Bleomycin Sulfate *(USAN, pINNM)*

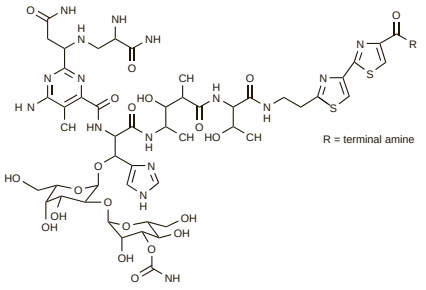
Bleomicino sulfatas; Bleomicin-szulfát; Bleomycin Sulphate *(BANM)*; Bléomycine, sulfate de; Bleomycini sulfas; Bleomycinsulfat; Bleomycin-sulfát; Bleomysiinisulfaatti; Sulfato de bleomicina.

Блеомицина Сульфат

CAS — 11056-06-7 (bleomycin); 67763-87-5 (bleomycin hydrochloride); 9041-93-4 (bleomycin sulfate).

ATC — L01DC01.

ATC Vet — QL01DC01.



(bleomycin)

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*. *Int.* and *Jpn* also include Bleomycin Hydrochloride. *Chin.* includes Bleomycin A5 Hydrochloride for Injection.

Ph. Eur. 6.2 (Bleomycin Sulphate). The sulfate of a mixture of glycopeptides obtained by the growth of *Streptomyces verticillus* or by any other means; the two principal components of the mixture are *N*-[3-(dimethylsulphonio)propyl]bleomycinamide (bleomycin A_2) and *N*-[4-(carbamimidoylamino)butyl]bleomycinamide (bleomycin B_2). A white or yellowish-white, very hygroscopic powder. It loses not more than 3% of its weight when dried. Very soluble in water; slightly soluble in dehydrated alcohol; practically insoluble in acetone. A 0.5% solution in water has a pH of 4.5 to 6.0. Store in airtight containers at a temperature of 2° to 8°.

USP 31 (Bleomycin Sulfate). The sulfate salt of a mixture of basic cytotoxic glycopeptides, produced by the growth of *Streptomyces verticillus* or produced by other means. It has a potency of not less than 1.5 units and not more than 2.0 units/mg. It contains between 55 and 70% of bleomycin A_2 and between 25 and 32% of bleomycin B_2; the content of bleomycin B_4 is not more than 1%. The combined percentage of bleomycin A_2 and B_2 is not less than 90%. A cream-coloured, amorphous powder. It loses not more than 6% of its weight when dried. Very soluble in water. A solution in water containing 10 units/mL has a pH of 4.5 to 6.0. Store in airtight containers.

Incompatibility. A loss of bleomycin activity was reported when bleomycin sulfate solutions were mixed with solutions of carbenicillin, cefazolin or cefalotin sodium, nafcillin sodium, benzylpenicillin sodium, methotrexate, mitomycin, hydrocortisone sodium succinate, aminophylline, ascorbic acid, or terbutaline.[1] The interactions of bleomycin have been summarised as the chelation of divalent and trivalent cations (especially copper), inactivation by compounds containing sulfhydryl groups, and precipitation by hydrophobic anions; solutions of bleomycin should not be mixed with solutions of essential amino acids, riboflavin, dexamethasone, or furosemide.[2]

1. Dorr RT, *et al*. Bleomycin compatibility with selected intravenous medications. *J Med* 1982; **13:** 121–30.
2. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; **17:** 532–8.

Stability. Bleomycin sulfate solutions appear to be equally stable in plastic or glass,[1,2] despite some earlier studies suggesting loss of potency in plastic.[3,4] There is some evidence[5] that bleomycin is more stable in sodium chloride 0.9% than glucose 5%, and sodium chloride 0.9% is the diluent recommended by the licensed product information. UK licensed product information states that bleomycin sulfate is chemically and physically stable, once reconstituted and diluted as directed, for 10 days when refrigerated at 2° to 8° and protected from light. From a microbiological point of view, solutions should be used immediately; storage for longer than 24 hours at 2° to 8° is not recommended, unless prepared under controlled and validated aseptic conditions.

