and that have a narrow therapeutic index. Significant effects on exemestane clearance by cytochrome P450 isoenzyme inhibitors are considered unlikely. Exemestane should not be given with oestrogen-containing drugs as these would negate its pharmacological action.

Pharmacokinetics

Exemestane is rapidly absorbed from the gastrointestinal tract. Its bioavailability is limited by first-pass metabolism, but is increased when taken with food. Exemestane is widely distributed, and is extensively bound to plasma proteins. It is metabolised via oxidation by the cytochrome P450 isoenzyme CYP3A4, and via reduction by aldoketoreductase. Metabolites are excreted in the urine and faeces, and less than 1% of a dose is excreted unchanged in the urine. Exemestane has a terminal elimination half-life of about 24 hours.

Uses and Administration

Exemestane is a selective inhibitor of the aromatase (oestrogen synthase) system, similar to formestane (p.726). It is used in the treatment of advanced breast cancer (p.661), in postmenopausal women who are no longer responsive to anti-oestrogen therapy. It is also used for adjuvant treatment of postmenopausal women with oestrogen-receptor positive early breast cancer, after 2 to 3 years of initial adjuvant tamoxifen treatment; a total of 5 years of adjuvant hormonal therapy should be given. The recommended oral dose is 25 mg once daily, preferably after a meal.

In patients receiving potent inducers of the cytochrome P450 isoenzyme CYP3A4 (such as rifampicin or phenytoin), the recommended oral dose of exemestane is 50 mg once daily, after a meal.

◊ References.

1. Clemett D, Lamb HM. Exemestane: a review of its use in postmenopausal women with advanced breast cancer. *Drugs* 2000; **59:** 1279–96.
2. Kaufmann M, *et al.* Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized double-blind trial. *J Clin Oncol* 2000; **18:** 1399–1411.
3. Lønning PE, *et al.* Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: a phase II trial. *J Clin Oncol* 2000; **18:** 2234–44.
4. Coombes RC, *et al.* A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 2004; **350:** 1081–92. Corrections. *ibid.*; **351:** 2461 and *ibid.* 2006; **355:** 1746.
5. Bertelli G, *et al.* Sequential treatment with exemestane and nonsteroidal aromatase inhibitors in advanced breast cancer. *Oncology* 2006; **69:** 471–7.
6. Bundred N. The evolving role of exemestane in the management of breast cancer. *Br J Hosp Med* 2006; **67:** 427–30.
7. Coombes RC, *et al.* Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet* 2007; **369:** 559–70. Correction. *ibid.*; 906.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Aromasin; ***Austral.:*** Aromasin; ***Austria:*** Aromasin; ***Belg.:*** Aromasin; ***Braz.:*** Aromasin; ***Canad.:*** Aromasin; ***Chile:*** Aromasin; ***Cz.:*** Aromasin; ***Denm.:*** Aromasin; ***Fin.:*** Aromasin; ***Fr.:*** Aromasine; ***Ger.:*** Aromasin; ***Gr.:*** Aromasin; ***Hong Kong:*** Aromasin; ***Hung.:*** Aromasin; ***Indon.:*** Aromasin; ***Irl.:*** Aromasin; ***Israel:*** Aromasin; ***Ital.:*** Aromasin; ***Malaysia:*** Aromasin; ***Neth.:*** Aromasin; ***Norw.:*** Aromasin; ***NZ:*** Aromasin; ***Philipp.:*** Aromasin; ***Pol.:*** Aromasin; ***Port.:*** Aromasin; ***Rus.:*** Aromasin (Аромазин); ***S.Afr.:*** Aromasin; ***Singapore:*** Aromasin; ***Spain:*** Aromasil; ***Swed.:*** Aromasin; ***Switz.:*** Aromasin; ***Thai.:*** Aromasin; ***Turk.:*** Aromasin; ***UK:*** Aromasin; ***USA:*** Aromasin; ***Venez.:*** Aromasin.

