majority of patients. Sustained effects were also found on long-term follow-up for up to 10 years.[2]

There have been reports of partial or complete remission of leucoplakia in studies of vitamin A or betacarotene given orally long-term,[3-5] but lesions have recurred when supplementation was stopped.[4] Topical treatment with retinoids such as tretinoin or isotretinoin has also been tried, with similar results to those of oral vitamin A and retinoid treatments.[6,7] A small open study has also suggested that topical calcipotriol may be effective.[8]

A systematic review of treatments for leucoplakia found that there were few controlled trials reported, and that although these treatments might be effective in the resolution of lesions, the rate of relapse was high, and there was no evidence that they prevent malignant transformation.[9]

1. Scully C, Porter S. ABC of oral health: swellings and red, white, and pigmented lesions. *BMJ* 2000; **321:** 225–8.
2. Epstein JB, *et al.* Topical bleomycin for the treatment of dysplastic oral leukoplakia. *Cancer* 1998; **83:** 629–34.
3. Issing WJ, *et al.* Long-term follow-up of larynx leukoplakia under treatment with retinyl palmitate. *Head Neck* 1996; **18:** 560–5.
4. Sankaranarayanan R, *et al.* Chemoprevention of oral leukoplakia with vitamin A and beta carotene: an assessment. *Oral Oncol* 1997; **33:** 231–6.
5. Garewal HS, *et al.* β-Carotene produces sustained remissions in patients with oral leukoplakia: results of a multicenter prospective trial. *Arch Otolaryngol Head Neck Surg* 1999; **125:** 1305–10.
6. Epstein JB, Gorsky M. Topical application of vitamin A to oral leukoplakia: a clinical case series. *Cancer* 1999; **86:** 921–7.
7. Gorsky M, Epstein JB. The effect of retinoids on premalignant oral lesions: focus on topical therapy. *Cancer* 2002; **95:** 1258–64.
8. Femiano F, *et al.* Oral leukoplakia: open trial of topical therapy with calcipotriol compared with tretinoin. *Int J Oral Maxillofac Surg* 2001; **30:** 402–6.
9. Lodi G, *et al.* Interventions for treating oral leukoplakia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 21/05/08).

Malignant effusions. Bleomycin is used for the sclerotherapy of malignant pleural and pericardial effusions (p.659).

Malignant neoplasms. Bleomycin is used in regimens for the management of Hodgkin's disease (p.655), non-Hodgkin's lymphomas, including AIDS-related lymphomas (see p.656 and p.657), and for germ-cell tumours of the ovary and testis (see p.670, and p.673), as well as for some other malignancies including those of the head and neck, (p.666), and Kaposi's sarcoma (p.675).

Pneumothorax. In a patient with AIDS and pneumocystis pneumonia who developed pneumothorax, instillation of bleomycin into each pleural cavity was successful in resolving the pneumothorax after tetracycline sclerotherapy failed to do so.[1]

1. Hnatiuk OW, *et al.* Bleomycin sclerotherapy for bilateral pneumothoraces in a patient with AIDS. *Ann Intern Med* 1990; **113:** 988–90.

Warts. A number of studies have examined the local use of bleomycin sulfate to treat severe or resistant warts (p.1584) of the common, plane, plantar, eponychial, and mosaic types, usually by intralesional injection.[1-3] At the doses used, adverse effects, other than pain at the injection site,[1-3] do not seem to be common; however, nail dystrophy and Raynaud's phenomenon have been reported (see under Effects on the Nails and Effects on the Vascular System, under Adverse Effects, above). Bleomycin has also been applied as a pressure-sensitive adhesive tape,[4] and various techniques for better intralesional use have been investigated.[5-7]