1. De Vroe C, *et al*. A study on the stability of three antineoplastic drugs and on their sorption by iv delivery systems and end-line filters. *Int J Pharmaceutics* 1990; **65:** 49–56.
2. Stajich GV, *et al*. In vitro evaluation of bleomycin-induced cell lethality from plastic and glass containers. *DICP Ann Pharmacother* 1991; **25:** 14–16.
3. Benvenuto JA, *et al*. Stability and compatibility of antitumor agents in glass and plastic containers. *Am J Hosp Pharm* 1981; **38:** 1914–18.
4. Adams J, *et al*. Instability of bleomycin in plastic containers. *Am J Hosp Pharm* 1982; **39:** 1636.
5. Koberda M, *et al*. Stability of bleomycin sulfate reconstituted in 5% dextrose injection or 0.9% sodium chloride injection stored in glass vials or polyvinyl chloride containers. *Am J Hosp Pharm* 1990; **47:** 2528–9.

Units

8910 units of bleomycin complex A_2/B_2 are contained in 5 mg of bleomycin complex in one ampoule of the first International Reference Preparation (1980). The Ph. Eur. 6.2 specifies a potency of not less than 1500 international units per mg, calculated with reference to the dried substance. These units differ from those used by the USP: Bleomycin Sulfate (USP 31) contains 1.5 to 2.0 units of bleomycin in each mg. A change in the labelling of preparations in the UK, from units equivalent to those of the USP to international units in line with the Ph. Eur., resulted in an apparent but artefactual increase in UK doses by a factor of 1000.

In some countries doses were *formerly* described in terms of mg-potency, where 1 mg-potency corresponded to 1 unit. In the original preparation 1 mg-potency was equivalent to 1 mg-weight but improvements in purification of the product led to a situation in which ampoules labelled as containing 15 mg (i.e. 15 units) contained far fewer mg-weight of bleomycin.

Adverse Effects and Treatment

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

The most frequent adverse effects with bleomycin involve the skin and mucous membranes and include rash, erythema, pruritus, vesiculation, hyperkeratosis, nail changes, alopecia, hyperpigmentation, striae, and stomatitis. Fever is also common, and acute anaphylactoid reactions with hyperpyrexia and cardiorespiratory collapse have been reported in about 1% of patients with lymphoma. There is little depression of the bone marrow. Local reactions and thrombophlebitis may occur at the site of parenteral dosage.

The most serious delayed effect is pulmonary toxicity; interstitial pneumonitis occurs in about 10% of patients and progresses to fibrosis and death in about 1% of patients treated with bleomycin. Pulmonary toxicity is more likely in elderly patients and those given total doses greater than 400 000 international units (400 USP units). It is also more likely in patients who have had previous radiotherapy to the chest.

Effects on the lungs. Pneumonitis induced by bleomycin can progress to fatal pulmonary fibrosis. The presentation is often delayed; clinical manifestations include non-productive cough, dyspnoea, and sometimes fever (see Effects on the Lungs, p.638). Pneumomediastinum has also been reported as an initial manifestation of fatal pulmonary toxicity due to bleomycin.[1] Risk factors for toxicity include increased age,[2,3] deteriorating renal function,[2] and concurrent or previous radiotherapy. The reaction is dose-related, and maximum doses have been set (see Uses and Administration, below). Other factors that may be implicated include the regimen used, concomitant oxygen supplementation, smoking history, underlying lung disease, and growth factor support.[2,3] For further details of some of these risk factors, see under Interactions, below. There is no standard treatment for bleomycin-induced pneumonitis. Bleomycin therapy is usually stopped, and corticosteroids may be given[3] although strong evidence to support their use is lacking.[2] There is some suggestion that giving bleomycin by intravenous infusion rather than bolus injection may reduce pulmonary toxicity.[2]

1. Keijzer A, Kuenen B. Fatal pulmonary toxicity in testis cancer with bleomycin-containing chemotherapy. *J Clin Oncol* 2007; **25:** 3543–4.
2. Sleijfer S. Bleomycin-induced pneumonitis. *Chest* 2001; **120:** 617–24.
3. Martin WG, *et al*. Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. *J Clin Oncol* 2005; **23:** 7614–20.

