis*-DDP; NSC-119875; Peyrone's Salt; Platinum Diamminodichloride; Sisplatiini; Sisplatin. *cis*-Diamminedichloroplatinum.

Цисплатин

$(NH_3)_2.PtCl_2$ = 300.1.
CAS — 15663-27-1.
ATC — L01XA01.
ATC Vet — QL01XA01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Cisplatin). A yellow powder or yellow or orange-yellow crystals. Slightly soluble in water; practically insoluble in alcohol; sparingly soluble in dimethylformamide. A 0.1% solution in sodium chloride 0.9% has a pH of 4.5 to 6.0 immediately after preparation. Store in airtight containers. Protect from light.
USP 31 (Cisplatin). Store in airtight containers. Protect from light.

Incompatibility. Cisplatin is rapidly degraded in the presence of bisulfite or metabisulfite,[1,2] and admixture with preparations containing these as preservatives may result in loss of activity.[2] Sodium bicarbonate may also increase the loss of cisplatin from solution, and in some cases may cause precipitation.[3] The stability of cisplatin when mixed with fluorouracil is reported to be limited, with 10% loss of cisplatin in 1.2 to 1.5 hours.[4] Mixtures with etoposide[5] in sodium chloride 0.9% injection formed a precipitate if mannitol and potassium chloride were present as additives, but not when the diluent was glucose 5% with sodium chloride 0.45%. Turbidity has been reported[6] within 4 hours of mixing 0.1% solutions of cisplatin and thiotepa in glucose 5%. Cisplatin exhibits variable incompatibility with paclitaxel, depending on the paclitaxel concentration and the temperature.[7]

Cisplatin reacts with aluminium causing loss of potency and precipitate formation. Needles, syringes, catheters or giving sets that contain aluminium should not be used for preparing or giving cisplatin.

1. Hussain AA, *et al.* Reaction of cis-platinum with sodium bisulfite. *J Pharm Sci* 1980; **69:** 364–5.
2. Garren KW, Repta AJ. Incompatibility of cisplatin and Reglan Injectable. *Int J Pharmaceutics* 1985; **24:** 91–9.
3. Hincal AA, *et al.* Cis-platin stability in aqueous parenteral vehicles. *J Parenter Drug Assoc* 1979; **33:** 107–16.
4. Stewart CF, Fleming RA. Compatibility of cisplatin and fluorouracil in 0.9% sodium chloride injection. *Am J Hosp Pharm* 1990; **47:** 1373–7.
5. Stewart CF, Hampton EM. Stability of cisplatin and etoposide in intravenous admixtures. *Am J Hosp Pharm* 1989; **46:** 1400–4.
6. Trissel LA, Martinez JF. Compatibility of thiotepa (lyophilized) with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1041–5.
7. Zhang Y, *et al.* Compatibility and stability of paclitaxel combined with cisplatin and with carboplatin in infusion solutions. *Ann Pharmacother* 1997; **31:** 1465–70.

Stability. Decomposition of cisplatin in aqueous solutions is primarily due to reversible substitution of water for chloride, and its stability is enhanced in sodium chloride solutions because of the excess of chloride ions available.[1,2] A solution in sodium chloride 0.9% injection has been reported to lose 3% of the drug in less than one hour and to remain stable at this equilibrium value for 24 hours at room temperature.[1] Stability is decreased if exposed to intense light, but the effect of normal lighting conditions is apparently smaller.[1,2] It has been recommended that admixtures of cisplatin with mannitol and magnesium sulfate (in glucose 5% with sodium chloride 0.45%) stored at room temperature in PVC bags should be used within 48 hours, but may be stored for 4 days at 4° or frozen and stored at –15° for up to 30 days.[3] However, solutions containing 600 micrograms/mL or more of cisplatin precipitate out when refrigerated and are slow to redissolve.[1]

1. Greene RF, *et al.* Stability of cisplatin in aqueous solution. *Am J Hosp Pharm* 1979; **36:** 38–43.
2. Hincal AA, *et al.* Cis-platin stability in aqueous parenteral vehicles. *J Parenter Drug Assoc* 1979; **33:** 107–16.
3. LaFollette JM, *et al.* Stability of cisplatin admixtures in polyvinyl chloride bags. *Am J Hosp Pharm* 1985; **42:** 2652.

Adverse Effects and Treatment

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

Severe nausea and vomiting occur in most patients during treatment with cisplatin; nausea may persist for up to a week.

Serious toxic effects on the kidneys, bone marrow, and ears have been reported in up to about one third of patients given a single dose of cisplatin; the effects are generally dose-related and cumulative.