1. Shumack PH, Haddock MJ. Bleomycin: an effective treatment for warts. *Australas J Dermatol* 1979; **20:** 41–2.
2. Bunney MH, *et al.* The treatment of resistant warts with intralesional bleomycin: a controlled clinical trial. *Br J Dermatol* 1984; **111:** 197–207.
3. Munkvad M, *et al.* Locally injected bleomycin in the treatment of warts. *Dermatologica* 1983; **167:** 86–9.
4. Takigawa M, *et al.* Treatment of viral warts with pressure-sensitive adhesive tape containing bleomycin sulfate. *Arch Dermatol* 1985; **121:** 1108.
5. Munn SE, *et al.* A new method of intralesional bleomycin therapy in the treatment of recalcitrant warts. *Br J Dermatol* 1996; **135:** 969–71.
6. van der Velden EM, *et al.* Dermatography with bleomycin as a new treatment for verrucae vulgaris. *Int J Dermatol* 1997; **36:** 145–50.
7. Pollock B, Sheehan-Dare R. Pulsed dye laser and intralesional bleomycin for treatment of resistant viol [sic] hand warts. *Lasers Surg Med* 2002; **30:** 135–40.

Preparations

BP 2008: Bleomycin Injection;
USP 31: Bleomycin for Injection.

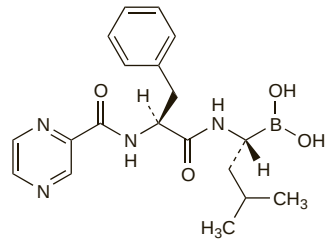
Proprietary Preparations (details are given in Part 3)
Arg.: Bileco; Bleocris; Blocamicina; Cytorich; ***Austral.:*** Blenamax; Blenoxane; ***Belg.:*** Bleomin; ***Braz.:*** Blenoxane; Bonar; Tecnomicina; ***Canad.:*** Blenoxane; ***Chile:*** Blexit; Nikableomicina; Oncobleocin; ***Cz.:*** Bleocin; ***Ger.:*** Bleo-cell; Bleomedac; ***Gr.:*** Bleocin; ***Hong Kong:*** Bleocin; ***Hung.:*** Bleocin; ***India:*** Bleochem; Bleocin; Bleocip; ***Indon.:*** Blenamax; Bleocin; ***Jpn:*** Bleo-S; Bleocin; ***Malaysia:*** Blenamax; Bleocin; ***Mex.:*** Blanoxan; Bleolem; ***NZ:*** Blenoxane; ***Philipp.:*** Blenoxane; Bloicin-S; ***Pol.:*** Bleocin; ***Port.:*** Blio†; ***Rus.:*** Blenamax (Бленамакс); ***S.Afr.:*** Blenoxane; Bleolem; ***Singapore:*** Bleocin; ***Thai.:*** Bleo-S; Bleocin; Bleolem; ***Turk.:*** Bleocin; Bleolem; ***UK:*** Bleo; ***USA:*** Blenoxane.

Bortezomib *(BAN, USAN, rINN)*

Bortézomib; Bortezomibum; LDP-341; MG-341; MLN-341; PS-341. *N*-((1*S*)-1-Benzyl-2-{[(1*R*)-1-(dihydroxyboranyl)-3-methylbutyl]amino}-2-oxoethyl)pyrazinecarboxamide; {(1*R*)-3-Methyl-1-[(2*S*)-3-phenyl-2-(pyrazin-2-carboxamido)propanamido]butyl}boronic acid; .

Бортезомиб

$C_{19}H_{25}BN_4O_4$ = 384.2.
CAS — 179324-69-7.
ATC — L01XX32.
ATC Vet — QL01XX32.



Adverse Effects, Treatment, and Precautions

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

The most common adverse effects of bortezomib include haematological toxicities (especially transient thrombocytopenia), decreased appetite, gastrointestinal disturbances, peripheral neuropathy, fatigue, fever, dyspnoea, rash, and myalgia. Complete blood counts including platelet counts should be monitored and therapy withheld or given at reduced doses if necessary. Peripheral neuropathy may also be dose-limiting.

