mide with corticosteroids may be considered for first-line treatment of severe or rapidly progressive mucous membrane pemphigoid.[7]

1. Pandya AG, Sontheimer RD. Treatment of pemphigus vulgaris with pulse intravenous cyclophosphamide. *Arch Dermatol* 1992; **128:** 1626–30.
2. Itoh T, *et al.* Successful treatment of bullous pemphigoid with pulsed intravenous cyclophosphamide. *Br J Dermatol* 1996; **134:** 931–3.
3. Kirtschig G, *et al.* Interventions for mucous membrane pemphigoid/cicatricial pemphigoid and epidermolysis bullosa acquisita: a systematic literature review. *Arch Dermatol* 2002; **138:** 380–4.
4. Elder MJ, *et al.* Role of cyclophosphamide and high dose steroid in ocular cicatricial pemphigoid. *Br J Ophthalmol* 1995; **79:** 264–6.
5. Harman KE, *et al.* British Association of Dermatologists. Guidelines for the management of pemphigus vulgaris. *Br J Dermatol* 2003; **149:** 926–37.
   Also available at: http://www.bad.org.uk/healthcare/guidelines/Pemphigus_Vulgaris.pdf (accessed 21/02/07)
6. Wojnarowska F, *et al.* British Association of Dermatologists. Guidelines for the management of bullous pemphigoid. *Br J Dermatol* 2002; **147:** 214–21.
   Also available at: http://www.bad.org.uk/healthcare/guidelines/Bullous_Pemphigoid.pdf (accessed 21/02/07)
7. Sacher C, Hunzelmann N. Cicatricial pemphigoid (mucous membrane pemphigoid): current and emerging therapeutic approaches. *Am J Clin Dermatol* 2005; **6:** 93–103.

Rheumatoid arthritis. Cyclophosphamide has been used as a disease-modifying antirheumatic drug in rheumatoid arthritis (p.11), usually in patients with severe disease unresponsive to other drugs; its severe toxicity limits its usefulness.[1] It is of most value in controlling antibody-mediated systemic complications of the disease such as vasculitis[2] through inhibition of B-cell function.

1. Suarez-Almazor ME, *et al.* Cyclophosphamide for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 12/05/05).
2. Choy E, Kingsley G. How do second-line agents work? *Br Med Bull* 1995; **51:** 472–92.

Sarcoidosis. Where drug therapy is required for sarcoidosis (p.1512), corticosteroids are the usual treatment. Cyclophosphamide is one of a number of cytotoxic immunosuppressants that have been tried, with variable results, as a second-line therapy; its use has been limited by toxicity.

Scleroderma. As discussed on p.1817 the role of drug treatment for scleroderma is not well determined, but cyclophosphamide may be useful with or without a corticosteroid for patients with lung involvement.

Vasculitic syndromes. Treatment of the systemic vasculitides has revolved around the use of corticosteroids and cyclophosphamide. The benefits are uncertain in polyarteritis nodosa (p.1510) and Takayasu's arteritis (p.1514), but the benefits of combined therapy are generally accepted in Churg-Strauss syndrome (p.1501) and microscopic polyangiitis (p.1510), and cyclophosphamide is the mainstay of effective treatment of Wegener's granulomatosis (p.1515). A number of regimens are in use; in particular intermittent high-dose intravenous ('pulsed') use is being evaluated in comparison with continuous therapy.[1]

1. Richmond R, *et al.* Optimisation of cyclophosphamide therapy in systemic vasculitis. *Clin Pharmacokinet* 1998; **34:** 79–90.