Effects on the skin, hair, and nails. Permanent nail loss and nail loss followed by regrowth with dystrophy have been reported after intralesional injection of bleomycin for periungual warts.[1-3] In 2 cases this was preceded by blistering and ulceration,[1] or swelling, severe pain, and a burning sensation.[2] All 3 patients had received injections on one or two previous occasions when 2 patients had reported only mild pain.[1,3] Other reported cutaneous adverse effects of bleomycin include flagellate erythema, Raynaud's phenomenon, gangrene, fibrotic or sclerotic skin changes, hyperpigmentation, and neutrophilic eccrine hidradenitis (an inflammatory dermatosis with erythematous plaques and nodules, neutrophilic infiltrates of eccrine glands, and degeneration of eccrine cells). Acute generalised exanthematous pustulosis and alopecia have also been reported.[4]

1. Czarnecki D. Bleomycin and periungual warts. *Med J Aust* 1984; **141:** 40.
2. Miller RAW. Nail dystrophy following intralesional injections of bleomycin for a periungual wart. *Arch Dermatol* 1984; **120:** 963–4.
3. Urbina González F, *et al*. Cutaneous toxicity of intralesional bleomycin administration in the treatment of periungual warts. *Arch Dermatol* 1986; **122:** 974–5.
4. Yamamoto T. Bleomycin and the skin. *Br J Dermatol* 2006; **155:** 869–75.

Effects on the vascular system. Although thromboembolic disorders and Raynaud's syndrome have been associated with use of bleomycin in combination regimens, particularly with cisplatin and the vinca alkaloids or etoposide (see Effects on the Cardiovascular System, p.636) there is some evidence for an association of Raynaud's syndrome with the use of bleomycin alone.[1,2]

There have also been cases of Raynaud's phenomenon reported after intralesional injection of bleomycin for treatment of warts on the hands and feet.[3-6] See also Effects on the Skin, Hair, and Nails, above.

1. Sundstrup B. Raynaud's phenomenon after bleomycin treatment. *Med J Aust* 1978; **2:** 266.
2. Adoue D, Arlet P. Bleomycin and Raynaud's phenomenon. *Ann Intern Med* 1984; **100:** 770.
3. Epstein E. Intralesional bleomycin and Raynaud's phenomenon. *J Am Acad Dermatol* 1991; **24:** 785–6.
4. Gregg LJ. Intralesional bleomycin and Raynaud's phenomenon. *J Am Acad Dermatol* 1992; **26:** 279–80.
5. de Pablo P, *et al*. Raynaud's phenomenon and intralesional bleomycin. *Acta Derm Venereol (Stockh)* 1992; **72:** 465.
6. Vanhooteghem O, *et al*. Raynaud phenomenon after treatment of verruca vulgaris of the sole with intralesional injection of bleomycin. *Pediatr Dermatol* 2001; **18:** 249–51.

Precautions

For reference to the precautions necessary with antineoplastics, see p.641.

Bleomycin should be used with caution in the elderly, in patients with renal impairment or pulmonary infection or pre-existing impairment of pulmonary function, and in those who have received radiotherapy, particularly to the thorax. Patients should undergo regular chest X-rays. If these show infiltrates, or if breathlessness occurs, bleomycin should be stopped.