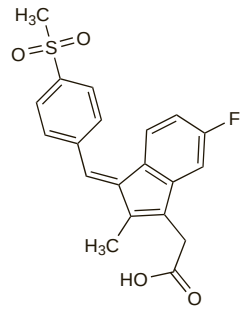
Exisulind *(rINN)*

Exisulindum; FGN-1; Sulindac Sulfone. 5-Fluoro-2-methyl-1-[(*Z*)-*p*-(methylsulfonyl)benzylidene]indene-3-acetic acid.

Эксисулинд

$C_{20}H_{17}FO_4S$ = 372.4.

CAS — 59973-80-7.



Profile

Exisulind is a sulfone metabolite of sulindac (p.126) that is reported to induce apoptosis in cancerous and precancerous cells. It has been studied for the treatment of familial adenomatous polyposis, with variable results. It is also being investigated for the prevention and treatment of malignant neoplasms, including those of the breast, prostate, and lung.

◊ References.

1. Goluboff ET. Exisulind, a selective apoptotic antineoplastic drug. *Expert Opin Invest Drugs* 2001; **10:** 1875–82.
2. Webster WS, Leibovich BC. Exisulind in the treatment of prostate cancer. *Expert Rev Anticancer Ther* 2005; **5:** 957–62.
3. Arber N, *et al.* Sporadic adenomatous polyp regression with exisulind is effective but toxic: a randomised, double blind, placebo controlled, dose-response study. *Gut* 2006; **55:** 367–73.

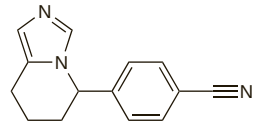
Fadrozole Hydrochloride *(USAN, rINNM)* ⊗

CGS-16949 (fadrozole); CGS-16949A; Fadrozole, Chlorhydrate de; Fadrozoli Hydrochloridum; Hidrocloruro de fadrozol. (±)-*p*-(5,6,7,8-Tetrahydroimidazo[1,5-*a*]pyridin-5-yl)benzonitrile monohydrochloride.

Фадрозола Гидрохлорид

$C_{14}H_{13}N_3HCl$ = 259.7.

CAS — 102676-47-1 (fadrozole); 102676-96-0 (fadrozole hydrochloride).



(fadrozole)

Profile

Fadrozole hydrochloride is a selective nonsteroidal inhibitor of the aromatase (oestrogen synthetase) system, similar to anastrozole (p.681). It is used for the treatment of breast cancer. It has been given in oral doses of 1 mg twice daily.

◊ References.

1. Buzdar AU, *et al.* Fadrozole HCl (CGS-16949A) versus megestrol acetate treatment of postmenopausal patients with metastatic breast carcinoma: results of two randomized double blind controlled multiinstitutional trials. *Cancer* 1996; **77:** 2503–13.
2. Miller AA, *et al.* Fadrozole hydrochloride in postmenopausal patients with metastatic breast carcinoma. *Cancer* 1996; **78:** 789–93.
3. Falkson CI, Falkson HC. A randomised study of CGS 16949A (fadrozole) versus tamoxifen in previously untreated postmenopausal patients with metastatic breast cancer. *Ann Oncol* 1996; **7:** 465–9.
4. Thurlimann B, *et al.* First-line fadrozole HCl (CGS 16949A) versus tamoxifen in postmenopausal women with advanced breast cancer: prospective randomised trial of the Swiss Group for Clinical Cancer Research SAKK 20/88. *Ann Oncol* 1996; **7:** 471–9.
5. Tominaga T, *et al.* Double-blind randomised trial comparing the non-steroidal aromatase inhibitors letrozole and fadrozole in postmenopausal women with advanced breast cancer. *Ann Oncol* 2003; **14:** 62–70.

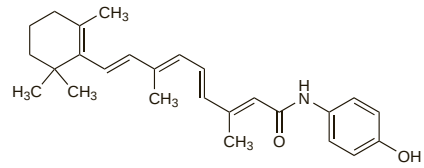
Fenretinide *(USAN, rINN)*

Fenretinida; Fenrétinide; Fenretinidum; 4-HPR; 4-Hydroxyphenylretinamide; McN-R-1967. *all-trans*-4′-Hydroxyretinanilide.

Фенретинид

$C_{26}H_{33}NO_2$ = 391.5.

CAS — 65646-68-6.