Other common adverse effects include hyperglycaemia, hypokalaemia, insomnia, anxiety, confusion, depression, blurred vision, eye pain, dizziness, dysgeusia, tremor, epistaxis, cough, rhinorrhoea, pruritus, arthralgia, oedema, and orthostatic hypotension. Tumour lysis syndrome, hypersensitivity, and seizures have been reported. Tachycardia, arrhythmias, palpitations, angina pectoris, and myocardial infarction have occurred. Congestive heart failure may be exacerbated and pulmonary oedema has been reported. There have been rare reports of acute respiratory distress syndrome, some of them fatal.

Renal impairment is common in patients with multiple myeloma and acute renal failure has developed in patients on bortezomib. Licensed product information in the UK considers that patients with compromised renal function should be monitored, and dose reductions considered if needed although in the USA this is considered unnecessary. Hepatotoxicity, which may be reversible, has included increases in liver enzyme values, hyperbilirubinaemia, and acute liver failure; bortezomib should be used with caution in hepatic impairment.

The impact of proteasome inhibition by bortezomib on disorders associated with protein accumulation such as amyloidosis is unknown and caution is advised in these patients.

Effects on the nervous system. Treatment with bortezomib is often associated with peripheral neuropathy, mainly sensory, although cases of motor neuropathy have been reported. Results from an analysis[1] found that the peripheral neuropathy associated with bortezomib seemed to be cumulative and dose-related, and increased in prevalence through the first 5 treatment cycles. Prolonged bortezomib exposure beyond this time did not seem to increase the incidence or severity of neuropathy. Development of neuropathy appeared to be independent of the previous neurotoxic therapy. In most patients, neuropathic pain resolved or improved after dose modification or upon completion of therapy.

1. Richardson PG, *et al.* Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. *J Clin Oncol* 2006; **24:** 3113–20.

Effects on the skin. In 3 studies of bortezomib in patients with non-Hodgkin's lymphoma, 26 of 140 patients developed an erythematous maculopapular rash. Six patients underwent biopsy; all cases revealed a small vessel necrotising vasculitis. Although some patients had dosage reductions implemented or therapy interrupted upon development of the rash, others were treated continuously without dose reduction, with no apparent adverse clinical consequences. In fact, analysis of the data supported a strong relationship between bortezomib-associated cutaneous vasculitis and a positive clinical response in patient with non-Hodgkin's lymphoma.[1] A macular brown-red eruption developed in a patient at the site of bortezomib infusions; abundant venous flushing was given from the fourth infusion, and the eruption did not recur, although hyperpigmentation persisted for several months.[2]

1. Gerecitano J, *et al.* Drug-induced cutaneous vasculitis in patients with non-Hodgkin lymphoma treated with the novel proteasome inhibitor bortezomib: a possible surrogate marker of response? *Br J Haematol* 2006; **134:** 391–8.
2. Mataix J, *et al.* Persistent supravenous eruption induced by intravenous bortezomib therapy. *Br J Dermatol* 2008; **158:** 863–4.

Interactions

Bortezomib is metabolised in the liver via the cytochrome P450 isoenzymes CYP3A4, CYP2C19, and CYP1A2; CYP2D6 and CYP2C9 are also thought to play minor roles. Consequently, patients should be monitored closely when bortezomib is used with other drugs that induce or inhibit these isoenzymes. Hypoglycaemia and hyperglycaemia have occurred in diabetic patients receiving oral antidiabetics who were given bortezomib. Caution may be required if bortezomib is used with drugs that are associated with peripheral neuropathy or hypotension.

Pharmacokinetics

After a single intravenous dose of bortezomib, plasma concentrations decline in a biphasic manner; a distribution phase with a half-life of less than 10 minutes is followed by a terminal elimination phase of about 5 to 15 hours. After multiple doses, clearance decreases and there is an increase in the terminal elimination phase. Protein binding has been reported to be over 80%. *In-vitro* studies indicate that bortezomib is primarily oxidatively metabolised via the cytochrome P450 isoenzymes CYP3A4, CYP2C19, and CYP1A2; minor metabolism via CYP2D6 and CYP2C9 also occurs. The major metabolic pathway is deboronation to inactive metabolites.

◊ References.

