Bexarotene *(BAN, USAN, rINN)*

Beksaroteeni; Beksaroten; Bexaroten; Bexarotène; Bexaroteno; Bexarotenum; LG-100069; LGD-1069. *p*-[1-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)vinyl]benzoic acid.

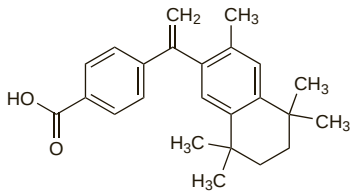
Бексаротен

$C_{24}H_{28}O_2$ = 348.5.

CAS — 153559-49-0.

ATC — L01XX25.

ATC Vet — QL01XX25.



Adverse Effects and Precautions

The main adverse effects noted after oral therapy with bexarotene include hyperlipidaemia, hypothyroidism, leucopenia, headache, oedema, altered liver function, rash, and pruritus. Exfoliative dermatitis, alopecia, and skin disorders may occur. Other common adverse effects include anaemia, insomnia, dizziness, eye or ear disorders, gastrointestinal disturbances, arthralgia, and myalgia. Acute pancreatitis has been associated with hypertriglyceridaemia, and patients with risk factors for pancreatitis should generally not be given bexarotene. If triglyceride concentrations rise during therapy, dose reductions are recommended, and lipid-lowering therapy may be instituted (with the exception of gemfibrozil, see below). The most common adverse events associated with topical therapy are rash, pruritus, and pain. Bexarotene capsules and gel should not be used during pregnancy because of the risk of fetal malformation.

◊ References.

1. Assaf C, *et al.* Minimizing adverse side-effects of oral bexarotene in cutaneous T-cell lymphoma: an expert opinion. *Br J Dermatol* 2006; **155:** 261–6.

Interactions

Gemfibrozil. Gemfibrozil inhibits clearance of bexarotene, resulting in extremely high triglyceride levels and pancreatitis.[1]

1. Talpur R, *et al.* Optimizing bexarotene therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 2002; **47:** 672–84.

Uses and Administration

Bexarotene is an agonist at the retinoid X receptor, which is involved in the regulation of cell differentiation and proliferation. It is used in the treatment of cutaneous T-cell lymphoma (see Mycosis Fungoides, p.657), in a usual initial oral dose of 300 mg/m^2 daily as a single dose taken with a meal. Dosage is adjusted according to toxicity. For the topical treatment of refractory disease a 1% gel may be applied on alternate days for the first week, gradually increased at weekly intervals to up to 4 times daily, depending on tolerance.

◊ References.

1. Anonymous. Bexarotene (Targretin) for cutaneous T-cell lymphoma. *Med Lett Drugs Ther* 2000; **42:** 31–2.
2. Lowe MN, Plosker GL. Bexarotene. *Am J Clin Dermatol* 2000; **1:** 245–50.
3. Duvic M, *et al.* Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. *J Clin Oncol* 2001; **19:** 2456–71.
4. Wong S-F. Oral bexarotene in the treatment of cutaneous T-cell lymphoma. *Ann Pharmacother* 2001; **35:** 1056–65.
5. Heald P, *et al.* Topical bexarotene therapy for patients with refractory or persistent early-stage cutaneous T-cell lymphoma: results of the phase III clinical trial. *J Am Acad Dermatol* 2003; **49:** 801–15.
6. Hanifin JM, *et al.* Novel treatment of chronic severe hand dermatitis with bexarotene gel. *Br J Dermatol* 2004; **150:** 545–53.
7. Farol LT, Hymes KB. Bexarotene: a clinical review. *Expert Rev Anticancer Ther* 2004; **4:** 180–8.
8. Gniadecki R, *et al.* The optimal use of bexarotene in cutaneous T-cell lymphoma. *Br J Dermatol* 2007; **157:** 433–40.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Targretin; ***Chile:*** Targretin; ***Cz.:*** Targretin; ***Denm.:*** Targretin; ***Fr.:*** Targretin; ***Ger.:*** Targretin; ***Gr.:*** Targretin; ***Hung.:*** Targretin; ***Irl.:*** Targretin; ***Ital.:*** Targretin; ***Neth.:*** Targretin; ***Port.:*** Targretin; ***Spain:*** Targretin; ***UK:*** Targretin; ***USA:*** Targretin.

Bicalutamide *(BAN, USAN, rINN)*

Bicalutamida; Bicalutamidum; Bikalutamid; Bikalutamidi; ICI-176334. (*RS*)-4′-Cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide.

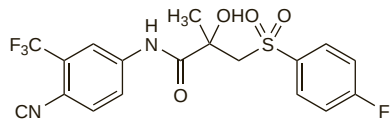
Бикалутамид

$C_{18}H_{14}F_4N_2O_4S$ = 430.4.