Preparations

BP 2008: Cyclophosphamide Injection; Cyclophosphamide Tablets; ***USP 31:*** Cyclophosphamide for Injection; Cyclophosphamide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Ciclokebir; Endoxan†; Genoxal†; ***Austral.:*** Cycloblastin; Endoxan; ***Austria:*** Endoxan; ***Belg.:*** Endoxan; ***Braz.:*** Ciclodrax†; Cyclan†; Fosfaseron†; Genuxal; ***Canad.:*** Cytoxan; Procytox; ***Chile:*** Endoxan; Ledoxina; ***Cz.:*** Cytoxan†; Endoxan; ***Denm.:*** Carloxan†; Sendoxan; ***Fin.:*** Sendoxan; ***Fr.:*** Endoxan; ***Ger.:*** Cyclostin†; Endoxan; ***Gr.:*** Endoxan; ***Hong Kong:*** Endoxan; ***Hung.:*** Cytoxan; Endoxan; ***India:*** Cycloxan; Endoxan; Oncophos; ***Indon.:*** Endoxan; ***Irl.:*** Endoxana; ***Israel:*** Cytophosphan; Cytoxan†; Endoxan; ***Ital.:*** Endoxan; ***Jpn:*** Endoxan†; ***Malaysia:*** Endoxan†; ***Mex.:*** Genoxal†; Hidrofosmin; Ledoxina; ***Neth.:*** Endoxan; ***Norw.:*** Sendoxan; ***NZ:*** Cycloblastin; Cytoxan; Endoxan; ***Philipp.:*** Cytoxan; Endoxan; Ledoxan; Xyclomed; ***Pol.:*** Endoxan; ***Port.:*** Endoxan; ***S.Afr.:*** Cycloblastin; Endoxan; ***Singapore:*** Alkyloxan†; Endoxan; ***Spain:*** Genoxal; ***Swed.:*** Sendoxan; ***Switz.:*** Endoxan; ***Thai.:*** Endoxan; Ledoxan; ***Turk.:*** Alkyloxan; Endoxan; ***UK:*** Endoxana†; ***USA:*** Cytoxan†; Neosar; ***Venez.:*** Biodoxan.

Cytarabine *(BAN, USAN, rINN)*

Arabinosylcytosine; Ara-C; Citarabin; Citarabina; Citarabinas; Cytarabin; Cytarabina; Cytarabinum; Cytosine Arabinoside; NSC-63878 (cytarabine hydrochloride); Sitarabin; Sytarabiini; U-19920; U-19920A (cytarabine hydrochloride); WR-28453. 1-β-D-Arabinofuranosylcytosine; 4-Amino-1-β-D-arabinofuranosylpyrimidin-2(1*H*)-one.

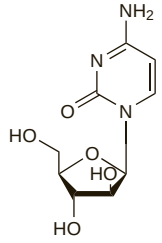
Цитарабин

$C_9H_{13}N_3O_5$ = 243.2.

CAS — 147-94-4 (cytarabine); 69-74-9 (cytarabine hydrochloride).

ATC — L01BC01.

ATC Vet — QL01BC01.



Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Chin. includes the hydrochloride.

Ph. Eur. 6.2 (Cytarabine). A white or almost white, crystalline powder. Freely soluble in water; very slightly soluble in alcohol and in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Cytarabine). An odourless, white to off-white, crystalline powder. Freely soluble in water; slightly soluble in alcohol and in chloroform. Protect from light.

Incompatibility. Although cytarabine has been stated in the literature to be incompatible with solutions of fluorouracil[1,2] and methotrexate[2] some studies have reported it to be stable for some hours when mixed with the latter.[3]

1. McRae MP, King JC. Compatibility of antineoplastic, antibiotic and corticosteroid drugs in intravenous admixtures. *Am J Hosp Pharm* 1976; **33:** 1010–13.
2. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; **17:** 532–8.
3. Cheung Y-W, *et al.* Stability of cytarabine, methotrexate sodium, and hydrocortisone sodium succinate admixtures. *Am J Hosp Pharm* 1984; **41:** 1802–6.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

The major dose-limiting adverse effect of cytarabine is bone-marrow depression, manifest as leucopenia (particularly granulocytopenia), thrombocytopenia, and anaemia, sometimes with striking megaloblastic changes. Myelosuppression appears to be more evident after continuous infusions. Leucopenia is biphasic, with a nadir at 7 to 9 days after a dose and another, more severe, at 15 to 24 days. The nadir of the platelet count occurs at about 12 to 15 days. Recovery generally occurs in a further 10 days.

Gastrointestinal disturbances may occur: nausea and vomiting may be more severe when doses are given rapidly (but other adverse effects are reported to be worse when the drug is given by infusion). Other adverse effects reported include hepatic dysfunction, renal dysfunction, neurotoxicity, bleeding complications, rashes, oral and anal ulceration, gastrointestinal haemorrhage, oesophagitis, and conjunctivitis. A syndrome of bone and muscle pain, fever, malaise, conjunctivitis, and rash, sometimes described as flu-like, has been reported 6 to 12 hours after cytarabine doses, and may be treated or prevented with corticosteroids. Anaphylactoid reactions and pancreatitis have occurred rarely. There may be local pain, cellulitis, and thrombophlebitis at the site of injection.

