6. Hale G, *et al.* Alemtuzumab (Campath-1H) for treatment of lymphoid malignancies in the age of nonmyeloablative conditioning? *Bone Marrow Transplant* 2002; **30:** 797–804.
7. Frampton JE, Wagstaff AJ. Alemtuzumab. *Drugs* 2003; **63:** 1229–43.
8. Keating M, *et al.* Management guidelines for use of alemtuzumab in B-cell chronic lymphocytic leukemia. *Clin Lymphoma* 2004; **4:** 220–7.
9. Faderl S, *et al.* The evolving role of alemtuzumab in management of patients with CLL. *Leukemia* 2005; **19:** 2147–52.
10. Morris PJ, Russell NK. Alemtuzumab (Campath-1H): a systematic review in organ transplantation. *Transplantation* 2006; **81:** 1361–7.
11. Magliocca JF, Knechtle SJ. The evolving role of alemtuzumab (Campath-1H) for immunosuppressive therapy in organ transplantation. *Transpl Int* 2006; **19:** 705–14.
12. Ravandi F, O'Brien S. Alemtuzumab in CLL and other lymphoid neoplasms. *Cancer Invest* 2006; **24:** 718–25.
13. Hillmen P, *et al.* Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. *J Clin Oncol* 2007; **25:** 5616–23.

Administration. Subcutaneous use of alemtuzumab has been investigated as a means of reducing adverse infusion reactions associated with intravenous dosage. Studies have found it to be safe and effective.[1,2] Similar blood concentrations are achieved to those after intravenous use, although accumulation in the blood took longer to achieve with subcutaneous use, and higher cumulative doses were required.[3] Prolonged treatment with subcutaneous low-dose alemtuzumab (10 mg three times weekly for 18 weeks) has been reported to be as effective as intravenous infusion in patients with chronic lymphocytic leukaemia and a poor prognosis.[4]

1. Montillo M, *et al.* Safety and efficacy of subcutaneous Campath-1H for treating residual disease with chronic lymphocytic leukemia responding to fludarabine. *Haematologica* 2002; **87:** 695–700.
2. Lundin J, *et al.* Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL). *Blood* 2002; **100:** 768–73.
3. Hale G, *et al.* Blood concentrations of alemtuzumab and antiglobulin responses in patients with chronic lymphocytic leukemia following intravenous or subcutaneous routes of administration. *Blood* 2004; **104:** 948–55.
4. Cortelezzi A, *et al.* A pilot study of low-dose subcutaneous alemtuzumab therapy for patients with hemotherapy-refractory [sic] chronic lymphocytic leukemia. *Haematologica* 2005; **90:** 410–12.

Preparations

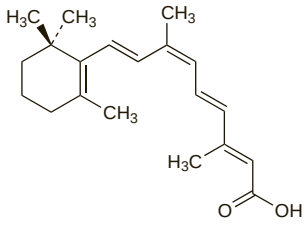
Proprietary Preparations (details are given in Part 3)
Arg.: Campath; ***Austria:*** MabCampath; ***Belg.:*** MabCampath; ***Braz.:*** Campath; ***Cz.:*** MabCampath; ***Denm.:*** MabCampath; ***Fin.:*** MabCampath; ***Fr.:*** MabCampath; ***Ger.:*** MabCampath; ***Gr.:*** MabCampath; ***Hung.:*** MabCampath; ***Irl.:*** MabCampath; ***Israel:*** MabCampath; ***Ital.:*** MabCampath; ***Malaysia:*** MabCampath; ***Neth.:*** MabCampath; ***Norw.:*** MabCampath; ***Pol.:*** MabCampath; ***Port.:*** MabCampath; ***Rus.:*** Campath (Кампас); ***S.Afr.:*** MabCampath; ***Singapore:*** MabCampath; ***Spain:*** MabCampath; ***Swed.:*** MabCampath; ***Switz.:*** MabCampath; ***UK:*** MabCampath; ***USA:*** Campath.

Alitretinoin *(BAN, USAN, rINN)*

AGN-192013; Alitretinoiini; Alitretinoína; Alitrétinoïne; Alitretinoinum; ALRT-1057; BAL-4079; LG-100057; LGD-1057; NSC-659772; 9-*cis*-Retinoic Acid. (2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid.

Алитретиноин

$C_{20}H_{28}O_2$ = 300.4.
CAS — 5300-03-8.
ATC — L01XX22.
ATC Vet — QL01XX22.