CAS — 90357-06-5.

ATC — L02BB03.

ATC Vet — QL02BB03.



Pharmacopoeias. In *US.*

USP 31 (Bicalutamide). A fine, white to off-white powder. Sparingly to slightly soluble in alcohol; freely soluble in acetone and in tetrahydrofuran; soluble in acetonitrile. Store in airtight containers.

Adverse Effects and Precautions

As for Flutamide, p.725. Pruritus, asthenia, alopecia, hair regrowth, and dry skin occur commonly with bicalutamide. Hypersensitivity reactions, including angioedema and urticaria, have been reported infrequently.

Cardiovascular effects including angina, heart failure, arrhythmias, and ECG changes have been reported rarely. Interstitial pneumonitis and pulmonary fibrosis have also been reported rarely.

Effects on the gastrointestinal tract. There is some evidence that bicalutamide is associated with a lower incidence of diarrhoea than flutamide.[1]

1. Schellhammer P, *et al.* A controlled trial of bicalutamide versus flutamide, each in combination with luteinizing hormone-releasing hormone analogue therapy, in patients with advanced prostate cancer. *Urology* 1995; **45:** 745–52.

Effects on the lungs. For a review of cases of pneumonitis associated with anti-androgens including bicalutamide, see under Flutamide, p.725.

Gynaecomastia. For a discussion of gynaecomastia, a frequent adverse effect of anti-androgen therapy, and its management, see under Flutamide, p.725.

Interactions

Bicalutamide inhibits various cytochrome P450 isoenzymes, particularly CYP3A4, *in vitro*, and licensed product information recommends that terfenadine, astemizole, and cisapride should not be given with bicalutamide, and that other drugs with a narrow therapeutic index that are metabolised by cytochrome P450 isoenzymes should be used with caution. *In vitro* studies have shown that bicalutamide can displace warfarin from its protein binding sites (see also Antineoplastics, p.1429).

Pharmacokinetics

Bicalutamide is well absorbed after oral doses. It undergoes extensive metabolism in the liver, the active *R*-enantiomer mainly by oxidation, the inactive *S*-enantiomer mainly by glucuronidation. It is excreted as metabolites in urine and faeces. The half-life of the *R*-enantiomer is about 6 to 7 days, and may be prolonged still further in severe hepatic impairment. The *S*-enantiomer is cleared more rapidly. Bicalutamide is about 96% bound to plasma proteins.

◊ References.

1. Cockshott ID. Bicalutamide: clinical pharmacokinetics and metabolism. *Clin Pharmacokinet* 2004; **43:** 855–78.

Uses and Administration

Bicalutamide is a nonsteroidal anti-androgen with actions and uses similar to those of flutamide (p.725). It is used orally in the treatment of prostatic cancer (p.671). When used with a gonadorelin analogue in the palliative treatment of advanced prostatic cancer the usual dose is 50 mg daily. In the UK treatment is started at least 3 days before starting the gonadorelin analogue to suppress any flare reaction, but in the USA treatment is started at the same time. A similar dose is used with surgical castration, starting on the same day as surgery.

Bicalutamide in a dose of 150 mg daily may be given as monotherapy or adjuvant therapy to surgery or radiotherapy in men with locally advanced disease at high risk for disease progression. It has been used as monotherapy in localised disease, but there is some evidence to suggest that in men without high risk of disease progression, who would otherwise be managed with watchful waiting, the immediate use of bicalutamide may increase the risk of death.

◊ References.