Damage to the renal tubules may be evident during the second week after a dose of cisplatin and renal function must return to normal before further cisplatin is given. Adequate hydration, and use of osmotic diuretics such as mannitol to increase urine volume and thus decrease the urinary concentration of platinum, can reduce the incidence of nephrotoxicity. Electrolyte disturbances, particularly hypomagnesaemia and hypocalcaemia, may occur, possibly as a result of renal tubular damage. Hyperuricaemia is also seen.

Bone-marrow depression may be severe with higher doses of cisplatin. Nadirs in platelet and leucocyte counts occur between days 18 and 23 and most patients recover by day 39; anaemia is common and may be

partly related to decreased production of erythropoietin after renal damage.

Ototoxicity may be more severe in children. It can manifest as tinnitus, loss of hearing in the high frequency range, and occasionally deafness or vestibular toxicity. Other neurological effects reported include peripheral neuropathies, loss of taste, and seizures. Ocular toxicities include optic neuritis, papilloedema, and cerebral blindness.

Anaphylactoid reactions and cardiac abnormalities have occurred. Injection site reactions, including localised oedema, pain, erythema, skin ulceration and phlebitis may occur. Extravasation may lead to tissue cellulitis, fibrosis, and necrosis.

Platinum derivatives are potentially mutagenic and teratogenic, and there is some evidence they may be associated with the development of secondary leukaemias—see Carcinogenicity, p.635.

Effects on the blood. Cisplatin-induced anaemia appears to be disproportionate to the effects on other blood cells, and to correlate with renal tubular dysfunction.[1] It may therefore be due to an erythropoietin deficiency state resulting from cisplatin-induced renal tubular damage. Haemolysis has also been reported.[2]

1. Wood PA, Hrushesky WJ. Cisplatin-associated anemia: an erythropoietin deficiency syndrome *J Clin Invest* 1995; **95:** 1650–9.
2. Rothmann SA, Weick JK. Cisplatin toxicity for erythroid precursors. *N Engl J Med* 1981; **304:** 360.

THROMBOEMBOLISM. For discussion of thromboembolic events possibly associated with cisplatin-containing chemotherapy regimens see Effects on the Cardiovascular System, p.636.

Effects on the ears. Ototoxicity is a well-established adverse effect of cisplatin.[1] It appears to be due to generation of reactive oxygen species that cause apoptosis of hair cells in the cochlea,[1] and results in hearing loss, particularly at high frequencies.[1,2] Risk factors include younger age,[1] larger cumulative doses[1] (one study[2] identified doses above 60 mg/m^2 as risk factors), pre-existing hearing loss or renal disease,[1] and irradiation of the brain or base of the skull.[1,3] Various substances including thiols, amifostine, ebselen, allopurinol, and salicylates have been investigated in *animals* for their protective effect against cisplatin-induced neurotoxicity[1] but although some promising results have been seen, benefit is yet to be demonstrated in large clinical studies, and there is some concern about the risk of reducing the antineoplastic effect of cisplatin as well. However, a small study comparing cisplatin chemoradiation with or without sodium thiosulfate tentatively concluded that thiosulfate did seem to offer some protection against hearing loss.[4]

1. Rybak LP, *et al.* Mechanisms of cisplatin-induced ototoxicity and prevention. *Hear Res* 2007; **226:** 157–67.
2. Rademaker-Lakhai JM, *et al.* Relationship between cisplatin administration and the development of ototoxicity. *J Clin Oncol* 2006; **24:** 918–24.
3. Low WK, *et al.* Sensorineural hearing loss after radiotherapy and chemoradiotherapy: a single, blinded, randomized study. *J Clin Oncol* 2006; **24:** 1904–9.
4. Zuur CL, *et al.* Ototoxicity in a randomized phase III trial of intra-arterial compared with intravenous cisplatin chemoradiation in patients with locally advanced head and neck cancer. *J Clin Oncol* 2007; **25:** 3759–65.

Effects on electrolytes. Renal-magnesium wasting and, less commonly, symptomatic hypomagnesaemia occurs with cisplatin therapy.[1,2] Adding magnesium to the pre- and posthydration fluids has been suggested.[2] When hypocalcaemia is also present, tetany may result,[1,3] although this has responded to electrolyte infusion without the need to interrupt chemotherapy.[1] Cisplatin therapy may also be associated with significant hypokalaemia[1] and hyponatraemia.[4,5]

See also Effects on the Kidneys, below.