In view of the risk of an anaphylactoid reaction it has been suggested that patients with lymphomas should receive two test doses of 2000 international units (2 USP units) or less initially (but see Administration, below).

AIDS. Cutaneous adverse effects occurred in 12 of 50 patients being treated with bleomycin for AIDS-associated Kaposi's sarcoma and increased in severity until bleomycin was withdrawn.[1] Bleomycin should be stopped in people with AIDS if cutaneous adverse effects are seen, and rechallenge should be avoided. However, the incidence of adverse effects did not appear to be higher in these patients than in cancer patients, and patients with AIDS seem to be less sensitive to bleomycin than to antibacterials such as co-trimoxazole and penicillins.

1. Caumes E, *et al*. Cutaneous side-effects of bleomycin in AIDS patients with Kaposi's sarcoma. *Lancet* 1990; **336:** 1593.

Diving. Since the partial pressure of oxygen in the inspired air of a scuba diver increases with increasing depth, a theoretical possibility exists of a toxic [pulmonary] reaction to oxygen in bleomycin-treated patients who subsequently go diving, and such a risk would increase with the depth and duration of each dive.[1] However, the risks associated with diving after uncomplicated bleomycin-based treatment have been questioned;[2] the authors considered that resuming diving was acceptable 6 to 12 months after completing treatment with BEP (bleomycin, etoposide, and cisplatin), and recommended caution only in those who developed pulmonary function impairment when given bleomycin.

1. Zanetti CL. Scuba diving and bleomycin therapy. *JAMA* 1990; **264:** 2869.
2. de Wit R, *et al*. Bleomycin and scuba diving: where is the harm? *Lancet Oncol* 2007; **8:** 954–5.

Handling and disposal. *Urine* produced for up to 72 hours after a dose of bleomycin should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Pregnancy. For a report of use of a bleomycin-containing chemotherapy regimen in a pregnant woman and subsequent adverse effects on the infant, see Pregnancy, under Cisplatin, p.699.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. There may be an increased risk of pulmonary toxicity in patients given bleomycin who receive oxygen, for example as part of a general anaesthetic procedure; a reduction in inspired oxygen concentration has been recommended.

Antineoplastics. Enhanced pulmonary toxicity, in some cases fatal, has been reported in patients given bleomycin and *cisplatin*,[1-4] presumably because cisplatin-induced renal impairment led to a decrease in bleomycin elimination. It seems reasonable to assume that similar interactions might occur if bleomycin were given with other nephrotoxic agents. It has been suggested that apart from a decrease in bleomycin dosage if nephrotoxicity occurs with such a combination, giving bleomycin by constant infusion rather than intermittent bolus might be less toxic.[1,5]

A study to investigate whether substitution of etoposide with *gemcitabine* would lead to a less leukaemogenic BEACOPP regimen was stopped early because of unexpectedly common pulmonary toxicity; one patient died. This toxicity was considered to be due to the use of gemcitabine with bleomycin.[6]

1. Bennett WM, *et al.* Fatal pulmonary bleomycin toxicity in cisplatin-induced acute renal failure. *Cancer Treat Rep* 1980; **64:** 921–4.
2. van Barneveld PWC, *et al.* Influence of platinum-induced renal toxicity on bleomycin-induced pulmonary toxicity in patients with disseminated testicular carcinoma. *Oncology* 1984; **41:** 4–7.
3. Brodsky A, *et al.* Stevens-Johnson syndrome, respiratory distress and acute renal failure due to synergic bleomycin-cisplatin toxicity. *J Clin Pharmacol* 1989; **29:** 821–3.
4. Sleijfer S, *et al.* Enhanced effects of bleomycin on pulmonary function disturbances in patients with decreased renal function due to cisplatin. *Eur J Cancer* 1996; **32A:** 550–2.
5. Chisholm RA, *et al.* Bleomycin lung: the effect of different chemotherapeutic regimens. *Cancer Chemother Pharmacol* 1992; **30:** 158–60.
6. Bredenfeld H, *et al.* Severe pulmonary toxicity in patients with advanced-stage Hodgkin's disease treated with a modified bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone, and gemcitabine (BEACOPP) regimen is probably related to the combination of gemcitabine and bleomycin: a report of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 2004; **22:** 2424–9.