1. Wirth M, *et al.* Bicalutamide (Casodex) 150 mg as immediate therapy in patients with localized or locally advanced prostate cancer significantly reduces the risk of disease progression. *Urology* 2001; **58:** 146–51.
2. Boccardo F, *et al.* Bicalutamide monotherapy versus flutamide plus goserelin in prostate cancer: updated results of a multicentric trial. *Eur Urol* 2002; **42:** 481–90.
3. See WA, *et al.* Bicalutamide as immediate therapy either alone or as adjuvant to standard care of patients with localized or locally advanced prostate cancer: first analysis of the early prostate cancer program. *J Urol (Baltimore)* 2002; **168:** 429–35.
4. See W, *et al.* Immediate treatment with bicalutamide 150 mg as adjuvant therapy significantly reduces the risk of PSA progression in early prostate cancer. *Eur Urol* 2003; **44:** 512–17.
5. Fradet Y. Bicalutamide (Casodex) in the treatment of prostate cancer. *Expert Rev Anticancer Ther* 2004; **4:** 37–48.
6. Schellhammer PF, Davis JW. An evaluation of bicalutamide in the treatment of prostate cancer. *Clin Prostate Cancer* 2004; **2:** 213–19.
7. Wirth MP, *et al.* Bicalutamide 150 mg in addition to standard care in patients with localized or locally advanced prostate cancer: results from the second analysis of the early prostate cancer program at median followup of 5.4 years. *J Urol (Baltimore)* 2004; **172:** 1865–70.
8. Iversen P, *et al.* Bicalutamide (150 mg) versus placebo as immediate therapy alone or as adjuvant to therapy with curative intent for early nonmetastatic prostate cancer: 5.3-year median followup from the Scandinavian Prostate Cancer Group Study Number 6. *J Urol (Baltimore)* 2004; **172:** 1871–6.
9. Klotz L, Schellhammer P. Combined androgen blockade: the case for bicalutamide. *Clin Prostate Cancer* 2005; **3:** 215–19.
10. Wirth M, *et al.* Bicalutamide ('Casodex') 150 mg in addition to standard care in patients with nonmetastatic prostate cancer: updated results from a randomised double-blind phase III study (median follow-up 5.1 y) in the early prostate cancer programme. *Prostate Cancer Prostatic Dis* 2005; **8:** 194–200.
11. Tyrell CJ, *et al.* Bicalutamide ('Casodex') 150 mg as adjuvant to radiotherapy in patients with localised or locally advanced prostate cancer: results from the randomised Early Prostate Cancer Programme. *Radiother Oncol* 2005; **76:** 4–10.
12. McLeod DG, *et al.* Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. *BJU Int* 2006; **97:** 247–54.
13. Wellington K, Keam SJ. Bicalutamide 150mg: a review of its use in the treatment of locally advanced prostate cancer. *Drugs* 2006; **66:** 837–50.
14. Iversen P, Roder MA. The Early Prostate Cancer program: bicalutamide in nonmetastatic prostate cancer. *Expert Rev Anticancer Ther* 2008; **8:** 361–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Androxinon†; Bicaprost†; Bidrostat; Biolutam; Bitakebir; Bosconar; Casodex; Codebup; Dimalan; Finaband; Gepeprostin; Imda†; Liberprost; Raffolutil; ***Austral.:*** Cosudex; ***Austria:*** Casodex; ***Belg.:*** Casodex; ***Braz.:*** Casodex; Gepeprostin; Lutamidal; ***Canad.:*** Casodex; ***Chile:*** Casodex; Lutamidal; ***Cz.:*** Bicaluplex; Calumid; Casodex; Lanbica; ***Denm.:*** Casodex; ***Fin.:*** Casodex; ***Fr.:*** Casodex; ***Ger.:*** Casodex; ***Gr.:*** Bicalut; Bicamide; Casodex; Verodex; ***Hong Kong:*** Casodex; ***Hung.:*** Bicatlon; Bilutamid; Calumid; Casodex; ***India:*** Caluran; Calutide; ***Indon.:*** Casodex; ***Irl.:*** Casodex; ***Israel:*** Casodex; ***Ital.:*** Casodex; ***Malaysia:*** Casodex; ***Mex.:*** Casodex; ***Neth.:*** Casodex; ***Norw.:*** Casodex; ***NZ:*** Cosudex; ***Philipp.:*** Casodex; ***Pol.:*** Casodex; ***Port.:*** Casodex; ***Rus.:*** Bilumid (Билумид); Calumid (Калумид); Casodex (Касодекс); ***S.Afr.:*** Casodex; ***Singapore:*** Casodex; ***Spain:*** Casodex; ***Swed.:*** Casodex; ***Switz.:*** Casodex; ***Thai.:*** Casodex; ***Turk.:*** Casodex; ***UK:*** Casodex; ***USA:*** Casodex; ***Venez.:*** Calutol; Casodex.

Multi-ingredient: ***Austral.:*** Zolacos CP.

Bleomycin Sulfate *(USAN, pINNM)*

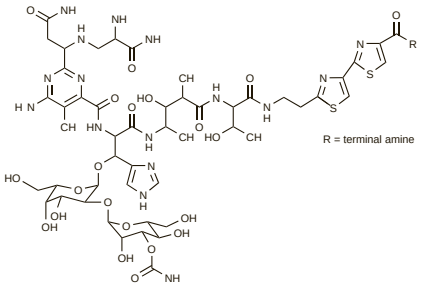
Bleomicino sulfatas; Bleomicin-szulfát; Bleomycin Sulphate *(BANM)*; Bléomycine, sulfate de; Bleomycini sulfas; Bleomycinsulfat; Bleomycin-sulfát; Bleomysiinisulfaatti; Sulfato de bleomicina.

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.