4. Richardson PG, *et al.* Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2005; **352:** 2487–98.
5. O'Connor OA. Marked clinical activity of the proteasome inhibitor bortezomib in patients with follicular and mantle-cell lymphoma. *Clin Lymphoma Myeloma* 2005; **6:** 191–9.
6. Popat R, *et al.* Bortezomib for multiple myeloma. *Expert Opin Pharmacother* 2006; **7:** 1337–46.
7. Wang M, *et al.* Use of bortezomib in B-cell non-Hodgkin's lymphoma. *Expert Rev Anticancer Ther* 2006; **6:** 983–91.
8. NICE. Bortezomib monotherapy for relapsed multiple myeloma (issued October 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA129Guidance.pdf (accessed 23/05/08)

Preparations

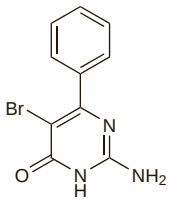
Proprietary Preparations (details are given in Part 3)
Arg.: Velcade; ***Austral.:*** Velcade; ***Belg.:*** Velcade; ***Canad.:*** Velcade; ***Chile:*** Velcade; ***Cz.:*** Velcade; ***Denm.:*** Velcade; ***Fin.:*** Velcade; ***Fr.:*** Velcade; ***Ger.:*** Velcade; ***Gr.:*** Velcade; ***Hong Kong:*** Velcade; ***Hung.:*** Velcade; ***Indon.:*** Velcade; ***Israel:*** Velcade; ***Ital.:*** Velcade; ***Malaysia:*** Velcade; ***Mex.:*** Velcade; ***Neth.:*** Velcade; ***Norw.:*** Velcade; ***NZ:*** Velcade; ***Philipp.:*** Velcade; ***Pol.:*** Velcade; ***Port.:*** Velcade; ***Rus.:*** Velcade (Велкейд); ***Singapore:*** Velcade; ***Spain:*** Velcade; ***Swed.:*** Velcade; ***Switz.:*** Velcade; ***Thai.:*** Velcade; ***UK:*** Velcade; ***USA:*** Velcade; ***Venez.:*** Velcade.

Bropirimine *(BAN, USAN, rINN)*

ABPP; Bropirimina; Bropiriminum; U-54461; U-54461S. 2-Amino-5-bromo-6-phenyl-4(3*H*)-pyrimidinone.

Бропиримин

$C_{10}H_8BrN_3O$ = 266.1.
CAS — 56741-95-8.



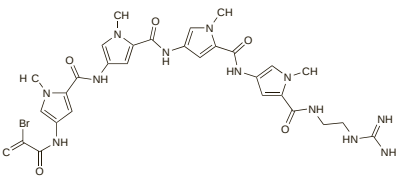
Profile
Bropirimine is reported to have immunomodulatory actions, possibly due to the induction of interferons. It has been investigated in the management of carcinoma in situ of the bladder (p.659).

Brostallicin *(rINN)*

Brostalicina; Brostallicine; Brostallicinum; PNU-166196 (hydrochloride). 4-(2-Bromoacrylamido)-*N*‴-(2-guanidinoethyl)-1,1′,-1″,1‴-tetramethyl-*N*,4′:*N*′,4″:*N*″,4‴-quater[pyrrole-2-carboxamide].

Бростальлицин

$C_{30}H_{35}BrN_{12}O_5$ = 723.6.
CAS — 203258-60-0.



Profile
Brostallicin is an antineoplastic that binds to DNA. It is under investigation for the treatment of soft-tissue sarcomas.

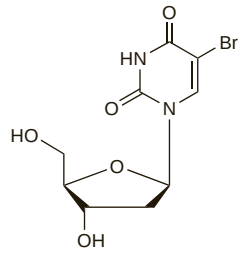
◊ References.
1. ten Tije AJ, *et al.* Phase I and pharmacokinetic study of brostallicin (PNU-166196), a new DNA minor-groove binder, administered intravenously every 3 weeks to adult patients with metastatic cancer. *Clin Cancer Res* 2003; **9:** 2957–64.
2. Broggini M, *et al.* Brostallicin: a new concept in minor groove DNA binder development. *Anticancer Drugs* 2004; **15:** 1–6.
3. Leahy M, *et al.* Brostallicin, an agent with potential activity in metastatic soft tissue sarcoma: a phase II study from the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 2007; **43:** 308–15.