Intrathecal use of the liposomal cytarabine formulation commonly causes chemical arachnoiditis manifesting as neck stiffness or pain, nausea, vomiting, headache, and fever. Dexamethasone should be used prophylactically to reduce the incidence and severity of this complication. Other rare adverse effects include encephalopathy, and focal seizures. Intrathecal use of conventional cytarabine formulations has rarely been associated with severe spinal cord toxicity, necrotising encephalopathy, blindness, and other neurotoxicities. If given intrathecally, preservative-free diluents must be used.

High-dose therapy has been associated with particularly severe gastrointestinal and CNS effects, including severe ulceration of the gastrointestinal tract, pneumatosis cystoides leading to peritonitis, necrotising colitis and bowel necrosis, peripheral neuropathy, and cerebral and cerebellar dysfunction, with personality changes, somnolence, and coma. There may also be corneal toxicity leading to punctate keratitis and haemorrhagic conjunctivitis, sepsis, liver abscess, severe skin rash leading to desquamation, alopecia, and cardiac disorders including pericarditis and fatal cardiomyopathy. Pulmonary oedema, sometimes fatal, has occurred.

Cytarabine is teratogenic in *animals* (but see Pregnancy, below).

In addition to frequent white blood cell and platelet counts, blood-uric acid should be monitored because of the risk of hyperuricaemia secondary to lysis of neoplastic cells, and renal and hepatic function should be periodically assessed. Cytarabine should be given with care to patients with impaired liver function; dosage reduction may be necessary.

◊ The toxicity of cytarabine has been reviewed.[1] The principal toxicity of standard dosage regimens is myelosuppression but bleeding complications and gastrointestinal toxicity are also major problems at standard doses. With the high-dose regimens neurological toxicity may be dose-limiting: severe and sometimes irreversible symptoms have been seen in some 6 to 10% of patients receiving a cumulative dose of 36 g/m^2. Ocular toxicity may occur in up to 80% of patients at the highest doses. Since cytarabine toxicity is largely dose-related, low-dose cytarabine is generally well tolerated, even in elderly patients (who are more susceptible): its only significant toxicity is myelosuppression.

1. Stentoft J. The toxicity of cytarabine. *Drug Safety* 1990; **5:** 7–27.

Effects on the nervous system. Although paraplegia has been reported with intrathecal cytarabine[1] (see also under Benzyl Alcohol, p.1631) and peripheral neuropathy has occurred in a patient who had received only conventional intravenous doses,[2] the majority of cases of neurotoxicity associated with cytarabine appear to be in patients given high-dose regimens.[3-7] Although some cases have manifested as demyelinating peripheral neuropathy,[3,4] including a syndrome of painful legs and involuntary movements in the toes which showed some response to carbamazepine,[3] most studies have reported in particular a syndrome of cerebellar toxicity,[5-8] with symptoms such as dysarthria, nystagmus, and ataxia. Toxicity appears to be dose-related: in one series[5] CNS toxicity occurred in none of 12 patients given total doses of up to 24 g/m^2 of cytarabine, 3 of 19 receiving 36 g/m^2, and 1 of 12 given 48 g/m^2, none of which were life-threatening or irreversible, whereas 4 of 6 given 54 g/m^2 (as 4.5 g/m^2 every 12 hours for 12 doses) developed neurotoxicity, which was fatal in one and irreversible in another. However, persistent, severe cerebellar toxicity has also been reported in a patient who had received a total dose of only 36 g/m^2 (as 3 g/m^2 every 12 hours).[8] There is some evidence[6] that patients aged over 50, and those who have recently received conventional-dose cytarabine[7] may be at increased risk. Intracranial hypertension (pseudotumor cerebri) has occurred rarely.[9]