Adverse Effects and Precautions

Local skin toxicity may occur with topical application of alitretinoin, in particular erythema and oedema, and in some patients this may be dose-limiting. Pain, paraesthesia, rashes, pruritus, exfoliative dermatitis, and other skin disorders may also occur locally. Lymphadenopathy, phlebitis, cellulitis, and bacterial infections have been reported. Alitretinoin may have a weak photosensitising effect, and patients should minimise exposure of treated areas to sunlight or other ultraviolet light during therapy.

Interactions

Use of products containing diethyltoluamide is not recommended during alitretinoin therapy, as *animal* studies indicate an increase in diethyltoluamide toxicity with concurrent use.

Pharmacokinetics

Systemic absorption of topical alitretinoin is not considered to be extensive. *In-vivo* studies of oral doses indicate that alitretinoin is metabolised to 4-oxo-9-*cis*-retinoic acid.

Uses and Administration

Alitretinoin is a retinoid related to tretinoin (p.1618). It is used topically, as a 0.1% gel, in the management of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma (p.675). It is applied directly to the lesions twice daily, increasing to up to 4 times daily if tolerated. Doses should be increased at intervals of at least 2 weeks. If local toxicity occurs, application frequency should be reduced, or treatment temporarily stopped, until the symptoms subside. EU licensed product information states that if no response is seen after 12 weeks, therapy should be stopped; however, US licensed product information states that some patients have required over 14 weeks to respond. Treatment may be continued as long as the patient responds. Oral formulations of alitretinoin are under investigation for the treatment of chronic hand dermatitis refractory to topical corticosteroids.

◊ References.

1. Cheer SM, Foster RH. Alitretinoin. *Am J Clin Dermatol* 2000; **1:** 307–14.
2. Bodsworth NJ, *et al.* Phase III vehicle-controlled, multi-centered study of topical alitretinoin gel 0.1% in cutaneous AIDS-related Kaposi's sarcoma. *Am J Clin Dermatol* 2001; **2:** 77–87.
3. Miles SA, *et al.* Antitumor activity of oral 9-cis-retinoic acid in HIV-associated Kaposi's sarcoma. *AIDS* 2002; **16:** 421–9.
4. Kurie JM, *et al.* Treatment of former smokers with 9-cis-retinoic acid reverses loss of retinoic acid receptor-beta expression in the bronchial epithelium: results from a randomized placebo-controlled trial. *J Natl Cancer Inst* 2003; **95:** 206–14.
5. Aboulafia DM, *et al.* 9-cis-Retinoic acid capsules in the treatment of AIDS-related Kaposi sarcoma: results of a phase 2 multicenter clinical trial. *Arch Dermatol* 2003; **139:** 178–86.
6. Ruzicka T, *et al.* Oral alitretinoin (9-cis-retinoic acid) therapy for chronic hand dermatitis in patients refractory to standard therapy: results of a randomized, double-blind, placebo-controlled, multicenter trial. *Arch Dermatol* 2004; **140:** 1453–9.
7. Ruzicka T, *et al.* Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Dermatol* 2008; **158:** 808–17.

Preparations

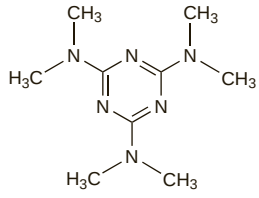
Proprietary Preparations (details are given in Part 3)
Arg.: Panretin; ***Cz.:*** Panretin; ***Fr.:*** Panretin; ***Ger.:*** Panretin; ***Gr.:*** Panretin; ***Neth.:*** Panretin; ***Port.:*** Panretin; ***USA:*** Panretin.

Altretamine *(BAN, USAN, rINN)*

Altretamiini; Altretamin; Altretamina; Altrétamine; Altretaminum; Hexamethylmelamine; HMM; NSC-13875; WR-95704. 2,4,6-Tris(dimethylamino)-1,3,5-triazine; N^2,N^2,N^4,N^4,N^6,N^6-Hexamethyl-1,3,5-triazine-2,4,6-triamine.

Альтретамин

$C_9H_{18}N_6$ = 210.3.
CAS — 645-05-6.
ATC — L01XX03.
ATC Vet — QL01XX03.