1. Winkler CF, *et al.* Cisplatin and renal magnesium wasting. *Ann Intern Med* 1979; **91:** 502.
2. Lajer H, Daugaard G. Cisplatin and hypomagnesemia. *Cancer Treat Rev* 1999; **25:** 47–58.
3. Stuart-Harris R, *et al.* Tetany associated with cis-platin. *Lancet* 1980; **ii:** 1303.
4. Hutchison FN, *et al.* Renal salt wasting in patients treated with cisplatin. *Ann Intern Med* 1988; **108:** 21–5.
5. Mariette X, *et al.* Cisplatin and hyponatremia. *Ann Intern Med* 1988; **108:** 770–1.

Effects on the kidneys. Nephrotoxicity is a well-established adverse effect of cisplatin, may be dose-limiting, and can manifest as acute or chronic renal failure, polyuria, or chronic hypomagnesaemia.[1] The mechanism appears to involve primarily damage to the proximal renal tubule; selective magnesium loss may be due to a specific membrane or transport system abnormality. Sulfhydryl metabolism and oxidative stress play a role in toxicity, and measures that reduce glutathione depletion and scavenge intracellular free oxygen radicals have been tried in an attempt to modulate nephrotoxicity.[1-3] However, the primary measures for reducing renal damage have been aggressive hydration with chloride-containing solutions, and the use of mannitol (see also Prophylaxis, below). It has been suggested that cisplatin may mobilise lead accumulated in bone and cause temporary accumulation in the kidney, with concomitant toxicity,[4] but this has been vigorously disputed.[5-7]

See also under Effects on Electrolytes, above.

1. Anand AJ, Bashey B. Newer insights into cisplatin nephrotoxicity. *Ann Pharmacother* 1993; **27:** 1519–25.
2. Meyer KB, Madias NE. Cisplatin nephrotoxicity. *Miner Electrolyte Metab* 1994; **20:** 201–13.
3. Kuhlmann MK, *et al.* Insights into potential cellular mechanisms of cisplatin nephrotoxicity and their clinical application. *Nephrol Dial Transplant* 1997; **12:** 2478–80.
4. El-Sharkawi AM, *et al.* Unexpected mobilisation of lead during cisplatin chemotherapy. *Lancet* 1986; **ii:** 249–50.
5. Tothill P, *et al.* Is lead mobilised by cisplatin? *Lancet* 1989; **ii:** 333.
6. Tothill P, *et al.* Mobilisation of lead by cisplatin. *Lancet* 1989; **ii:** 1342.
7. Hainsworth IR, Morgan WD. Plasma lead and cisplatin. *Lancet* 1989; **ii:** 624.

PROPHYLAXIS. Hydration with 1 to 2 litres of fluid before treatment, and infusion of cisplatin in a further 2 litres of infusion fluid containing an osmotic diuretic such as mannitol reduces the nephrotoxicity of cisplatin, but does not abolish it. Maintaining adequate hydration and urinary output post-treatment is also important. Giving cisplatin over 6 to 8 hours rather than 1 to 2 hours may also decrease renal toxicity.

Sulfur-containing nucleophiles can inactivate cisplatin, and have therefore been investigated for their chemoprotective potential. Amifostine is a prodrug that is selectively activated by normal tissue, and has been shown to protect normal tissue (principally the kidney) against the cytotoxicity of cisplatin without affecting antitumour activity (for references, see Cytoprotection, p.1437). Glutathione (p.1448) is a similar agent, which may be selectively taken up by kidney and neural tissue. Sodium thiosulfate (p.1466) does not show selective activation or uptake, and its use is therefore limited to situations where cisplatin is given locally (e.g. intraperitoneal[1,2]) or directly (e.g. intra-arterial[3]).

1. Malmstrom H, *et al.* Intraperitoneal high-dose cisplatin and etoposide with systemic thiosulfate protection in second-line treatment of advanced ovarian cancer. *Gynecol Oncol* 1993; **49:** 166–71.
2. van Rijswijk RE, *et al.* Experience with intraperitoneal cisplatin and etoposide and i.v. sodium thiosulphate protection in ovarian cancer patients with either pathologically complete response or minimal residual disease. *Ann Oncol* 1997; **8:** 1235–41.
3. Rohde S, *et al.* Intra-arterial high-dose chemotherapy with cisplatin as part of a palliative treatment concept in oral cancer. *Am J Neuroradiol* 2005; **26:** 1804–9.