Colony-stimulating factors. An increased incidence of pulmonary toxicity has been reported in patients receiving bleomycin as part of the ABVD regimen (with doxorubicin, vinblastine, and dacarbazine) who were given granulocyte colony-stimulating factor to alleviate neutropenia.[1] Another case of rapidly developing and fatal pneumonitis in a patient given BEP (bleomycin, etoposide, and cisplatin) with granulocyte colony-stimulating factor has been reported.[2]

Analyses of study data failed to show increased pulmonary toxicity when granulocyte colony-stimulating factor was added to bleomycin-containing regimens in patients with germ cell tumours or non-Hodgkin's lymphomas.[3-5] In a retrospective review of patients with Hodgkin's lymphoma, however, use of bleomycin with granulocyte colony-stimulating factor was associated with a statistically significant increase of pulmonary toxicity.[6]

1. Matthews JH. Pulmonary toxicity of ABVD chemotherapy and G-CSF in Hodgkin's disease: possible synergy. *Lancet* 1993; **342:** 988.
2. Dirix LY, *et al.* Pulmonary toxicity and bleomycin. *Lancet* 1994; **344:** 56.
3. Bastion Y, *et al.* Possible toxicity with the association of G-CSF and bleomycin. *Lancet* 1994; **343:** 1221–2.
4. Bastion Y, Coiffier B. Pulmonary toxicity of bleomycin: is G-CSF a risk factor? *Lancet* 1994; **344:** 474.
5. Saxman SB, *et al.* Pulmonary toxicity in patients with advanced-stage germ cell tumors receiving bleomycin with and without granulocyte colony stimulating factor. *Chest* 1997; **111:** 657–60.
6. Martin WG, *et al.* Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. *J Clin Oncol* 2005; **23:** 7614–20.

Oxygen. Because bleomycin is thought to cause pulmonary toxicity partly by induction of free radicals, use with high concentrations of oxygen could be hazardous,[1] and reductions in inspired oxygen concentration have been recommended by licensed product information where oxygen supplementation is unavoidable. *Animal* studies show an increased risk of mortality with use of bleomycin and oxygen, although data in humans are lacking. The need for oxygen restriction in bleomycin-treated patients has, however, been questioned.[2]

1. Sleijfer S. Bleomycin-induced pneumonitis. *Chest* 2001; **120:** 617–24.
2. Donat SM, Levy DA. Bleomycin associated pulmonary toxicity: is perioperative oxygen restriction necessary? *J Urol (Baltimore)* 1998; **160:** 1347–52.

Pharmacokinetics

Bleomycin is thought to be poorly absorbed from the gastrointestinal tract. Absorption is rapid after parenteral, intraperitoneal, or intrapleural use. Bioavailability is 100% and 70% after intramuscular and subcutaneous dosage, respectively. A bioavailability of 45% has been reported after intraperitoneal or intrapleural use. Plasma protein binding is low. Enzymic degradation of bleomycin occurs, primarily in plasma, the liver and other organs, and to a much lesser extent in skin and lungs. Elimination is biphasic: mean initial and terminal half-lives of 0.5 and 4 hours respectively have been reported after an intravenous bolus. Elimination may be more prolonged after continuous intravenous infusion and mean half-lives of 1.3 and 9 hours respectively have been reported. About two-thirds of a dose is excreted unchanged in the urine; the rate of excretion is determined by renal function. Drug concentrations in the CSF are low. Bleomycin crosses the placenta.

◊ References.