Profile

Fenretinide is a retinoid derivative that is given orally and is being studied in the management of breast and prostate cancer, malignant bone tumours, soft-tissue sarcoma, and some other malignancies. It has also been tried in oral lichen planus and leucoplakia. Fenretinide has been investigated in the treatment of psoriasis, but was associated with unacceptable adverse effects such as night blindness and severe toxic erythema.

◊ Fenretinide has been studied for the treatment of breast cancer and cutaneous malignancies but early results were disappointing and night blindness and mucocutaneous effects have been associated with this use.[1] Fenretinide has been investigated for the prevention of breast cancer (p.662), but a large randomised study of secondary prevention failed to show any benefit.[2] A follow-up of the same study[3] found that patients receiving fenretinide had a lower incidence of ovarian carcinoma during the 5-year treatment period, but that this apparently protective effect disappeared after treatment was stopped. Combinations of tamoxifen and fenretinide, given intermittently (for treatment or prevention), have been reported to be well tolerated.[4-6]

1. Modiano MR, *et al.* Phase II study of fenretinide (N-[4-hydroxyphenyl]retinamide) in advanced breast cancer and melanoma. *Invest New Drugs* 1990; **8:** 317–19.
2. Veronesi U, *et al.* Randomized trial of fenretinide to prevent second breast malignancy in women with early breast cancer. *J Natl Cancer Inst* 1999; **91:** 1847–56.
3. De Palo G, *et al.* Effect of fenretinide on ovarian carcinoma occurrence. *Gynecol Oncol* 2002; **86:** 24–7.
4. Cobleigh MA, *et al.* Phase I/II trial of tamoxifen with or without fenretinide, an analog of vitamin A, in women with metastatic breast cancer. *J Clin Oncol* 1993; **11:** 474–7.
5. Conley B, *et al.* Pilot trial of the safety, tolerability, and retinoid levels of N-(4-hydroxyphenyl) retinamide in combination with tamoxifen in patients at high risk for developing invasive breast cancer. *J Clin Oncol* 2000; **18:** 275–83.
6. Guerrieri-Gonzaga A. *et al.* Preliminary results on safety and activity of a randomized, double-blind, 2 x 2 trial of low-dose tamoxifen and fenretinide for breast cancer prevention in premenopausal women. *J Clin Oncol* 2006; **24:** 129–35.

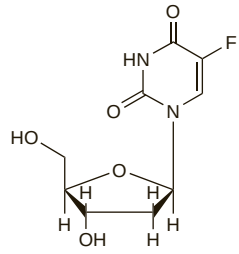
Floxuridine *(USAN, rINN)*

Floxuridina; Floxuridinum; 5-Fluorouracil Deoxyriboside; FUDR; NSC-27640; WR-138720. 2′-Deoxy-5-fluorouridine; 5-Fluoro-2′-deoxyuridine; 1-(2-Deoxy-β-D-ribofuranosyl)-5-fluoropyrimidine-2,4(1*H*,3*H*)-dione.

Флоксуридин

$C_9H_{11}FN_2O_5$ = 246.2.

CAS — 50-91-9.



Pharmacopoeias. In *US.*

USP 31 (Floxuridine). Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Fluorouracil, p.722. Adverse reactions after intra-arterial infusion often include local reactions, thromboembolic complications, and infection or bleeding at the catheter site, or blockage of the catheter. Erythema, stomatitis, and gastrointestinal disturbances are relatively common. There have also been signs of liver dysfunction.

Effects on the liver. Serious biliary toxicity has been reported in over half of all patients receiving hepatic arterial infusions of floxuridine, usually manifesting as sclerosing cholangitis or acalculous cholecystitis;[1] as a result some surgeons routinely remove the gallbladder at the time of infusion pump implantation.[2] Extrahepatic biliary stenosis with jaundice and cholestasis has also been described;[3] the authors suggest that this could lead to intrahepatic biliary damage from bile stasis and infection, recurrent

cholangitis, and biliary sclerosis. Floxuridine infusions have also been associated with a case of fatal progressive cirrhosis of the liver in the absence of overt cholestasis.[4] Pseudoaneurysms of the hepatic artery, leading to serious retroperitoneal or gastrointestinal bleeding, have also been described.[5]