Effects on the nervous system. The features of cisplatin-induced peripheral neuropathy are consistent with damage predominantly to sensory fibres, with numbness, tingling, and decreased vibratory sensation and deep tendon reflexes, progressing in severe cases to disabling sensory ataxia.[1] The toxicity is dose-dependent, with symptoms usually appearing in patients who have received cumulative doses of 300 to 600 mg/m^2, although individuals vary in susceptibility. Neuropathy is reversible but recovery may take a year or more. The pathophysiology is unknown. Peripheral neuropathy can be a dose-limiting toxicity for cisplatin and agents such as Org-2766 (a corticotropin analogue) and amifostine (p.1436) have been investigated for their potential in protecting peripheral nerves.[1-3] Vitamin E has been reported to be effective in reducing peripheral neuropathy.[4] Glutathione is also under investigation for the prevention of neurotoxicity (see p.1448). However, a systematic review considered that the evidence for most of the interventions intended to reduce cisplatin neurotoxicity was insufficient to demonstrate benefit.[5] Autonomic neuropathy, with, in some cases, consequent orthostatic hypotension, has also been described after treatment with cisplatin-containing regimens.[6] Apart from ototoxicity (see above), cisplatin has also been associated with central neurotoxicity, including focal encephalopathy, seizures, aphasia, confusion, agitation, and cortical blindness.[7-10] It has been suggested that the mechanism of focal encephalopathy may be vascular,[7] although this is uncertain.

1. Mollman JE. Cisplatin neurotoxicity. *N Engl J Med* 1990; **322:** 126–7.
2. Alberts DS, Noel JK. Cisplatin-associated neurotoxicity: can it be prevented? *Anticancer Drugs* 1995; **6:** 369–83.
3. Cavaletti G, *et al.* Neuroprotectant drugs in cisplatin neurotoxicity. *Anticancer Res* 1996; **16:** 3149–59.
4. Pace A, *et al.* Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy. *J Clin Oncol* 2003; **21:** 927–31.
5. Albers J, *et al.* Interventions for preventing neuropathy caused by cisplatin and related compounds. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 25/07/08).
6. Richardson P, Cantwell BMJ. Autonomic neuropathy after cisplatin based chemotherapy. *BMJ* 1990; **300:** 1466–7.
7. Lindeman G, *et al.* Cisplatin neurotoxicity. *N Engl J Med* 1990; **323:** 64–5.
8. Philip PA, *et al.* Convulsions and transient cortical blindness after cisplatin. *BMJ* 1991; **302:** 416.
9. Higa GM, *et al.* Severe, disabling neurologic toxicity following cisplatin retreatment. *Ann Pharmacother* 1995; **29:** 134–7.
10. Steeghs N, *et al.* Cisplatin-induced encephalopathy and seizures. *Anticancer Drugs* 2003; **14:** 443–6.

Extravasation. For discussion of the management of extravasation, including methods to manage cisplatin extravasation, see under Treatment of the Adverse Effects of Antineoplastics, p.640.

Hypersensitivity. Anaphylactoid reactions to intravenous cisplatin generally appear within a few minutes of dosage and have manifested as facial oedema, wheezing, tachycardia, and hypotension.[1] A high incidence of anaphylactoid reaction has also been seen after intravesical instillation in patients with bladder cancer,[2] but intraperitoneal or intrapleural use does not seem to be associated with an enhanced risk of hypersensitivity,[3] although anaphylactoid reactions have occurred when cisplatin is given intraperitoneally.[4] Anaphylactoid symptoms and ischaemia of the hands accompanied severe exfoliative dermatitis in one patient on the second cycle of cisplatin-based chemotherapy;[5] she had earlier experienced exfoliative dermatitis associated with carboplatin. Palmar-plantar erythrodysesthesia (p.639) has also occurred.[6]

1. Von Hoff DD, *et al.* Allergic reactions to cis platinum. *Lancet* 1976; **i:** 90.
2. Denis L. Anaphylactic reactions to repeated intravesical instillation with cisplatin. *Lancet* 1983; **i:** 1378–9.
3. Markman M. No increase in allergic reactions with intracavitary administration of cisplatin. *Lancet* 1984; **ii:** 1164.
4. Hebert ME, *et al.* Anaphylactoid reactions with intraperitoneal cisplatin. *Ann Pharmacother* 1995; **29:** 260–3.
5. Lee TC, *et al.* Severe exfoliative dermatitis associated with hand ischemia during cisplatin therapy. *Mayo Clin Proc* 1994; **69:** 80–2.
6. Vakalis D, *et al.* Acral erythema induced by chemotherapy with cisplatin. *Br J Dermatol* 1998; **139:** 750–1.