Pharmacopoeias. In *Chin.* and *US*.
USP 31 (Altretamine). A white crystalline powder. Insoluble in water; soluble in chloroform. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

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

Bone-marrow depression is usually moderate, manifesting as leucopenia, thrombocytopenia, and anaemia, and may require dosage reduction; blood counts should be monitored regularly. Nausea and vomiting are common and usually moderate although they may be dose-limiting. Prolonged or high-dose therapy may be associated with neurotoxicity, both peripheral (neuropathies) and central (ataxia, depression, confusion, drowsiness, and hallucinations); neurological examination should be performed regularly and treatment interrupted or the dose reduced as appropriate. Renal toxicity may also be dose-limiting. Other rare adverse effects include rashes, alopecia, and hepatic toxicity.

Handling. Altretamine is irritant; avoid contact with skin and mucous membranes.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. Pyridoxine appears to reduce the activity of altretamine.

Antidepressants. Severe and potentially life-threatening orthostatic hypotension developed in 3 patients who took *amitriptyline* or *imipramine* with altretamine and in a fourth patient who took *phenelzine* and altretamine.[1] One patient was able to tolerate the antineoplastic with *nortriptyline*.

1. Bruckner HW, Schleifer SJ. Orthostatic hypotension as a complication of hexamethylmelamine antidepressant interaction. *Cancer Treat Rep* 1983; **67:** 516.

Pharmacokinetics

Altretamine is well absorbed from the gastrointestinal tract after oral doses, but is rapidly demethylated in the liver producing variation in plasma-altretamine concentrations. The principal metabolites are pentamethylmelamine and tetramethylmelamine, which are excreted in urine. The elimination half-life has been reported to be 4 to 10 hours.

◊ References.

1. Damia G, D'Incalci M. Clinical pharmacokinetics of altretamine. *Clin Pharmacokinet* 1995; **28:** 439–48.

Uses and Administration

Altretamine is an antineoplastic agent structurally similar to the alkylating agent tretamine (triethylenemelamine) although its mode of action may be different. It is given orally and is licensed for use as a single agent in the palliative treatment of ovarian carcinoma (p.670). Altretamine has also been tried in lung cancer. The usual dose as a single agent in ovarian cancer is 260 mg/m^2 daily in four divided doses, for 14 or 21 consecutive days out of a 28-day cycle. Up to 12 cycles may be given. Therapy should be interrupted for at least 14 days, and subsequently restarted at a lower dose of 200 mg/m^2 daily, if the white cell count falls below 2000 cells/mm^3 or the platelet count below 75 000 cells/mm^3 or if neurotoxic or intolerable gastrointestinal symptoms occur. Lower doses are also used in combination regimens.

◊ Reviews.

1. Lee CR, Faulds D. Altretamine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in cancer chemotherapy. *Drugs* 1995; **49:** 932–53.
2. Manetta A, *et al.* Hexamethylmelamine as a single second-line agent in ovarian cancer: follow-up report and review of the literature. *Gynecol Oncol* 1997; **66:** 20–6.

Preparations

USP 31: Altretamine Capsules.

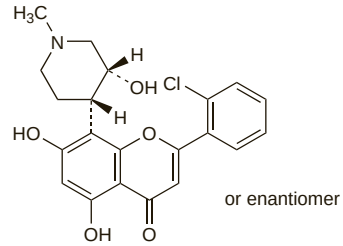
Proprietary Preparations (details are given in Part 3)
Austral.: Hexalen; ***Cz.:*** Tretax†; ***Neth.:*** Hexalen; ***Norw.:*** Hexalen†; ***NZ:*** Hexalen†; ***Rus.:*** Hexalen (Гексален); ***Swed.:*** Hexalen†; ***Thai.:*** Hexalen; ***USA:*** Hexalen.

Alvocidib *(rINN)*

Alvocidibum; Avodenib; Flavopiridol. (–)-*cis*-2-(2-Chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methylpiperidin-4-yl)-4*H*-1-benzopyran-4-one.

Альвоцидиб

$C_{21}H_{20}ClNO_5$ = 401.8.
CAS — 146426-40-6.



Alvocidib Hydrochloride *(rINNM)*

Alvocidib *(USAN)*; Alvocidib, Chlorhydrate d'; Alvocidibi Hydrochloridum; Hidrocloruro de alvocidib; HL-275; HMR-1275; L-868275; MDL-107826A; NSC-649890. (–)-*cis*-2-(2-Chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methylpiperidin-4-yl)-4*H*-1-benzopyran-4-one hydrochloride.

Альвоцидиба Гидрохлорид

$C_{21}H_{20}ClNO_5$,HCl = 438.3.
CAS — 131740-09-5.

Profile

Alvocidib is an inhibitor of cyclin-dependent kinase that is under investigation as an antineoplastic for the treatment of chronic lymphocytic leukaemia.