1. Sherlock S. The spectrum of hepatotoxicity due to drugs. *Lancet* 1986; **ii:** 440–4.
2. Anonymous. An implanted infusion pump for chemotherapy of liver metastases. *Med Lett Drugs Ther* 1984; **26:** 89–90.
3. Aldrighetti L, *et al.* Extrahepatic biliary stenoses after hepatic arterial infusion (HAI) of floxuridine (FUdR) for liver metastases from colorectal cancer. *Hepatogastroenterology* 2001; **48:** 1302–7.
4. Pettavel J, *et al.* Fatal liver cirrhosis associated with long-term arterial infusion of floxuridine. *Lancet* 1986; **ii:** 1162–3.
5. Samaras P, *et al.* Hemorrhage associated with hepatic artery pseudoaneurysms after regional chemotherapy with floxuridine: case report. *Int Semin Surg Oncol* 2008; **5:** 17.

Interactions

As for Fluorouracil, p.723.

Pharmacokinetics

Floxuridine is poorly absorbed from the gastrointestinal tract and it is usually given by injection. Floxuridine is metabolised mainly in the liver to fluorouracil after rapid injection. When given by slow intra-arterial infusion, more of the drug is metabolised to floxuridine monophosphate (F-dUMP). It is excreted as carbon dioxide via the lungs; some is excreted, as unchanged drug and metabolites, in urine. Floxuridine crosses the blood-brain barrier to some extent and is found in CSF.

Uses and Administration

Floxuridine is an antineoplastic which acts as an antimetabolite, either by conversion to fluorouracil (after rapid injection), or, when given by slow intra-arterial infusion, partly via floxuridine monophosphate (F-dUMP), which produces greater inhibition of DNA synthesis.

Floxuridine is used in the palliative treatment of hepatic metastases of colorectal cancer—see Malignant Neoplasms of the Liver, p.667. It has been tried in some other solid neoplasms. Doses of 100 to 600 micrograms/kg daily are given by continuous hepatic arterial infusion, usually with the aid of an infusion pump, until toxicity occurs.

White cell and platelet counts should be carried out regularly during therapy and treatment should be stopped if the white cell count falls rapidly or if the white cell or platelet count falls below acceptable levels (see also Bone-marrow Depression, p.639), or if major adverse effects occur.

◊ References.

1. Fordy C, *et al.* Hepatic arterial floxuridine as second-line treatment for systemic fluorouracil-resistant colorectal liver metastases. *Br J Cancer* 1998; **78:** 1058–60.
2. Kemeny N, *et al.* Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999; **341:** 2039–48.
3. Lorenz M, Muller HH. Randomized, multicenter trial of fluorouracil plus leucovorin administered either via hepatic arterial or intravenous infusion versus fluorodeoxyuridine administered via hepatic arterial infusion in patients with nonresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2000; **18:** 243–54.
4. Fiorentini G, *et al.* Locoregional therapy for liver metastases from colorectal cancer: the possibilities of intraarterial chemotherapy, and new hepatic-directed modalities. *Hepatogastroenterology* 2001; **48:** 305–12.
5. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. *N Engl J Med* 2005; **352:** 734–5.

Preparations

USP 31: Floxuridine for Injection.

Proprietary Preparations (details are given in Part 3)
USA: FUDR.

Fludarabine Phosphate

(BAN, USAN, rINNM)

2-F-ara-AMP; Fludarabiinifosfaatti; Fludarabin Fosfat; Fludarabine Monophosphate; Fludarabine, phosphate de; Fludarabinfosfat; Fludarabin-fosfát; Fludarabini phosphas; Fludarabino fosfatas; 2-Fluoro-ara-AMP; Fosfato de fludarabina; NSC-312887. 9-β-D-Arabinofuranosyl-2-fluoroadenine 5′-dihydrogenphosphate.

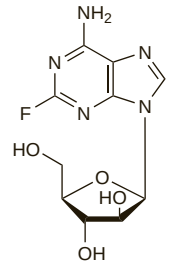
Флударабина Фосфат

$C_{10}H_{13}FN_5O_7P$ = 365.2.