1. Saleh MN, *et al.* Intrathecal cytosine arabinoside-induced acute, rapidly reversible paralysis. *Am J Med* 1989; **86:** 729–30.
2. Russell JA, Powles RL. Neuropathy due to cytosine arabinoside. *BMJ* 1974; **4:** 652–3.
3. Malapert D, Degos JD. Jambes douloureuses et orteils instables: neuropathie induite par la cytarabine. *Rev Neurol (Paris)* 1989; **145:** 869–71.
4. Openshaw H, *et al.* Acute polyneuropathy after high dose cytosine arabinoside in patients with leukemia. *Cancer* 1996; **78:** 1899–1905.
5. Lazarus HM, *et al.* Central nervous system toxicity of high-dose systemic cytosine arabinoside. *Cancer* 1981; **48:** 2577–82.
6. Graves T, Hooks MA. Drug-induced toxicities associated with high-dose cytosine arabinoside infusions. *Pharmacotherapy* 1989; **9:** 23–8.
7. Barnett MJ, *et al.* Neurotoxicity of high-dose cytosine arabinoside. *Prog Exp Tumor Res* 1985; **29:** 177–82.
8. Dworkin LA, *et al.* Cerebellar toxicity following high-dose cytosine arabinoside. *J Clin Oncol* 1985; **3:** 613–16.
9. Fort JA, Smith LD. Pseudotumor cerebri secondary to intermediate-dose cytarabine HCl. *Ann Pharmacother* 1999; **33:** 576–8.

Effects on the skin. A syndrome of pain and erythema of the palms and soles, progressing to bullae and desquamation, has been seen in patients receiving intermediate- or high-dose cytarabine.[1-3] The syndrome is similar to the palmar-plantar erythrodysesthesia syndrome (p.639) reported in patients receiving chemotherapy not including cytarabine,[4] although some considered the two forms of toxicity distinct.[5] Cutaneous small vessel necrotising vasculitis has been reported after high-dose therapy with cytarabine.[6]

1. Baer MR, *et al.* Palmar-plantar erythrodysesthesia and cytarabine. *Ann Intern Med* 1985; **102:** 556.
2. Peters WG, Willemze R. Palmar-plantar skin changes and cytarabine. *Ann Intern Med* 1985; **103:** 805.
3. Calista D, Landi C. Cytarabine-induced acral erythema: a localized form of toxic epidermal necrolysis? *J Eur Acad Dermatol Venereol* 1998; **10:** 274–5.
4. Lokich JJ, Moore C. Chemotherapy-associated palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med* 1984; **101:** 798–800.
5. Vogelzang NJ, Ratain MJ. Cancer chemotherapy and skin changes. *Ann Intern Med* 1985; **103:** 303–4.
6. Ahmed I, *et al.* Cytosine arabinoside-induced vasculitis. *Mayo Clin Proc* 1998; **73:** 239–42.

Pregnancy. Although there has been a report of limb and ear deformities in the infant of a woman given cytarabine at the estimated time of conception and 4 to 8 weeks later,[1] no congenital abnormalities were noted in 17 infants, 5 therapeutic abortions, and one still-birth (after pre-eclamptic toxaemia) resulting from over 20 known cases in which cytarabine was given during pregnancy.[2]

1. Wagner VM, *et al.* Congenital abnormalities in baby born to cytarabine treated mother. *Lancet* 1980; **ii:** 98–9.
2. Morgenstern G. Cytarabine in pregnancy. *Lancet* 1980; **ii:** 259.

Interactions

For a general outline of antineoplastic drug interactions, see p.642.

Antifungals. Cytarabine has been reported to inhibit the action of *flucytosine*—see p.534.

Antineoplastics. Acute pancreatitis has been reported in patients given cytarabine who had previously received *asparaginase* therapy.[1] Subclinical damage to the pancreas by asparaginase may have rendered it susceptible to cytarabine.

For a report of hepatic dysfunction in patients who had received cytarabine and *daunorubicin* see under Daunorubicin Hydrochloride, p.709.

Giving cytarabine after *fludarabine* is reported to result in a five-fold increase in intracellular cytarabine concentrations in leukaemic cells,[2] producing improved clinical response rates.

1. Altman AJ, *et al.* Acute pancreatitis in association with cytosine arabinoside therapy. *Cancer* 1982; **49:** 1384–6.
2. Avramis VI, *et al.* Pharmacokinetic and pharmacodynamic studies of fludarabine and cytosine arabinoside administered as loading boluses followed by continuous infusions after a phase I/II study in pediatric patients with relapsed leukemias. *Clin Cancer Res* 1998; **4:** 45–52.