Nausea and vomiting. For discussion of the management of chemotherapy-induced nausea and vomiting, see under Nausea and Vomiting, p.1700.

Precautions

For reference to the precautions necessary with antineoplastics, see p.641. Cisplatin is generally contra-indicated in patients with renal or hearing impairment, or bone-marrow depression. Renal and neurological function and hearing should be monitored during treatment, and regular blood counts performed. Electrolytes should be measured before starting therapy, and before each subsequent course. Adequate hydration and urinary output must be maintained before, and for 24 hours after, a dose.

Patients are recommended to use appropriate contraceptive measures during treatment and for 6 months after stopping treatment.

Breast feeding. Platinum concentrations in a patient receiving cisplatin were 0.9 micrograms/mL in breast milk and 0.8 micrograms/mL in plasma.[1] Although most of the platinum in breast milk is probably protein-bound the authors considered that a mother should not breast feed while receiving cisplatin chemotherapy. However, in another report,[2] cisplatin was undetectable in breast milk and the American Academy of Pediatrics[3] considers its use to be compatible with breast feeding.

1. de Vries EGE, *et al.* Excretion of platinum into breast milk. *Lancet* 1989; **i:** 497. Correction. *ibid.*; 798.
2. Egan PC, *et al.* Doxorubicin and cisplatin excretion into human milk. *Cancer Treat Rep* 1985; **69:** 1387–9.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 29/06/04)

Handling and disposal. Methods for the destruction of *cisplatin wastes* by reduction with zinc powder under acidic conditions or by reaction with ditiocarb sodium have been described.[1] Residue produced by the degradation of cisplatin by either method showed no mutagenicity *in vitro*.

Urine produced for up to 7 days after a dose of cisplatin should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73*. Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Pregnancy. Cisplatin was given with etoposide and bleomycin to a pregnant woman at 26 weeks of gestation for carcinoma of uncertain primary origin. At 27 weeks of gestation, she developed profound neutropenia followed by septicaemia and went into premature labour. The infant developed profound leucopenia and neutropenia by day 3, which was attributed to chemotherapy given 6 days before delivery; prophylactic antibacterials including gentamicin were given. Hair loss at the age of 10 days was attributed to etoposide. At 1 year of age, the child exhibited moderate bilateral sensorineural hearing loss; this was considered to be either due to cisplatin exposure *in utero* or to gentamicin use.[1] However, there are other reports of cisplatin use during the second or third trimester of pregnancy with no subsequent apparent adverse effects on the infant.[2-5] In most cases, cisplatin had been given with cyclophosphamide,[2-4] although in one

instance it was given with paclitaxel.[5] In one report, cisplatin-induced maternal ototoxicity led to it being replaced after 2 courses by carboplatin.[4]

1. Raffles A, *et al.* Transplacental effects of maternal cancer chemotherapy: case report. *Br J Obstet Gynaecol* 1989; **96:** 1099–1100.
2. Malfetano JH, Goldkrand JW. Cis-platinum combination chemotherapy during pregnancy for advanced epithelial ovarian carcinoma. *Obstet Gynecol* 1990; **75:** 545–7.
3. King LA, *et al.* Treatment of advanced epithelial ovarian carcinoma in pregnancy with cisplatin-based chemotherapy. *Gynecol Oncol* 1991; **41:** 78–80.
4. Henderson CE, *et al.* Platinum chemotherapy during pregnancy for serous cystadenocarcinoma of the ovary. *Gynecol Oncol* 1993; **49:** 92–4.
5. Sood AK, *et al.* Paclitaxel and platinum chemotherapy for ovarian carcinoma during pregnancy. *Gynecol Oncol* 2001; **83:** 599–600.

Radiotherapy. Enhanced ototoxicity has been reported in patients given cisplatin for brain tumours who also had cranial irradiation.[1,2]

1. Granowetter L, *et al.* Enhanced cis-platinum neurotoxicity in pediatric patients with brain tumors. *J Neurooncol* 1983; **1:** 293–7.
2. Mahoney DH, *et al.* Ototoxicity with cisplatin therapy. *J Pediatr* 1983; **103:** 1006.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. Use with other myelosuppressive, nephrotoxic or ototoxic drugs may exacerbate the adverse effects of cisplatin. The effects of cisplatin on renal function may also affect the pharmacokinetics of other drugs excreted by the renal route.

Antibacterials. Although the use of cisplatin with other nephrotoxic or ototoxic drugs requires great caution, there is some evidence that *aminoglycosides* can be used in patients who have recently received cisplatin if appropriate supportive care is available.[1]

1. Cooper BW, *et al.* Renal dysfunction during high-dose cisplatin therapy and autologous hematopoietic stem cell transplantation: effect of aminoglycoside therapy. *Am J Med* 1993; **94:** 497–504.