CAS — 21679-14-1 (fludarabine); 75607-67-9 (fludarabine phosphate).

ATC — L01BB05.

ATC Vet — QL01BB05.



(fludarabine)

NOTE. The name FluCam has been used for a regimen of fludarabine with alemtuzumab. Distinguish from Flucam, which is ampiroxicam (p.19).

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

Ph. Eur. 6.2 (Fludarabine Phosphate). A white or almost white, hygroscopic, crystalline powder. Slightly soluble in water; very slightly soluble in dehydrated alcohol; freely soluble in dimethylformamide. Store in airtight containers at a temperature of 2° to 8°. Protect from light.

USP 31 (Fludarabine Phosphate). A white to off-white, hygroscopic, crystalline powder. Slightly soluble in water and in 0.1M hydrochloric acid; practically insoluble in dehydrated alcohol; freely soluble in dimethylformamide. Store at 2° to 8°. Protect from light.

Adverse Effects, Treatment, and Precautions

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

Bone-marrow suppression from fludarabine is dose-limiting, manifesting as neutropenia, thrombocytopenia, and anaemia; the nadir of the white cell and platelet counts usually occurs after about 13 to 16 days. Myelosuppression can be severe and cumulative; prolonged lymphopenia with concomitant risk of opportunistic infections may occur. Bone marrow hypoplasia or aplasia resulting in pancytopenia may sometimes be fatal.

Other common adverse effects include fever, fatigue, chills, cough, weakness, malaise, anorexia, gastrointestinal disturbances, mucositis, stomatitis, oedema, and skin rashes. Pulmonary toxicity, including pulmonary fibrosis, pneumonitis, and dyspnoea can occur. Other adverse effects include dysuria, haematuria, epistaxis, and abnormalities in hepatic or pancreatic enzymes. Tumour lysis syndrome has been reported, especially in patients with large tumour burdens. Autoimmune disorders, including auto-immune haemolytic anaemia, have been reported, and may be life-threatening or fatal. Patients should be monitored for signs of haemolysis and therapy stopped if it occurs. Rarely reported effects include heart failure, arrhythmias, anaphylaxis, and haemorrhagic cystitis. Neurological disturbances include peripheral neuropathy, agitation, confusion, visual disturbances, hearing loss, headache, sleep disorders, and seizures; high doses have been associated with progressive encephalopathy, blindness, coma, and death.

Exacerbation of existing skin cancer lesions as well as new onset of skin cancer has been reported in some patients. Transfusion-associated graft-versus-host disease has been seen after transfusion of non-irradiated blood in patients treated with fludarabine, and fatalities have occurred; patients should only receive irradiated blood.

Dosage should be reduced in renal impairment (see below). It should also be avoided in patients with decompensated haemolytic anaemia.

Carcinogenicity. A study in patients with chronic lymphocytic leukaemia who were treated with fludarabine found that there was no significantly increased risk of secondary malignancy following therapy, despite the immunosuppressive properties of this drug.[1] A review[2] of this and other studies concluded that no significant increase in the risk of secondary malignancy had been shown, but also that long-term follow-up of patients treated with fludarabine was needed.

1. Cheson BD, *et al.* Second malignancies as a consequence of nucleoside analog therapy for chronic lymphoid leukaemias. *J Clin Oncol* 1999; **17:** 2454–60.
2. Van Den Neste E, *et al.* Second primary tumors and immune phenomena after fludarabine or 2-chloro-2′-deoxyadenosine treatment. *Leuk Lymphoma* 2001; **40:** 541–50.

Effects on the eyes. See under Effects on the Nervous System, below.

Effects on the lungs. Pulmonary toxicity manifest as dyspnoea, fever, hypoxaemia, and radiographic evidence of interstitial and alveolar infiltrates was diagnosed in 9 patients of a cohort of 105 treated with fludarabine.[1] Lung biopsies were performed in 6 patients and showed diffuse chronic interstitial inflammation and fibrosis. Patients with chronic lymphocytic leukaemia appeared to be at greater risk of developing this complication than those with non-Hodgkin's lymphoma.

1. Helman DL, *et al.* Fludarabine-related pulmonary toxicity: a distinct clinical entity in chronic lymphoproliferative syndromes. *Chest* 2002; **122:** 785–90.