Pharmacokinetics

Cytarabine is not effective orally due to rapid deamination in the gastrointestinal tract; less than 20% of an oral dose is absorbed. After intravenous injection it disappears rapidly from the plasma with an initial half-life of about 10 minutes; the terminal elimination half-life ranges from 1 to 3 hours. It is converted by phosphorylation to an active form, which is rapidly deaminated, mainly in the liver and the kidneys, to inactive 1-β-D-arabinofuranosyluracil (uracil arabinoside, ara-U). The majority of an intravenous dose is excreted in the urine within 24 hours, mostly as the inactive metabolite with about 10% as unchanged cytarabine.

There is only moderate diffusion of cytarabine across the blood-brain barrier after intravenous injection, but, because of low deaminase activity in the CSF, concentrations achieved after continuous intravenous infusion or intrathecal injection are maintained for longer in the CSF than are those in plasma, with a terminal elimination half-life of 3.5 hours. After intrathecal doses of the liposomal formulation, a terminal elimination half-life of 100 to 263 hours was seen. Cytarabine also crosses the placenta.

◊ References.

1. Slevin ML, *et al.* The pharmacokinetics of subcutaneous cytosine arabinoside in patients with acute myelogenous leukaemia. *Br J Clin Pharmacol* 1981; **12:** 507–10.
2. DeAngelis LM, *et al.* Pharmacokinetics of ara-C and ara-U in plasma and CSF after high-dose administration of cytosine arabinoside. *Cancer Chemother Pharmacol* 1992; **29:** 173–7.
3. Hamada A, *et al.* Clinical pharmacokinetics of cytarabine formulations. *Clin Pharmacokinet* 2002; **41:** 705–18.

Uses and Administration

Cytarabine, a pyrimidine nucleoside analogue, is an antimetabolite antineoplastic that inhibits the synthesis of deoxyribonucleic acid. Its actions are specific for the S phase of the cell cycle. It also has antiviral and immunosuppressant properties. Cytarabine is one of the mainstays of the treatment of acute myeloid leukaemias, together with an anthracycline, (see p.652), and is used for the prophylaxis of meningeal leukaemia, as well as in regimens for consolidation, in patients with acute lymphoblastic leukaemia (p.651). It has also been investigated in the blast crisis of chronic myeloid leukaemia (p.653) and the myelodysplasias (p.654) (see also Low-dose Therapy, under Administration, below). It may be used in salvage regimens for Hodgkin's disease (p.655), as part of the complex regimens sometimes employed in aggressive intermediate- and high-grade non-Hodgkin's lymphomas (p.656), and for meningeal lymphoma.

Cytarabine is usually given intravenously. Higher doses can be tolerated when given by rapid injection rather than slow infusion, because of the rapid clearance of cytarabine, but there is little evidence of clinical advantage either way. Cytarabine may be given intrathecally for leukaemic or lymphomatous meningitis.

For the induction of remission in adults and children with acute leukaemias many dosage regimens have been used: 100 mg/m^2 twice daily by rapid intravenous injection, or 100 mg/m^2 daily by continuous intravenous infusion, have often been employed. These doses are generally given for 5 to 10 days, depending on therapeutic response and toxicity. Children reportedly tolerate high doses better than adults.

For maintenance 1 to 1.5 mg/kg once or twice weekly has been given intravenously or subcutaneously; other regimens have been used.

In the treatment of refractory disease high-dose regimens have been used, with cytarabine given in doses of up to 3 g/m^2 every 12 hours for up to 6 days. These doses should be given by intravenous infusion over at least 1 hour.

In leukaemic meningitis cytarabine has been given intrathecally, often in a dose of 10 to 30 mg/m^2 every 2 to 4 days; it has also been used prophylactically. A liposomal formulation is available in some countries for intrathecal use, and permits less frequent dosing because of its longer duration of action: the recommended dose for lymphomatous meningitis is 50 mg intrathecally every 2 weeks for 5 doses then every 4 weeks for 5 doses.

White cell and platelet counts should be determined regularly during treatment with cytarabine and therapy should be stopped immediately if the count falls rapidly or to low values (see also Bone-marrow Depression, p.639).

Cytarabine ocfosfate is an orally active prodrug of cytarabine under investigation in chronic myeloid leukaemia.