Antineoplastics. The ototoxicity of cisplatin was reportedly enhanced by *ifosfamide*,[1] a drug that is not ototoxic when given alone, although it does have nephrotoxic potential, making reports of increased nephrotoxicity in patients who have received both unsurprising.[2,3]

For a report of increased toxicity with *etoposide*, see p.718. Cisplatin may reduce the clearance of *paclitaxel*, see p.759.

1. Meyer WH, *et al.* Ifosfamide and exacerbation of cisplatin-induced hearing loss. *Lancet* 1993; **341:** 754–5.
2. Rossi R, Ehrich JHH. Partial and complete de Toni-Debré-Fanconi syndrome after ifosfamide chemotherapy of childhood malignancy. *Eur J Clin Pharmacol* 1993; **44** (suppl 1): S43–S45.
3. Martinez F, *et al.* Ifosfamide nephrotoxicity: deleterious effect of previous cisplatin administration. *Lancet* 1996; **348:** 1100–1.

Cardiovascular drugs. A patient whose renal function was unaffected by cisplatin alone developed nephrotoxicity when given cisplatin and antihypertensive therapy with *furosemide*, *hydralazine*, *diazoxide*, and *propranolol*.[1] Previous results in *animals* suggest that furosemide may aggravate cisplatin nephrotoxicity, while the other antihypertensives might have contributed to a transient fall in renal-blood flow with resultant increased renal-tubular cisplatin concentration.

1. Markman M, Trump DL. Nephrotoxicity with cisplatin and antihypertensive medications. *Ann Intern Med* 1982; **96:** 257.

Gastrointestinal drugs. For mention of 2 retrospective studies, one showing a decreased area under the plasma-concentration time curve of high-dose cisplatin with *ondansetron* and the other an increase, see p.703.

Pharmacokinetics

After intravenous doses cisplatin disappears from the plasma in a biphasic manner and half-lives of 25 to 49 minutes and 3 to 4 days have been reported for total platinum. More than 90% of the platinum from a dose is protein bound within 2 to 4 hours; only the unbound fraction has significant antineoplastic activity. Cisplatin is concentrated in the liver, kidneys, and large and small intestines. Penetration into the CNS appears to be poor. Excretion is mainly in the urine but is incomplete and prolonged: up to about 50% of a dose has been reported to be excreted in urine over 5 days, and platinum may be detected in tissue for several months afterwards. The unbound fraction, which is more rapidly cleared, may be actively secreted by the renal tubules.

Cisplatin is well-absorbed on intraperitoneal use. Cisplatin may be distributed into breast milk (see Breast Feeding, above).

◊ References.

1. Loh GW, *et al.* A systematic review of limited sampling strategies for platinum agents used in cancer chemotherapy. *Clin Pharmacokinet* 2007; **46:** 471–94.
2. Jehn CF, *et al.* Pharmacokinetics of liposomal cisplatin (lipoplatin) in combination with 5-FU in patients with advanced head and neck cancer: first results of a phase III study. *Anticancer Res* 2007; **27:** 471–5.

Uses and Administration

The antineoplastic cisplatin is a platinum-containing complex that may act similarly to the alkylating agents. Its antineoplastic actions are cell-cycle non-specific and are dependent upon its *cis* configuration; they appear to be related to its hydrolysis in the body to form reactive aquated species. Although it causes immunosuppression, stimulation of the host immune response against the tumour has been suggested as contributing to cisplatin's antineoplastic action.

Cisplatin is of value in the treatment of tumours of the testis, usually as a major component of combination chemotherapy regimens, and particularly with bleomycin and etoposide (BEP), or with bleomycin and a vinca alkaloid. It is also used in metastatic ovarian tumours, cervical tumours, lung cancer, advanced bladder cancer, and squamous cell carcinoma of the head and neck. It has been reported to be active against many other solid tumours, as indicated by the cross references given below.

Cisplatin is given by intravenous infusion in sodium chloride 0.9% or in a mixture of sodium chloride and glucose. In monotherapy, it is usually given as a single dose of 50 to 120 mg/m^2 every 3 to 4 weeks. Alternatively, 15 to 20 mg/m^2 is given daily for 5 days, every 3 to 4 weeks. Lower doses are generally used for combination chemotherapy regimens than for single agent therapy; 20 mg/m^2 or more is given once every 3 to 4 weeks. A dose of 20 mg/m^2 daily for 5 days every 3 to 4 weeks has been used in combination chemotherapy of testicular tumours.