Effects on the nervous system. High doses (of the order of 100 mg/m^2 daily intravenously) of fludarabine are associated with severe, life-threatening neurotoxicity. However, a few cases of progressive multifocal leukoencephalopathy have also been reported in patients given fludarabine in usual doses.[1-4] The prolonged immunosuppression caused by fludarabine might increase the risk of developing this fatal demyelinating disease, which is caused by opportunistic JC virus infection. Ocular toxicity, including irreversible loss of vision, has also been reported occasionally, including with low-dose regimens.[5]

1. Zabernigg A, *et al.* Late-onset fatal neurological toxicity of fludarabine. *Lancet* 1994; **344:** 1780.
2. Gonzalez H, *et al.* Progressive multifocal leukoencephalitis (PML) in three patients treated with standard-dose fludarabine (FAMP). *Hematol Cell Ther* 1999; **41:** 183–6.
3. Cid J, *et al.* Progressive multifocal leukoencephalopathy following oral fludarabine treatment of chronic lymphocytic leukemia. *Ann Hematol* 2000; **79:** 392–5.
4. Vidarsson B, *et al.* Progressive multifocal leukoencephalopathy after fludarabine therapy for low-grade lymphoproliferative disease. *Am J Hematol* 2002; **70:** 51–4.
5. Ding X, *et al.* Ocular toxicity of fludarabine: a purine analog. *Expert Rev Ophthalmol* 2008; **3:** 97–109.

Graft-versus-host disease. Transfusion-associated graft-versus-host disease has been reported when blood products were used in patients treated with fludarabine.[1] Fludarabine-treated patients should receive irradiated red cells and platelets (to inactivate any viable T-cells) if they require a transfusion.

1. Williamson LM, *et al.* Fludarabine treatment and transfusion-associated graft-versus-host disease. *Lancet* 1996; **348:** 472–3.

Infection. A review[1] of patients treated with fludarabine-containing regimens showed that therapy was associated with serious infections including listeriosis, pneumocystis pneumonia, mycobacterial infections, and opportunistic fungal and viral infections. The risk was exacerbated by previous or current corticosteroid therapy. Prophylactic therapy with co-trimoxazole, triazole antifungals, aciclovir, and colony-stimulating factors was recommended in at-risk patients. A high incidence of herpesvirus infections was also found in another review[2] of patients treated with fludarabine. Combination therapy using chlorambucil and fludarabine resulted in more infections than when either was used alone,[3] but single-agent fludarabine was associated with more major infections and herpesvirus infections than chlorambucil alone. The frequency of serious infection has also been reported[4] to be increased in patients after their conditions became refractory to fludarabine and they were being treated with conventional chemotherapy.

For reports of progressive multifocal leukoencephalopathy caused by opportunistic JC virus infection in patients receiving fludarabine, see Effects on the Nervous System, above.

1. Anaissie EJ, *et al.* Infections in patients with chronic lymphocytic leukemia treated with fludarabine. *Ann Intern Med* 1998; **129:** 559–66.
2. Byrd JC, *et al.* Herpes virus infections occur frequently following treatment with fludarabine: results of a prospective natural history study. *Br J Haematol* 1999; **105:** 445–7.
3. Morrison VA, *et al.* Impact of therapy with chlorambucil, fludarabine, or fludarabine plus chlorambucil on infections in patients with chronic lymphocytic leukemia: Intergroup Study Cancer and Leukemia Group B 9011. *J Clin Oncol* 2001; **19:** 3611–21.
4. Perkins JG, *et al.* Frequency and type of serious infections in fludarabine-refractory B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma: implications for clinical trials in this patient population. *Cancer* 2002; **94:** 2033–9.

Interactions

Increased pulmonary toxicity, sometimes fatal, has been reported in patients given fludarabine with pentostatin. Pretreatment with cytarabine may reduce the metabolic activation of fludarabine, but pretreatment with fludarabine results in increased intracellular concentrations of cytarabine—see p.706. The therapeutic efficacy of fludarabine may also be reduced by dipyridamole and other inhibitors of adenosine uptake.