Broxuridine *(rINN)*

Bromodeoxyuridine; Broxuridina; Broxuridinum; BUDR; NSC-38297. 5-Bromo-2′-deoxyuridine; 5-Bromo-1-(2-deoxy-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione.

Броксуридин

$C_9H_{11}BrN_2O_5$ = 307.1.
CAS — 59-14-3.



Profile
Broxuridine is a thymidine analogue which acts as a radiosensitiser to enhance the effects of radiotherapy. It is also reported to possess antiviral activity. A related compound brivudine (p.867) is used as an antiviral.

Broxuridine has been given by intra-arterial infusion, with radiotherapy and other antineoplastic agents, in the treatment of tumours of the brain, head, and neck. It has also been used diagnostically.

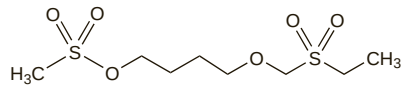
◊ References.
1. Freese A, *et al.* The application of 5-bromodeoxyuridine in the management of CNS tumors. *J Neurooncol* 1994; **20:** 81–95.
2. Phillips TL, *et al.* Results of a randomized comparison of radiotherapy and bromodeoxyuridine with radiotherapy alone for brain metastases: report of RTOG trial 89-05. *Int J Radiat Oncol Biol Phys* 1995; **33:** 339–48.
3. Prados MD, *et al.* Influence of bromodeoxyuridine radiosensitization on malignant glioma patient survival: a retrospective comparison of survival data from the Northern California Oncology Group (NCOG) and Radiation Therapy Oncology Group trials (RTOG) for glioblastoma multiforme and anaplastic astrocytoma. *Int J Radiat Oncol Biol Phys* 1998; **40:** 653–9.
4. Prados MD, *et al.* Phase III randomized study of radiotherapy plus procarbazine, lomustine, and vincristine with or without BUdR for treatment of anaplastic astrocytoma: final report of RTOG 9404. *Int J Radiat Oncol Biol Phys* 2004; **58:** 1147–52.

Busulfan *(BAN, rINN)*

Bussulfam; Busulfaani; Busulfanas; Busulfano; Busulfanum; Busulphan; Buszulfán; CB-2041; GT-41; Myelosan; NSC-750; WR-19508. Tetramethylene di(methanesulphonate); Butane-1,4-diol di(methanesulphonate).

Бусульфан

$C_6H_{14}O_6S_2$ = 246.3.
CAS — 55-98-1.
ATC — L01AB01.
ATC Vet — QL01AB01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Busulfan). A white or almost white, crystalline powder. Very slightly soluble in water and in alcohol; freely soluble in acetone and in acetonitrile. Store in airtight containers. Protect from light.
USP 31 (Busulfan). A white, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; soluble 1 in 45 of acetone. Store in airtight containers.

Adverse Effects and Treatment

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

The major adverse effect of busulfan with standard doses is bone-marrow depression, manifest as leucopenia, thrombocytopenia, and sometimes, anaemia. The nadir of the granulocyte count usually occurs after about 10 to 30 days with recovery occurring over up to 5 months, but busulfan has sometimes caused irreversible or extremely-prolonged bone-marrow depression.

Hyperpigmentation is common, and in a few cases after long-term therapy may be part of a syndrome simulating Addison's disease.

Rarely, progressive interstitial pulmonary fibrosis, known as 'busulfan lung', can occur on prolonged treatment. Gastrointestinal disturbances are rare at usual therapeutic doses but may be dose-limiting where high doses are given before bone marrow transplantation. Other rare adverse effects include dry skin and other skin reactions, liver damage, gynaecomastia, cataract formation, and, at high doses, CNS effects including convulsions.

Busulfan may result in impaired fertility and gonadal function. As with other alkylating agents, it is potentially carcinogenic, mutagenic, and teratogenic.

Effects on the bladder. Haemorrhagic cystitis occurred in a patient who had received prolonged therapy with busulfan.[1] High-dose busulfan used in conditioning regimens for haematopoietic stem cell transplantation may increase the risk of late-onset haemorrhagic cystitis.[2,3]

1. Pode D, *et al.* Busulfan-induced hemorrhagic cystitis. *J Urol (Baltimore)* 1983; **130:** 347–8.
2. Kondo M, *et al.* Late-onset hemorrhagic cystitis after hematopoietic stem cell transplantation in children. *Bone Marrow Transplant* 1998; **22:** 995–8.
3. Leung AYH, *et al.* Clinicopathological features and risk factors of clinically overt haemorrhagic cystitis complicating bone marrow transplantation. *Bone Marrow Transplant* 2002; **29:** 509–13.