Licensed product information recommends that cisplatin is given in 2 litres of chloride-containing infusion fluid. In practice, volumes of less than 2 litres have been used in expert centres. The infusion may be given over 1 to 2 hours, although licensed product information generally recommends a longer infusion time of 6 to 8 hours in order to reduce renal and gastrointestinal toxicities.

To aid diuresis and protect the kidneys, 37.5 g of mannitol (e.g. 375 mL of mannitol 10%) is usually added to the infusion or is infused separately immediately before cisplatin. In order to begin diuresis the patient is usually hydrated by the infusion of 1 to 2 litres of a suitable fluid over several hours before giving cisplatin. Adequate hydration must also be maintained for up to 24 hours after a dose. Renal, haematological, auditory, and neurological function should be monitored during therapy, and dosage adjusted accordingly.

Cisplatin has also been given by the intra-arterial and intraperitoneal routes, and by instillation into the bladder. It is being investigated as a liposomal formulation, and as a collagen-based injectable gel containing cisplatin and adrenaline (MPI-5010) to localise the effect. An oral formulation of cisplatin is also under investigation.

Various analogues of cisplatin have been developed or investigated including those with fewer adverse effects (e.g. carboplatin, p.693; nedaplatin, p.755), an altered spectrum of activity (oxaliplatin, p.757), or activity on oral dosage (satraplatin, p.769).

Administration. Various adjustments to the administration of cisplatin have been suggested in an attempt to improve effectiveness while reducing toxicity.

Hydration before and after a dose of cisplatin, together with the use of mannitol to promote diuresis, is now standard (see Uses and Administration, above). Higher doses of cisplatin (up to 200 mg/m^2 per treatment cycle) have been successfully given by infusion in hypertonic sodium chloride, accompanied by intensive hydration.[1,2] Sodium chloride 3% infusion solution has been used.[3] However, while such a regimen may limit nephrotoxicity, other toxic effects, such as peripheral neuropathy, are not prevented;[1,2,4,5] myelosuppression may be less if the total dose is given in 2 divided doses rather than divided over 5 days.[2] High-dose cisplatin has been given once weekly; haematological toxicity may be dose-limiting with this regimen.[3]

Toxicity has been reported to be reduced when cisplatin was given by continuous intra-arterial[6] or intravenous[7] infusion. It has also been suggested that giving cisplatin in the evening rather than the morning results in less damage to renal function, apparently because of circadian variations in urine production.[8] However, another study[9] found that morning, rather than evening, doses of cisplatin resulted in less renal damage. Noting the inconsistency with previous reports, the authors concluded that use of a prolonged hydration protocol and concomitant furosemide might have been responsible for these results (see also under Interactions, Cardiovascular Drugs, above). It was also found that morning dosage of cisplatin may be more emetogenic than evening dosage, although the use of prophylactic ondansetron before cisplatin reduced this apparent circadian effect on vomiting.

A suggested alternative way to increase the platinum dose without producing incapacitating toxicity has been the combination of cisplatin and carboplatin.[10]

Various drugs have been investigated to reduce toxicity, including amifostine, glutathione, and thiosulfate, as discussed under Effects on the Kidneys, and Effects on the Nervous System, above.

A retrospective study of patients with bladder cancer found that calculation of creatinine clearance (CC) by mathematical formulas was inadequate in determining renal eligibility for treatment with cisplatin, especially in patients over 65 years of age; up to 44% of patients who were treated with cisplatin based on measured CC would have been deemed ineligible using mathematical calculations.[11]

