Preparations

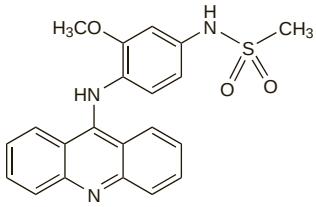
Proprietary Preparations (details are given in Part 3)
Jpn: Calsed.

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

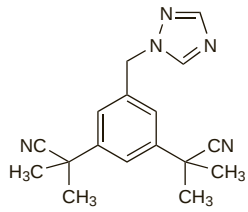
Proprietary Preparations (details are given in Part 3)
Austral.: Amsidyl; ***Belg.:*** Amsidine; ***Canad.:*** Amsa PD; ***Cz.:*** Amsidyl†; ***Denm.:*** Amekrin; ***Fin.:*** Amekrin†; ***Fr.:*** Amsalyo†; ***Ger.:*** Amsidyl†; ***Irl.:*** Amsidine; ***Neth.:*** Amsidine; ***Swed.:*** Amekrin; ***Switz.:***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