Effects on the liver. Jaundice in the terminal phase of chronic myeloid leukaemia in a 31-year-old man was attributed to busulfan which had been taken for 6 years.[1] Busulfan toxicity involving the liver was also reported in a patient who had taken busulfan for 54 months,[2] while hepatitis possibly associated with busulfan therapy has also been described.[3] Dose-dependent veno-occlusive disease (VOD) has been reported in 20 to 40% of patients receiving high-dose busulfan before bone marrow transplantation.[4] Licensed product information from 1 manufacturer (*Pierre Fabre, UK*) states that previous radiotherapy, progenitor cell transplantation, or three cycles of chemotherapy or more, can increase the risk of hepatic VOD; another (*GSK*) lists concurrent use of multiple alkylating agents, or total doses of busulfan in excess of 16 mg/kg, as possible risk factors. A reduced incidence of hepatic VOD has been seen in those patients given high-dose busulfan and cyclophosphamide when the first dose of cyclophosphamide has been delayed for more than 24 hours after the last dose of busulfan.

1. Underwood JCE, *et al.* Jaundice after treatment of leukaemia with busulphan. *BMJ* 1971; **1:** 556–7.
2. Foadi MD, *et al.* Portal hypertension in a patient with chronic myeloid leukaemia. *Postgrad Med J* 1977; **53:** 267–9.
3. Morris L, Guthrie T. Busulfan-induced hepatitis. *Am J Gastroenterol* 1988; **83:** 682–3.
4. Hassan M. The role of busulfan in bone marrow transplantation. *Med Oncol* 1999; **16:** 166–76.

Effects on the nervous system. High-dose busulfan, used in conditioning regimens for bone marrow transplantation, has been associated with the development of convulsions,[1-4] both generalised[1,3,4] and myoclonic.[2,4] As a result, the use of prophylactic antiepileptic therapy has been suggested as a component of such regimens.[1,3,4] However, some do not consider the routine use of prophylactic antiepileptics justified,[5] and the potential for phenytoin to increase the metabolism of busulfan, thereby possibly decreasing its myeloablative efficacy, has been pointed out.[6] In addition, phenytoin plasma concentrations have been found to be subtherapeutic in patients who developed convulsions despite a standard prophylactic dose,[4] and the regimen was subsequently adjusted to take account of plasma concentrations. Clobazam has been suggested as an alternative to phenytoin for prophylaxis of busulfan-induced seizures.[7] Licensed product information from one manufacturer (*GSK, UK*) recommends the use of prophylactic anticonvulsants, and prefers a benzodiazepine to phenytoin. However, other manufacturers suggest use with phenytoin; *Otsuka* in the USA state that the recommended dose of their parenteral product is based on studies in which phenytoin was given, and that if other anticonvulsants are used exposure should be monitored, as a 15% increase in plasma-busulfan may be expected, with increased risk of toxicity.

1. Marcus RE, Goldman JM. Convulsions due to high-dose busulphan. *Lancet* 1984; **ii:** 1463.
2. Martell RW, *et al.* High-dose busulfan and myoclonic epilepsy. *Ann Intern Med* 1987; **106:** 173.
3. Sureda A, *et al.* High-dose busulfan and seizures. *Ann Intern Med* 1989; **111:** 543–4.
4. Grigg AP, *et al.* Busulphan and phenytoin. *Ann Intern Med* 1989; **111:** 1049–50. Correction. *ibid.*; **112:** 313.
5. Hugh-Jones K, Shaw PJ. No convulsions in children on high-dose busulphan. *Lancet* 1985; **i:** 220.
6. Fitzsimmons WE, *et al.* Anticonvulsants and busulfan. *Ann Intern Med* 1990; **112:** 552–3.
7. Schwarer AP, *et al.* Clobazam for seizure prophylaxis during busulfan chemotherapy. *Lancet* 1995; **346:** 1238.

Effects on the skin and hair. For the effect of radiotherapy in activating skin lesions in busulfan-treated patients, see under Precautions, below.

Permanent alopecia has been reported after use of busulfan.[1]

1. Tosti A, *et al.* Permanent alopecia after busulfan chemotherapy. *Br J Dermatol* 2005; **152:** 1056–8.

Precautions

For reference to the precautions necessary with antineoplastics, see p.641. Careful attention should be given to monitoring blood counts during therapy. This should be done at least weekly at the start of standard dose therapy. With high dose therapy blood counts should be monitored daily, as should liver function. Prophy-