Preparations

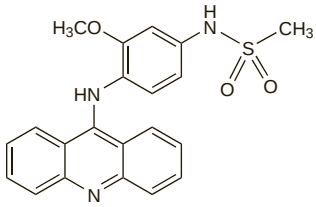
Proprietary Preparations (details are given in Part 3)
Jpn: Calsed.

Amsacrine *(BAN, USAN, pINN)*

Acridinyl Anisidide; *m*-AMSA; Amsacrina; Amsacrinum; Amsakriini; Amsakrin; CI-880; NSC-249992. 4′-(Acridin-9-ylamino)methanesulphon-*m*-anisidide.

Амсакрин

$C_{21}H_{19}N_3O_3S$ = 393.5.
CAS — 51264-14-3.
ATC — L01XX01.
ATC Vet — QL01XX01.



Incompatibility. Amsacrine is incompatible with sodium chloride 0.9% injection and with other chloride-containing solutions,[1,2] apparently because of the poor solubility of the hydrochloride salt in aqueous solution.[2] Amsacrine reacts with certain plastics.[1]

1. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; **17:** 532–8.
2. Trissel LA, *et al.* Visual compatibility of amsacrine with selected drugs during simulated Y-site injection. *Am J Hosp Pharm* 1990; **47:** 2525–8.

Adverse Effects, Treatment, and Precautions

For a general outline see Antineoplastics, p.635, p.639, and p.641.

Bone-marrow depression is usually dose-limiting and may be severe. The nadir of the white cell count has been reported at about 12 days after treatment, with recovery usually by the 25th day. Pancytopenia and haemorrhage may develop. Nausea and vomiting (mild to moderate), stomatitis (mild to life-threatening), rashes, and alopecia may occur. Grand mal seizures, renal dysfunction, hepatotoxicity, and cardiotoxicity have also been reported. Amsacrine is irritant: there may be phlebitis and local tissue necrosis particularly when given in high concentrations.

Amsacrine should be given with caution to patients with liver or kidney disease, who may require dosage adjustments.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. Use with diuretics or nephrotoxic drugs such as the aminoglycosides may theoretically increase the risk of cardiotoxicity with amsacrine by precipitating hypokalaemia.

Pharmacokinetics

Amsacrine is poorly absorbed after oral doses. When given intravenously it has a reported terminal half-life of about 5 to 8 hours. It is metabolised in the liver and excreted primarily in the bile, mostly as metabolites. It is reported to be about 98% protein bound.

Uses and Administration

Amsacrine is an antineoplastic agent that appears to act by intercalation with DNA and inhibition of nucleic acid synthesis. It may also exert an action on cell membranes. Cells in G_2 or S phases may be most sensitive to its actions.

It is used for the induction and maintenance of remission in adult acute leukaemias, particularly acute myeloid leukaemia.

Amsacrine is prepared as a solution in lactic acid and dimethylacetamide, and is given, diluted in glucose 5%, by intravenous infusion over 60 to 90 minutes.

For the induction of remission, amsacrine may be given at a dose of 90 mg/m^2 daily for 5 to 8 days, depending on clinical response. Courses may be repeated at 2- to 4-week intervals according to response, and the dose may be increased to 120 mg/m^2 daily in subsequent courses if tolerated. Maintenance doses of 150 mg/m^2 as a single dose or divided over 3 consecutive days have been given every 3 to 4 weeks, adjusted if necessary according to response.

Complete blood counts should be performed regularly, and cardiac, liver, kidney, and CNS function should be monitored.

Doses should be reduced in patients with hepatic or renal impairment (see below).

◊ References.