1. Ozols RF, *et al.* High-dose cisplatin in hypertonic saline. *Ann Intern Med* 1984; **100:** 19–24.
2. Gandara DR, *et al.* Cisplatin dose intensity in non-small cell lung cancer: phase II results of a day 1 and day 8 high-dose regimen. *J Natl Cancer Inst* 1989; **81:** 790–4.
3. de Jongh FE, *et al.* Weekly high-dose cisplatin is a feasible treatment option: analysis on prognostic factors for toxicity in 400 patients. *Br J Cancer* 2003; **88:** 1199–1206.
4. Bagley CM, *et al.* High-dose cisplatin therapy for cancer of the ovary: neurotoxicity. *Ann Intern Med* 1985; **102:** 719.
5. Ozols RF, Young RC. High-dose cisplatin therapy for cancer of the ovary: neurotoxicity. *Ann Intern Med* 1985; **102:** 719.
6. Jacobs SC, *et al.* Intraarterial cisplatin infusion in the management of transitional cell carcinoma of the bladder. *Cancer* 1989; **64:** 388–91.
7. Salem P, *et al.* Cis-diamminedichloroplatinum (II) by 5-day continuous infusion: a new dose schedule with minimal toxicity. *Cancer* 1984; **53:** 837–40.
8. Hrushesky WJM, *et al.* Circadian time dependence of cisplatin urinary kinetics. *Clin Pharmacol Ther* 1982; **32:** 330–9.
9. Kobayashi M, *et al.* Cisplatin-induced vomiting depends on circadian timing. *Chronobiol Int* 2001; **18:** 851–63.
10. Piccart MJ, *et al.* Cisplatin combined with carboplatin: a new way of intensification of platinum dose in the treatment of advanced ovarian cancer. *J Natl Cancer Inst* 1990; **82:** 703–7.
11. Raj GV, *et al.* Formulas calculating creatinine clearance are inadequate for determining eligibility for cisplatin-based chemotherapy in bladder cancer. *J Clin Oncol* 2006; **24:** 3095–3100.

Malignant neoplasms. Cisplatin is used in the management of many solid malignancies, notably those of the bladder, cervix, lung, ovary, and testis, as discussed on p.659, p.663, p.668, p.670, and p.673 respectively. Other malignancies where cisplatin may be employed, as discussed in the introduction to this chapter, include non-Hodgkin's lymphomas (p.656), tumours of brain (p.660), endometrium (p.663), oesophagus, stomach, and anus (p.664, p.664, and p.666), head and neck (p.666), and thymus (p.674), neuroblastoma (p.674), and sarcoma of bone and soft tissue (p.675 and p.676).

Preparations

BP 2008: Cisplatin Injection;
USP 31: Cisplatin for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Ciskebir; Elvecis; Platamine; Platino II; Platinol†; Sicatem; ***Austria:*** Cishexal; Platinol; Platosin; ***Belg.:*** Platinol; Platistine†; Platosin; ***Braz.:*** Astaplatin†; Bioplatino†; C-Platin; Cisplatex; Citoplax; Incel; Laxifos†; Platiran; Platistine; Tecnoplatin; Unistin†; ***Chile:*** Blastolem; ***Cz.:*** Cisanplat†; Platidiam; ***Denm.:*** Lederplatin; Platinol; ***Fin.:*** Platinol; ***Fr.:*** Cisplatyl; ***Ger.:*** Cis-Gry; Platinex; ***Gr.:*** Cisplamol; Cisplatyl†; Oncoplat; Platamine; Platinol; Platosin; ***Hung.:*** Platidiam; ***India:*** Cisplat; Cytoplatin; Kemoplat; Platin; ***Indon.:*** Platinox; Platosin; ***Israel:*** Abiplatin; ***Ital.:*** Citoplatino; Platamine; Platinex; Pronto Platamine; ***Jpn:*** Platosin; Randa; ***Malaysia:*** Platosin; ***Mex.:*** Blastolem; Metalino†; Niyaplat†; Noveldexis; Platinol; Platistil†; Tecnoplatin; ***Neth.:*** Platosin; ***Norw.:*** Platinol; Platistin; ***NZ:*** Platinol; ***Philipp.:*** Ciplexal; Cytoplat; Docistin; Kemoplat; Platamine; Platinol; Platinoxan; Platosin; ***Pol.:*** Platidiam; ***Port.:*** Faulplatin; ***Rus.:*** Blastolem (Бластолем); Platidiam (Платидиам); ***S.Afr.:*** Abiplatin; Platosin; ***Spain:*** Neoplatin; Placis; Platistil†; ***Swed.:*** Platinol; ***Switz.:*** Platiblastin-S; Platinol; ***Thai.:*** Abiplatin; Blastolem; Kemoplat; Platinol; Platosin; ***Turk.:*** Placis; Platosin-S; ***UK:*** Platinex†; ***USA:*** Platinol†; ***Venez.:*** Cytoplatin.

Cladribine *(BAN, USAN, rINN)*

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

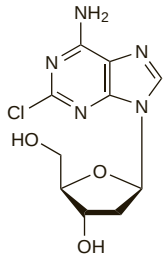
Кладрибин

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

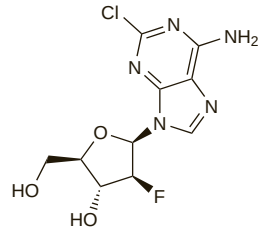
Кльофарабин

$C_{10}H_{11}ClFN_5O_3$ = 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-