Administration. ***Intrathecal.*** Intrathecal doses of the liposomal formulation of cytarabine result in prolonged drug exposure when compared with intrathecal doses of the conventional formulation (see Pharmacokinetics, above). In a randomised study,[1] the liposomal formulation given once every 2 weeks produced a higher response rate and improved Karnofsky score compared with the conventional formulation given twice a week in patients with lymphomatous meningitis secondary to lymphoma. The use of liposomal formulations intrathecally to treat leukaemic or lymphomatous meningitis has been reviewed.[2,3]

1. Glantz MJ, *et al.* Randomized trial of a slow-release versus a standard formulation of cytarabine for the intrathecal treatment of lymphomatous meningitis. *J Clin Oncol* 1999; **17:** 3110–16.
2. Rueda Domínguez A, *et al.* Liposomal cytarabine (DepoCyte) for the treatment of neoplastic meningitis. *Clin Transl Oncol* 2005; **7:** 232–8.
3. Benesch M, Urban C. Liposomal cytarabine for leukemic and lymphomatous meningitis: recent developments. *Expert Opin Pharmacother* 2008; **9:** 301–9.

Low-dose therapy. Because of initial suggestions that low doses of cytarabine might induce differentiation and maturation of leukaemic cells, low-dose therapy has been tried in patients with myelodysplastic syndrome and acute myeloid leukaemia. Although complete remission may occur in about 20% of patients with myelodysplastic syndromes a similar proportion succumb to treatment-related mortality, and remissions do not appear to be particularly long-lasting. Bone-marrow suppression may be marked even at these doses.[1] Low-dose subcutaneous cytarabine (20 mg twice daily for 10 days, at intervals of 4 to 6 weeks) was found to be superior to hydroxycarbamide (with or without all-trans retinoic acid) in elderly patients with acute myeloid leukaemia. Although the authors considered the prognosis for these patients to still be unsatisfactory, they suggested that therapy with low-dose cytarabine could represent a baseline against which other promising treatments might be compared.[2]

1. Aul C, Gattermann N. The role of low-dose chemotherapy in myelodysplastic syndrome. *Leuk Res* 1992; **16:** 207–15.
2. Burnett AK, *et al.* The National Cancer Research Institute Haematological Oncology Study Group Adult Leukemia Working Party. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. *Cancer* 2007; **109:** 1114–24.

Leukoencephalopathy. There are anecdotal reports[1-3] of marked improvement in patients with progressive multifocal leukoencephalopathy secondary to AIDS or chemotherapy-induced immunosuppression who were given intravenous or intrathecal cytarabine. However, a randomised multicentre study[4] indicated that cytarabine was ineffective and had no role in this condition (see also Infections in Immunocompromised Patients, p.859). Others[5] have suggested that even intrathecal dosage may not provide adequate delivery of cytarabine to target cells, and that delivering the drug directly into the brain under pressure might be an alternative. Cytarabine has also been used with cidofovir.[6]

1. O'Riordan T, *et al.* Progressive multifocal leukoencephalopathy-remission with cytarabine. *J Infect* 1990; **20:** 51–4.
2. Portegies P, *et al.* Response to cytarabine in progressive multifocal leucoencephalopathy in AIDS. *Lancet* 1991; **337:** 680–1.
3. Nicoli F, *et al.* Efficacy of cytarabine in progressive multifocal leucoencephalopathy in AIDS. *Lancet* 1992; **339:** 306.
4. Hall CD, *et al.* Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. *N Engl J Med* 1998; **338:** 1345–51.
5. Levy RM, *et al.* Convection-enhanced intraparenchymal delivery (CEID) of cytosine arabinoside (AraC) for the treatment of HIV-related progressive multifocal leukoencephalopathy (PML). *J Neurovirol* 2001; **7:** 382–5.
6. Terrier B, *et al.* Leucoencéphalite multifocale progressive en dehors du sida: efficacité de l'association cytarabine-cidofovir. *Rev Med Interne* 2007; **28:** 488–91.