1. Ghaddar HM, *et al.* Amsacrine and continuous-infusion high-dose cytosine arabinoside as induction therapy for patients with newly-diagnosed acute myelogenous leukemia. *Leuk Lymphoma* 1996; **22:** 71–6.
2. Reman O, *et al.* Groupe d'Étude et de Traitement de la Leucémie Aiguë Lymphoblastique de l'Adulte. Rescue therapy combining intermediate-dose cytarabine with amsacrine and etoposide in relapsed adult acute lymphoblastic leukemia. *Hematol J* 2004; **5:** 123–9.
3. Sung WJ, *et al.* Phase II trial of amsacrine plus intermediate-dose Ara-C (IDAC) with or without etoposide as salvage therapy for refractory or relapsed acute leukemia. *Jpn J Clin Oncol* 2005; **35:** 612–16.
4. Horstmann MA, *et al.* Amsacrine combined with etoposide and high-dose methylprednisolone as salvage therapy in acute lymphoblastic leukemia in children. *Haematologica* 2005; **90:** 1701–3.
5. Kessler T, *et al.* Amsacrine containing induction therapy in elderly AML patients: comparison to standard induction regimens in a matched-pair analysis. *Leuk Res* 2008; **32:** 491–4.

Administration in hepatic impairment. In moderate to severe hepatic impairment, dosage of amsacrine may need to be reduced by up to 50%. Some licensed product information recommends an initial reduction of 20 to 30%, to a dose between 60 and 75 mg/m^2 daily.

Administration in renal impairment. In moderate to severe renal impairment, dosage of amsacrine may need to be reduced by up to 50%. Some licensed product information recommends an initial reduction of 20 to 30%, to a dose between 60 and 75 mg/m^2 daily.

Preparations

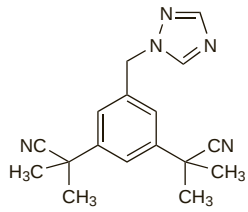
Proprietary Preparations (details are given in Part 3)
Austral.: Amsidyl; ***Belg.:*** Amsidine; ***Canad.:*** Amsa PD; ***Cz.:*** Amsidyl†; ***Denm.:*** Amekrin; ***Fin.:*** Amekrin†; ***Fr.:*** Amsalyo†; ***Ger.:*** Amsidyl†; ***Irl.:*** Amsidine; ***Neth.:*** Amsidine; ***Swed.:*** Amekrin; ***Switz.:*** Amsidyl; ***UK:*** Amsidine.

Anastrozole *(BAN, USAN, rINN)* ⊗

Anastrotsoli; Anastrozol; Anastrozolum; ICI-D1033; ZD-1033. 2,2′-Dimethyl-2,2′-[5-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]bis(propiononitrile); α,α,α′,α′-Tetramethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-*m*-benzenediacetonitrile.

Анастрозол

$C_{17}H_{19}N_5$ = 293.4.
CAS — 120511-73-1.
ATC — L02BG03.
ATC Vet — QL02BG03.



Adverse Effects, Treatment, and Precautions

The most frequent adverse effects are gastrointestinal disturbances including anorexia, nausea and vomiting, and diarrhoea; asthenia; hot flushes; dizziness; drowsiness; headache; and rash. Other reported effects include hair thinning, vaginal dryness or bleeding, myalgia, arthralgia, and bone fractures, Abnormalities in liver enzyme values, thromboembolism, and increases in total cholesterol, have occurred in some patients receiving anastrozole. Very rare cases of erythema multiforme, Stevens-Johnson syndrome, and allergic reactions (including angioedema, urticaria, and anaphylaxis) have occurred.

Reductions in bone mineral density can occur during use of anastrozole. Patients with or at risk of osteoporosis should therefore have their bone density assessed at the start of therapy and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be started as appropriate and carefully monitored.

The use of anastrozole is contra-indicated in premenopausal women (particularly in pregnancy).

Effects on the liver. A case of acute hepatitis was attributed to anastrozole, 3 weeks after starting therapy.[1]

1. de la Cruz L, *et al.* Severe acute hepatitis in a patient treated with anastrozole. *Lancet* 2007; **369:** 23–4.