1. Broughton A, *et al.* Clinical pharmacology of bleomycin following intravenous infusion as determined by radioimmunoassay. *Cancer* 1977; **40:** 2772–8.
2. Alberts DS, *et al.* Bleomycin pharmacokinetics in man I: intravenous administration. *Cancer Chemother Pharmacol* 1978; **1:** 177–81.
3. Yee GC, *et al.* Bleomycin disposition in children with cancer. *Clin Pharmacol Ther* 1983; **33:** 668–73.

Uses and Administration

Bleomycin is an antineoplastic antibiotic that binds to DNA and causes strand scissions, and is probably most effective in the G_2 and M phases of the cell cycle. It is widely used to treat malignant disease; particularly squamous cell carcinomas, including those of the cervix and external genitalia, oesophagus, skin, and head and neck; Hodgkin's disease and other lymphomas; malignant neoplasms of the testis, and malignant effusions. It has also been tried in other malignancies, including carcinoma of the bladder, lung, and thyroid, and some sarcomas, including Kaposi's sarcoma.

Bleomycin is often used with other antineoplastics, notably with doxorubicin, vinblastine, and dacarbazine (ABVD) for Hodgkin's disease, and with etoposide and cisplatin (BEP) in testicular tumours. Bleomycin is given as the sulfate by either the intramuscular, intravenous, or subcutaneous route. It may also be given intra-arterially or instilled intrapleurally or intraperitoneally. If intramuscular injections are painful they may be given in a 1% solution of lidocaine.

Doses are calculated in terms of the base, and are given in ***units****, but the units used for preparations in the UK, which were formerly equivalent to those of the USP, are now international units equivalent to those of the Ph. Eur. (see Units, above). Since 1000 international units is equivalent to 1 USP unit, UK doses now appear to be 1000 times greater than those previously in use, or than those in use in the USA, and care is recommended in evaluating the literature.*

In the UK the licensed dose as a single agent for **squamous cell** or **testicular tumours** is 15 000 international units (15 USP units) three times a week, or 30 000 international units twice a week, by intramuscular or intravenous injection, although in practice treatment of malignancy will generally be with combination regimens. This may be repeated, at usual intervals of 3 to 4 weeks, up to a total cumulative dose of 500 000 international units. The dose and total cumulative dose should be reduced in those over 60 years of age (see below). Doses should be adjusted according to tolerance, and may need to be adjusted as part of combination chemotherapy. Continuous intravenous infusion at a rate of 15 000 international units per 24 hours for up to 10 days or 30 000 international units per 24 hours for up to 5 days may also be used. In patients with **lymphoma** a dose of 15 000 international units once or twice weekly by intramuscular injection has been suggested, to a total dose of 225 000 international units. Again, dosage should be reduced in older patients and in combination regimens if necessary. In the treatment of **malignant effusions** a solution of 60 000 international units in 100 mL of sodium chloride 0.9% may be instilled into the affected serous cavity. Treatment may be repeated as necessary up to a total cumulative dose of 500 000 international units depending on the patient's age. Local anaesthetics or analgesics are given concomitantly.

In the USA licensed doses for **lymphomas** as well as **squamous cell** and **testicular** neoplasms are 250 to 500 international units/kg (0.25 to 0.5 USP units/kg), or 10 000 to 20 000 international units/m^2 (10 to 20 USP units/m^2), given once or twice weekly. In view of the risk of an anaphylactoid reaction it has been suggested that patients with lymphomas should receive two test doses of 2000 international units (2 USP units) or less initially (but see Administration, below). In patients with Hodgkin's disease, once a 50% response has been achieved it may be maintained with 1000 international units (1 USP unit) of bleomycin daily, or 5000 international units (5 USP units) weekly.