1. Pekol T, *et al.* Human metabolism of the proteasome inhibitor bortezomib: identification of circulating metabolites. *Drug Metab Dispos* 2005; **33:** 771–7.

Uses and Administration

Bortezomib is an inhibitor of the 26S proteasome, a large protein complex in cells that is responsible for breaking down regulatory proteins of the cell cycle. Such inhibition disrupts tumour cell turnover and induces apoptosis. Bortezomib is used for the treatment of multiple myeloma (p.658) in patients who have failed at least one previous therapy. In the USA, it is also used similarly for mantle cell lymphoma in patients given at least one previous therapy. Bortezomib is given in initial doses of 1.3 mg/m^2 intravenously on days 1, 4, 8, and 11 of a 21-day cycle. At least 72 hours should elapse between consecutive doses of bortezomib. In the UK, licensed product information recommends that patients with a confirmed complete response should receive 2 additional cycles of bortezomib, and that those who respond but do not achieve complete remission receive a total of 8 cycles. In the USA, extended therapy of more than 8 cycles may be given, either on the standard schedule recommended above, or on a maintenance schedule of one dose weekly for 4 weeks (days 1, 8, 15, and 22 of a 35-day cycle).

The dose should be reduced, or treatment withdrawn, according to toxicity, particularly when peripheral neuropathy, neuropathic pain, and haematological toxicity occur.

◊ References.

1. Goy A, Gilles F. Update on the proteasome inhibitor bortezomib in hematologic malignancies. *Clin Lymphoma* 2004; **4:** 230–7.
2. Orlowski RZ. Bortezomib and its role in the management of patients with multiple myeloma. *Expert Rev Anticancer Ther* 2004; **4:** 171–9.
3. Jagannath S, *et al.* Bortezomib in recurrent and/or refractory multiple myeloma: initial clinical experience in patients with impaired renal function. *Cancer* 2005; **103:** 1195–1200.

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

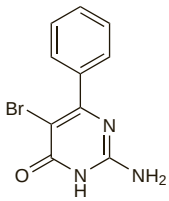
Proprietary Preparations (details are given in Part 3)
Arg.: Velcade; ***Austral.:*** Velcade; ***Belg.:*** Velcade; ***Canad.:*** Velcade; ***Chile:*** Velcade; ***Cz.:*** Velcade; ***Denm.:*** Velcade; ***Fin.:*** Velcade; ***Fr.:*** Velcade; ***Ger.:*** Velcade; ***Gr.:*** Velcade; ***Hong Kong:*** 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.



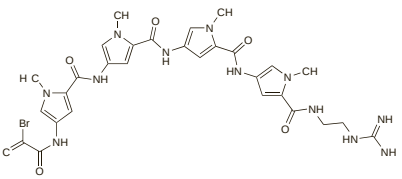
Profile
Bropirimine is reported to have immunomodulatory actions, possibly due to the induction of interferons. It has been investigated in the management of carcinoma in situ of the bladder (p.659).

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.

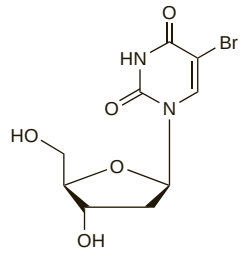
◊ References.
1. ten Tije AJ, *et al.* Phase I and pharmacokinetic study of brostallicin (PNU-166196), a new DNA minor-groove binder, administered intravenously every 3 weeks to adult patients with metastatic cancer. *Clin Cancer Res* 2003; **9:** 2957–64.
2. Broggini M, *et al.* Brostallicin: a new 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.

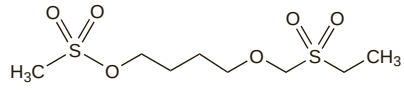
◊ References.
1. Freese A, *et al.* The application of 5-bromodeoxyuridine in the management of CNS tumors. *J Neurooncol* 1994; **20:** 81–95.
2. Phillips TL, *et al.* Results of a randomized comparison of radiotherapy and bromodeoxyuridine with radiotherapy alone for brain metastases: report of RTOG 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-