Effects on the musculoskeletal system. In a series of 77 postmenopausal women treated with anastrozole for metastatic breast cancer, 12 complained of joint pains within 2 months of beginning therapy. Based on this experience and the incidence of arthralgia reported during clinical studies, the authors estimated that arthralgia occurs in 10 to 15% of patients treated with anastrozole, possibly as a result of the very low oestrogen concentrations achieved.[1]

Adjuvant anastrozole therapy for postmenopausal women with early breast cancer was associated with accelerated bone loss, but the risk appeared to be confined to those with osteopenia at baseline.[2] These patients should be assessed for the risk of osteoporosis before starting therapy, and the decision to treat should be made on an individual basis.[3]

1. Donnellan PP, *et al.* Aromatase inhibitors and arthralgia. *J Clin Oncol* 2001; **19:** 2767.
2. Eastell R, *et al.* Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. *J Clin Oncol* 2008; **26:** 1051–8.
3. Chien AJ, Goss PE. Aromatase inhibitors and bone health in women with breast cancer. *J Clin Oncol* 2006; **24:** 5305–12.

Pharmacokinetics

Anastrozole is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses, with peak plasma concentrations within about 2 hours. Food decreases the rate of absorption, though this is not considered clinically significant. Anastrozole is 40% bound to plasma proteins. It is metabolised in the liver, and excreted in urine, chiefly as metabolites. The terminal plasma elimination half-life is about 40 to 50 hours, and steady-state concentrations are achieved after about 7 days in patients receiving once-daily doses.

Uses and Administration

Anastrozole is a potent and selective nonsteroidal inhibitor of the aromatase (oestrogen synthetase) system, which converts adrenal androgens to oestrogens in peripheral tissue. It is used in the treatment of advanced or locally advanced breast cancer, and as adjuvant treatment in early breast cancer (p.661), in postmenopausal women in an oral dose of 1 mg daily. Responses are unlikely in patients with oestrogen receptor-negative disease. Adjuvant therapy may be continued for up to 5 years, although the optimum duration is uncertain.

◊ References.

1. Bonneterre J, *et al.* Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. *J Clin Oncol* 2000; **18:** 3748–57.
2. Nabholtz JM, *et al.* Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. *J Clin Oncol* 2000; **18:** 3758–67.
3. The ATAC (Arimidex, Tamoxifen Alone or in Combination) trialists' group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002; **359:** 2131–9.
4. Wellington K, Faulds DM. Anastrozole in early breast cancer. *Drugs* 2002; **62:** 2483–90.
5. Baum M, *et al.* Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. *Cancer* 2003; **98:** 1802–10.
6. ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005; **365:** 60–2.
7. Jakesz R, *et al.* Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet* 2005; **366:** 455–62.
8. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group. Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. *Lancet Oncol* 2006; **7:** 633–43.
9. Jonat W, *et al.* Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. *Lancet Oncol* 2006; **7:** 991–6. Correction. *ibid.* 2007; **8:** 6.
10. Jakesz R, *et al.* Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. *J Natl Cancer Inst* 2007; **99:** 1845–53. Correction. *ibid.* 2008; **100:** 226.
11. Forbes JF, *et al.* Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncol* 2008; **9:** 45–53.

Endometriosis. In a small, open-label study,[1] *oral* anastrozole 1 mg, given daily with a low-strength oral contraceptive for 6 months, reduced pelvic pain scores in women with refractory endometriosis (p.2091). Adverse effects were mild, although most patients had breakthrough bleeding, which exacerbated pain. The authors supposed that a higher dose of oral contraceptive should be considered in future studies.

In a small pilot study of patients with rectovaginal endometriosis,[2] anastrozole 250 micrograms was given *vaginally* once daily

for 6 months. Dysmenorrhoea improved significantly although chronic pelvic pain was unchanged. Adverse effects were mild.

1. Amsterdam LL, *et al.* Anastrazole [sic] and oral contraceptives: a novel treatment for endometriosis. *Fertil Steril* 2005; **84:** 300–4.
2. Hefler LA, *et al.* Role of the vaginally administered aromatase inhibitor anastrozole in women with rectovaginal endometriosis: a pilot study. *Fertil Steril* 2005; **84:** 1033–6.

Gynaecomastia. Anastrozole has been reported[1] to be under investigation for the treatment of gynaecomastia, but controlled studies suggest that it may be no better than placebo—see Gynaecomastia (p.2092) and Gynaecomastia under Adverse Effects and Precautions of Flutamide (p.725).