In the UK, licensed product information suggests that a **total dose** of 500 000 international units (500 USP units) should not be exceeded. Total cumulative dose should not exceed 300 000 international units in those aged 60 to 69 years, 200 000 international units in those 70 to 79, and 100 000 international units in those 80 and over; the weekly dose should be no more than 60 000, 30 000 and 15 000 international units respectively. In the USA the recommended maximum total dose is 400 000 international units (400 USP units); it is generally agreed that patients receiving 400 000 international units or more are at increased risk of pulmonary toxicity (see Adverse Effects, above).

Dosage should be reduced in patients with renal impairment (see below).

Bleomycin hydrochloride has also been given parenterally for malignant neoplasms, and bleomycin sulfate has been applied topically for the local treatment of skin tumours.

Administration. Although test doses have been suggested as a way of avoiding anaphylactoid reactions in patients with lymphoma being treated with bleomycin, a review[1] of the literature concluded that the evidence did not support such a strategy, since the onset of the reaction was unpredictable, and not associated with any particular dose. It had also been suggested that reactions were less frequent with intramuscular rather than intravenous dosage, but evidence for this was conflicting.

There is some suggestion that giving bleomycin by intravenous infusion rather than bolus injection in combination regimens may result in reduced pulmonary toxicity.[2,3]

1. Lam MSH. The need for routine bleomycin test dosing in the 21st century. *Ann Pharmacother* 2005; **39:** 1897–1902.
2. Chisholm RA, *et al.* Bleomycin lung: the effect of different chemotherapeutic regimens. *Cancer Chemother Pharmacol* 1992; **30:** 158–60.
3. Sleijfer S. Bleomycin-induced pneumonitis. *Chest* 2001; **120:** 617–24.

Administration in renal impairment. A significant portion of a dose of bleomycin is excreted largely unchanged in the urine, and dose reduction should be considered in patients with renal impairment. UK licensed product information suggests a 50% dose reduction when the serum creatinine concentration is between 20 and 40 micrograms/mL and further reduction for serum creatinine above this. US licensed product information gives the following proposed percentages of the initial dose, based on creatinine clearance (CC):

- CC 5 to 10 mL/minute: 40%
- CC 10 to 20 mL/minute: 45%
- CC 20 to 30 mL/minute: 55%
- CC 30 to 40 mL/minute: 60%
- CC 40 to 50 mL/minute: 70%
- CC 50 mL/minute and above: 100%

Leucoplakia. Leucoplakia is used to describe a white patch or plaque in the mouth which cannot be otherwise characterised. Such lesions are of concern because they may be pre-malignant, and patients with evidence of dysplasia may be at higher risk of transformation (see also Malignant Neoplasms of the Head and Neck, p.666). Leucoplakia must be distinguished from other conditions such as candidiasis, lichen planus, and oral hairy leucoplakia which is associated with HIV infection.[1]

Leucoplakia is often associated with tobacco smoking, and smoking cessation can result in regression.[1] Where active treatment is desirable, small and easily accessible lesions can be removed surgically or by laser therapy, although they may recur.[1] For extensive patches or those in which surgery would be difficult, the treatments described include topical bleomycin 1%, dissolved in dimethyl sulfoxide and applied for 5 minutes daily for 14 consecutive days. In a group of 19 patients with dysplastic leucoplakia, improvement in the appearance of lesions and histological evidence of remission of the dysplasia occurred in the

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.

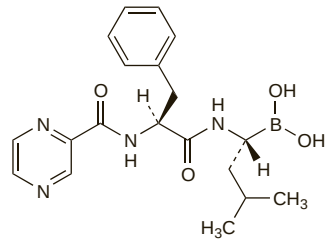
Proprietary Preparations (details are given in Part 3)
Arg.: Bileco; Bleocris; Blocamicina; Cytorich; ***Austral.:*** Blenamax; Blenoxane; ***Belg.:*** Bleomin; ***Braz.:*** Blenoxane; Bonar; Tecnomicina; ***Canad.:*** Blenoxane; ***Chile:*** Blexit; Nikableomicina; Oncobleocin; ***Cz.:*** Bleocin; ***Ger.:*** 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.