Preparations

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

Proprietary Preparations (details are given in Part 3)
Arg.: Aracytin†; Citagenin; ***Austria:*** Alexan; ARA-cell; ***Belg.:*** Cyta-Cell; Cytosar; DepoCyte; ***Braz.:*** Aracytin; Citab†; Citarax; Darbin; Serotabir†; Tabine†; ***Canad.:*** Cytosar; DepoCyt†; ***Chile:*** Alexan; Aracytin; Laracit; ***Cz.:*** Alcysten†; Alexan; Cytosar; DepoCyte; ***Denm.:*** Arabine; Cytosar†; DepoCyte; ***Fin.:*** Arabine; DepoCyte; ***Fr.:*** Aracytine; DepoCyte; ***Ger.:*** Alexan; ARA-cell; DepoCyte; Udicil; ***Gr.:*** Aracytin; Citabion; ***Hong Kong:*** Alexan; Cytosar; ***Hung.:*** Alexan; Cytosar; ***India:*** Biobin; Cytarine; ***Indon.:*** Cytosar-U; ***Irl.:*** Cytosar†; ***Israel:*** Alexan; Cytosar; ***Ital.:*** Aracytin; DepoCyte; Erpalfa; ***Jpn:*** Cylocide; Starasid; ***Malaysia:*** Cytosar-U; ***Mex.:*** Alexan†; Cytosar; Ifarab; Laracit; Medsara; Novumtrax; ***Neth.:*** Alexan; Cytosar; DepoCyte; ***Norw.:*** Cytosar†; DepoCyte; ***Philipp.:*** Cytosar-U; Leucyt; Tabine; ***Pol.:*** Alexan; Cytosar; DepoCyte; ***Port.:*** Alexan†; ARA-cell; Citaloxan; Cytosar; Depocyte; ***Rus.:*** Alexan (Алексан); Cytosar (Цитозар); ***S.Afr.:*** Alexan; Cytosar; ***Singapore:*** Alexan†; Cytosar†; ***Spain:*** DepoCyte; ***Swed.:*** Arabine; Cytosar†; DepoCyte; ***Switz.:*** Cytosar; ***Thai.:*** Alexan†; Cytarine; Cytosar; ***Turk.:*** Alexan; ARA-cell; Cytonal; ***UK:*** DepoCyte; ***USA:*** Cytosar-U†; DepoCyt; ***Venez.:*** Cytosar.

Dacarbazine *(BAN, USAN, rINN)*

Dacarbazina; Dacarbazinum; Dakarbatsiini; Dakarbazin; DIC; DTIC; Imidazole Carboxamide; NSC-45388; WR-139007. 5-(3,3-Dimethyltriazeno)imidazole-4-carboxamide.

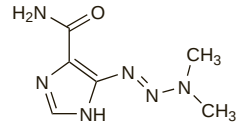
Дакарбазин

$C_6H_{10}N_6O$ = 182.2.

CAS — 4342-03-4 (dacarbazine); 64038-56-8 (dacarbazine citrate).

ATC — L01AX04.

ATC Vet — QL01AX04.



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

Ph. Eur. 6.2 (Dacarbazine). A white or slightly yellowish, crystalline powder. Slightly soluble in water and in anhydrous alcohol; practically insoluble in dichloromethane. Store at 2° to 8°. Protect from light.

USP 31 (Dacarbazine). Store in airtight containers at 2° to 8°. Protect from light.

Incompatibility. Dacarbazine has been reported to be incompatible with hydrocortisone sodium succinate but not with the sodium phosphate.[1] It has been reported to be incompatible with heparin,[2] although only with concentrated dacarbazine solutions (25 mg/mL).

1. Dorr RT. Incompatibilities with parenteral anticancer drugs. *Am J Intravenous Ther* 1979; **6:** 42–52.
2. Nelson RW, *et al.* Visual incompatibility of dacarbazine and heparin. *Am J Hosp Pharm* 1987; **44:** 2028.

Stability. References to the photodegradation of dacarbazine solution.[1-4] Dacarbazine is more sensitive to direct sunlight than to artificial lighting or diffuse daylight.

1. Stevens MFG, Peatey L. Photodegradation of solutions of the antitumour drug DTIC. *J Pharm Pharmacol* 1978; **30** (suppl): 47P.
2. Horton JK, Stevens MFG. Search for drug interactions between the antitumour agent DTIC and other cytotoxic agents. *J Pharm Pharmacol* 1979; **31** (suppl): 64P.
3. Kirk B. The evaluation of a light-protecting giving set. *Intensive Therapy Clin Monit* 1987; **8:** 78–86.
4. El Aatmani M, *et al.* Stability of dacarbazine in amber glass vials and polyvinyl chloride bags. *Am J Health-Syst Pharm* 2002; **59:** 1351–6.