1. Gruntmanis U, Braunstein GD. Treatment of gynecomastia. *Curr Opin Investig Drugs* 2001; **2:** 643–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Anaskebir; Anastraze; Anebol; Arimidex; Aromenal; Asiolex†; Distalene; Gondonar; Leprofen; Lezole†; Pantestone; Puricap; Trozolite; ***Austral.:*** Arimidex; ***Austria:*** Arimidex; ***Belg.:*** Arimidex; ***Braz.:*** Arimidex; ***Canad.:*** Arimidex; ***Chile:*** Arimidex; Trozolet; ***Cz.:*** Anabrest; Anaya; Arimidex; Egistrozol; OncoFem; Zynzol; ***Denm.:*** Arimidex; ***Fin.:*** Arimidex; ***Fr.:*** Arimidex; ***Ger.:*** Arimidex; ***Gr.:*** Arimidex; ***Hong Kong:*** Arimidex; ***Hung.:*** Arimidex; ***India:*** Altraz; Armotraz; ***Indon.:*** Arimidex; ***Irl.:*** Arimidex; ***Israel:*** Arimidex; ***Ital.:*** Arimidex; ***Malaysia:*** Arimidex; ***Mex.:*** Arimidex; ***Neth.:*** Arimidex; ***Norw.:*** Arimidex; ***NZ:*** Arimidex; ***Philipp.:*** Arimidex; ***Pol.:*** Arimidex; Atrozol; ***Port.:*** Arimidex; Remidex; ***Rus.:*** Arimidex (Аримидекс); ***S.Afr.:*** Arimidex; ***Singapore:*** Arimidex; ***Spain:*** Arimidex; ***Swed.:*** Arimidex; ***Switz.:*** Arimidex; ***Thai.:*** Arimidex; ***Turk.:*** Arimidex; ***UK:*** Arimidex; ***USA:*** Arimidex; ***Venez.:*** Arimidex; Trozolet.

Antineoplaston A10

3-Phenylacetylamino-2,6-piperidinedione.
$C_{13}H_{14}N_2O_3$ = 246.3.

Profile
Antineoplaston A10, one of a group of peptide derivatives isolated from blood and urine, has been investigated for the treatment of breast cancer, brain stem glioma, and other malignant neoplasms although its value has been questioned (see below).

◊ A critical review of the antineoplastons[1] noted that most work had been done with antineoplaston A10, which is insoluble in aqueous solutions, and its derivatives antineoplaston AS2.5 (phenylacetylglutamine), and antineoplaston AS2.1 (a 4:1 mixture of phenylacetic acid and phenylacetylglutamine), which had not been independently shown to be active against cancer. However, some interest in the antineoplastons subsequently continued.[2-4]

1. Green S. Antineoplastons: an unproved cancer therapy. *JAMA* 1992; **267:** 2924–8.
2. Buckner JC, *et al.* Phase II study of antineoplastons A10 (NSC 648539) and AS2-1 (NSC 620261) in patients with recurrent glioma. *Mayo Clin Proc* 1999; **74:** 137–45.
3. Badria F, *et al.* Immune modulatory potentials of antineoplaston A-10 in breast cancer patients. *Cancer Lett* 2000; **157:** 57–63.
4. Burzynski SR, *et al.* Targeted therapy with antineoplastons A10 and AS2-1 of high-grade, recurrent, and progressive brainstem glioma. *Integr Cancer Ther* 2006; **5:** 40–7.

AP-12009

TGF-β2 antisense oligonucleotide; Transforming growth factor-β2-specific phosphorothioate antisense oligodeoxynucleotide.

Profile
AP-12009 is an antisense oligonucleotide that specifically suppresses the production of transforming growth factor-beta-2, an immunosuppressive protein produced by tumour cells. It is under investigation for the treatment of high-grade glioma (see Malignant Neoplasms of the Brain, p.660).

AS-1411

AGRO-100.

Profile
AS-1411 is a selective oligonucleotide ligand (aptamer) that binds to the protein nucleolin, inducing apoptosis in cancer cells. It is under investigation for the treatment of renal cell carcinoma, pancreatic cancer, and acute myelogenous leukaemia.

Asparaginase *(USAN)*

Asparaginasa; L-Asparaginase; L-Asparagine Amidohydrolase; L-Asparaginaz; L-Asparaginaasi; L-Asparaginas; L-Asparaginasum; MK-965; NSC-109229; Re-82-TAD-15.
CAS — 9015-68-3.
ATC — L01XX02.
ATC Vet — QL01XX02.

NOTE. Asparaginase (*USAN*) is an enzyme isolated from *Escherichia coli*, or obtained from other sources. See also Colaspase and Crisantaspase, below.

Incompatibility. Asparaginase is incompatible with rubber. Licensed product information recommends that it should not be mixed with other drugs.

Storage. Asparaginase should be stored at 2° to 8° (see also Stability, below).

Colaspase *(BAN)*

CAS — 9015-68-3.
ATC — L01XX02.
ATC Vet — QL01XX02.

NOTE. Colaspase (*BAN*) is asparaginase obtained from selected strains of *Escherichia coli*, such as ATCC 9637.

Pharmacopoeias. *Chin.* includes Asparaginase obtained from *Escherichia coli* ASI 357.

Crisantaspase *(BAN)*

Crisantaspasum; Erwinia L-asparaginase; Krisantaspaasi; Krisantaspas.
CAS — 9015-68-3.
ATC — L01XX02.
ATC Vet — QL01XX02.

NOTE. Crisantaspase (*BAN*) is asparaginase obtained from cultures of *Erwinia chrysanthemi* (*E. carotovora*).

Pegaspargase *(USAN, rINN)*

PEG-L-asparaginase; Pegaspargasa; Pégaspargase; Pegaspargasum. A conjugate of colaspase with a polyethylene glycol of molecular weight 5000; Monomethoxypolyethylene glycol succinimidyl L-asparaginase.

Пэгаспаргаза
CAS — 130167-69-0.
ATC — L01XX24.
ATC Vet — QL01XX24.

Stability. Although asparaginase was routinely kept under refrigeration,[1] information from a manufacturer (*Merck Sharp & Dohme*) indicated that it would remain stable for 48 hours at 15° to 30°. Licensed product information for pegaspargase states it should not be used if stored at room temperature for more than 48 hours.

1. Vogenberg FR, Souney PF. Stability guidelines for routinely refrigerated drug products. *Am J Hosp Pharm* 1983; **40:** 101–2.

Storage. Pegaspargase should be stored at 2° to 8°.

Units
One international unit of asparaginase splits 1 micromole of ammonia from L-asparagine in 1 minute under standard conditions.

Adverse Effects
Asparaginase is a protein and may produce anaphylaxis and other hypersensitivity reactions including fever, rashes, and bronchospasm; there does not appear to be cross-sensitivity between asparaginase derived from *Escherichia coli* and that from *Erwinia chrysanthemi*. Hypersensitivity to pegaspargase is less common, but about 30% of patients hypersensitive to the native enzyme experience hypersensitivity to pegaspargase treatment.

Liver function abnormalities occur in many patients, and there may be decreased blood concentrations of fibrinogen and clotting factors, alterations in blood lipids and cholesterol, and hypoalbuminaemia. Hyperammonaemia, due to the production of ammonia from asparagine, may occur. Uraemia, and occasionally renal failure, have been reported. Pancreatitis may occur and may be fatal: there may also be hyperglycaemia due to decreased insulin production, and death from ketoacidosis has occurred.

Gastrointestinal disturbances, including nausea and vomiting, and CNS disturbances, including drowsiness, depression, coma, hallucinations, and a Parkinson-like syndrome, have also been reported. Transient bone-marrow depression has occurred rarely, as has marked leucopenia.

Effects on the blood. Central thrombosis or intracranial haemorrhage as well as peripheral thrombosis and haemorrhage have been reported after asparaginase therapy.[1-4] Although the precise mechanism for this effect remains unclear, asparaginase appears to deplete certain clotting factors as well as antithrombin III, plasminogen, and fibrinogen.[4] These decreases may be dependent on the formulation and resultant asparaginase activity of preparations,[5] and there is some suggestion that crisantaspase may affect coagulation factors less severely than colaspase.[6] A multicentre, retrospective survey[3] of paediatric patients with acute lymphoblastic leukaemia found that use of corticosteroids with colaspase may be an additional risk factor for thromboembolic events.

1. Priest JR, *et al.* A syndrome of thrombosis and hemorrhage complicating L-asparaginase therapy for childhood acute lymphoblastic leukemia. *J Pediatr* 1982; **100:** 984–9.
2. Ott N, *et al.* Sequelae of thrombotic or hemorrhagic complications following L-asparaginase therapy for childhood lymphoblastic leukemia. *Am J Pediatr Hematol Oncol* 1988; **10:** 191–5.
3. Sutor AH, *et al.* Bleeding and thrombosis in children with acute lymphoblastic leukaemia, treated according to the ALL-BFM-90 protocol. *Klin Padiatr* 1999; **211:** 201–4.
4. Alberts SR, *et al.* Thrombosis related to the use of L-asparaginase in adults with acute lymphoblastic leukemia: a need to consider coagulation monitoring and clotting factor replacement. *Leuk Lymphoma* 1999; **32:** 489–96.
5. Nowak-Göttl U, *et al.* Influence of two different Escherichia coli asparaginase preparations on fibrinolytic proteins in childhood ALL. *Haematologica* 1996; **81:** 127–31.
6. Carlsson H, *et al.* Effects of Erwinia-asparaginase on the coagulation system. *Eur J Haematol* 1995; **55:** 289–93.

Precautions
Asparaginase is contra-indicated in patients with pancreatitis, and should be avoided in pregnancy. It should be given cautiously to patients with hepatic impairment. Facilities for the management of anaphylaxis (see p.1205) should be available during treatment. Some manufacturers recommend an intradermal test dose at the start of asparaginase treatment to check for hypersensitivity, as described under Uses, below, although such tests may not always be predictive. Retreatment with asparaginase may be associated with an increased risk of allergic reactions. Serum amylase concentrations should be monitored regularly as should blood glucose concentrations. Asparaginase has been reported to interfere with tests of thyroid function by transient reduction of concentrations of thyroxine-binding globulin.

Interactions
If asparaginase is given before, rather than after, methotrexate the activity of the latter may be reduced (see below). Vincristine neurotoxicity may possibly be increased by use with intravenous asparaginase (see p.787).

Methotrexate. Asparaginase inhibits protein synthesis and cell replication, and therefore may interfere with the action of drugs such as methotrexate that require cell replication for their antineoplastic effect.[1] It has been suggested that a 24-hour interval between methotrexate and a subsequent dose of asparaginase permits at least an additive therapeutic effect.[2]

1. Jolivet J, *et al.* Prevention of methotrexate cytotoxicity by asparaginase inhibition of methotrexate polyglutamate formation. *Cancer Res* 1985; **45:** 217–20.
2. Capizzi RL. Asparaginase-methotrexate in combination chemotherapy: schedule-dependent differential effects on normal versus neoplastic cells. *Cancer Treat Rep* 1981; **65** (suppl 4): 115–21.

Pharmacokinetics
After intravenous injection the plasma half-life of the native enzyme has varied from about 8 to 30 hours; half-lives of up to 49 hours may be seen after intramuscular dosage. The mean half-life of pegaspargase is reported to be between 6 and 14 days. Asparaginase is found in the lymph at about 20% of the concentration in plasma. There is virtually no diffusion into the CSF. Little is excreted in the urine.

Uses and Administration
Asparaginase is an enzyme that acts by breaking down the amino acid L-asparagine to aspartic acid and ammonia. It interferes with the growth of those malignant cells which, unlike most healthy cells, are unable to synthesise L-asparagine for their metabolism, but resistance to its action develops fairly rapidly. Its action is reportedly specific for the G_1 phase of the cell cycle.

Asparaginase is used mainly for the induction of remissions in acute lymphoblastic leukaemia (p.651). Regimens vary, and dosage should follow local protocols, but it may be given intravenously in a dose of 1000 units/kg daily for 10 days after treatment with vincristine and prednisone or prednisolone, or intramuscularly in a dose of 6000 units/m^2 given every third day for 9 doses during treatment with vincristine and prednisone or prednisolone. Alternatively it may