Uses and Administration

Verteporfin is a photosensitiser used in photodynamic therapy (see under Porfimer Sodium, p.764). It is used to treat neovascular (wet) age-related macular degeneration (see below). After intravenous dosage verteporfin accumulates preferentially in the endothelial cells of actively growing blood vessels, including those in the choroid. When activated by laser light it produces local vascular occlusion and this inhibits neovascularisation and reduces the decline in visual acuity. It is given by intravenous infusion over 10 minutes at a dose of 6 mg/m^2. This is followed 15 minutes after the start of the infusion by activation using a laser tuned to a wavelength of 689 nanometres and delivered to the eye via a fibre optic device and a slit lamp, together with a suitable contact lens. The recommended light dose is 50 J/cm^2, given over 83 seconds. Therapy may be repeated every 3 months for recurrent choroidal neovascular leakage. Verteporfin has also been investigated in the photodynamic therapy of a variety of other disorders including malignant neoplasms.

Age-related macular degeneration. Age-related macular degeneration (AMD) is a degenerative disease usually occurring in people over the age of 50 years.[1-3] The central portion of the retina (the macula) deteriorates[2,4,5] and it is a major cause of severe visual loss in people over 60 years old in North America and Europe.[4,6] There are two main types of AMD.

- In geographic atrophy or *non-neovascular* or *non-exudative (dry) AMD*, which occurs at an early stage of AMD, the retinal pigment epithelium is lost completely in localised areas, causing a gradual loss of central vision in the affected eye(s). It is characterised by retinal hypo- or hyperpigmentation, and yellow deposits of acellular amorphous debris beneath the retina, called drusen. These are usually large, or soft (with indistinct margins); small hard drusen occur naturally with ageing but, unlike drusen in AMD, do not progress.
- In *neovascular* or *exudative (wet) AMD*, new blood vessels develop in the choroidal layer beneath the retina; leaks or haemorrhage from these lead to macular oedema, retinal scarring, and often acute, significant loss of vision.[2,4,5,7-10] This process of *choroidal neovascularisation* (CNV) is defined as classic or occult according to its appearance on fluorescein angiography;[2,5,9,11] the classic form is associated with more rapid progression than the occult form.[2,9] CNV lesions are also classified according to their location relative to the fovea.[1,2,12] Although the neovascular form accounts for only about 20% of all cases of AMD, the risk of severe visual loss with this form is much higher than with dry AMD.[1,9] However, about 10 to 20% of patients with dry AMD can progress to the neovascular form,[1,10] and both forms can occasionally co-exist in the same patient.[11]

Risk factors, besides older age, include a family history of the disorder, the presence of a mutation in the complement factor H (CFH) gene, smoking, white race, and increased body-mass index;[3,8,13] female sex, atherosclerosis, dietary fat or fish intake, alcohol or caffeine consumption, refractive error, iris colour, and increased exposure to sunlight have also been proposed as risk factors but have not consistently been related to development of AMD.[13]

There is currently no **treatment** that effectively prevents visual loss or improves vision in all patients with AMD.[14]

- Laser photocoagulation treatment is of proven efficacy for neovascular AMD, especially for extrafoveal CNV; however, rates of recurrence are high.[1,6,8,13,14]
- Photodynamic therapy (see under Porfimer Sodium, p.764) with verteporfin has been shown to decrease the risk of visual loss in patients with neovascular AMD, including subfoveal CNV.[1,4,8,9,11,12,14-18] Systematic reviews have noted that although photodynamic therapy with verteporfin is probably effective in preventing visual loss in those with classic and occult CNV due to AMD, the size of the effect remains in doubt.[5,19] Furthermore, the therapy can only be effective during the proliferative stage of the disease while the neovascular process is active.[5]

  In the UK, NICE guidelines considered the evidence to show a larger treatment effect in patients with classic CNV, and recommend photodynamic therapy in those patients with neovascular AMD with a confirmed diagnosis of classic, with no occult, subfoveal CNV.[2] However, other guidelines[20] on the use of verteporfin recommend that verteporfin treatment be considered for patients with minimally classic subfoveal CNV who have relatively small lesions, or where the proportion of classic CNV is increasing. For those patients with occult CNV and who are presumed to have recent disease progression, verteporfin may be considered in those with smaller lesions or lower levels of visual acuity; for those with large occult lesions, treatment may be considered if levels of visual acuity are rapidly decreasing. Patients should be followed up at least as often as every 3 months after initial therapy, and re-treated if necessary.[20]

  While photodynamic therapy is considered to have minimal adverse effects and a low complication rate, some have cautioned that patients should be counselled that verteporfin therapy rarely leads to an improvement in vision.[21]
- Vascular endothelial growth factor (VEGF) plays a role in the development of CNV secondary to AMD; pegaptanib and ranibizumab are VEGF inhibitors used in the treatment of neovascular (wet) AMD.[22-24] Systematic reviews[25,26] of randomised controlled studies of these drugs concluded that both show benefit in slowing or stopping the progression of disease. Greater effect was seen with ranibizumab than with pegaptanib, although head-to-head comparative studies are needed to confirm this. Bevacizumab has also been tried, although its use is controversial.[6,22,27] Triamcinolone acetonide, a corticosteroid that may also downregulate VEGF, has been given intravitreally with variable results; combination treatment with photodynamic therapy is under investigation.[10,13,28]
- Angiogenesis inhibitors such as anecortave are under investigation for neovascular AMD.[3,10,13,14,28] Interferon alfa showed encouraging preliminary results, but controlled data showed no benefit.[8,10,13] Thalidomide has been tried, but trials were stopped due to adverse effects.[10,13]
- Vitamin and mineral supplements may be of use in selected patients; the AREDS trial found that antoxidants (vitamin C, vitamin E, and betacarotene) plus zinc modestly benefited those with moderate to severe signs of the disease.[11,14] However, betacarotene should be avoided in smokers.[3,6,10] The carotenoids, lutein and zeaxanthin, have been promoted as retinal protectants, but controlled data are lacking.[10,11,14,29] Some recommend that those at risk of AMD should be encouraged to stop smoking and to consume a diet including vegetables, fish, nuts, and to reduce consumption of fats especially vegetable oil.[7,29] A prospective cohort study found that a high dietary intake of vitamin E and zinc, or an above-median intake of the combination of vitamins C and E, betacarotene, and zinc were associated with a lower risk of incident AMD.[30] However, systematic reviews[31,32] have found no evidence to support the role of antoxidant vitamin and mineral supplements in the primary prevention of AMD.
- Retinal or macular surgery, and transpupillary thermotherapy are under investigation.[1,8,11,13,14,28] Radiotherapy has also been tried with mixed results.[10,13] Retinal transplantation is under investigation.[6,8,11,14] Gene silencing with bevasiranib, a short interfering RNA (siRNA) therapeutic designed to turn off or silence the gene that produces VEGF, is also under investigation for wet AMD.[33]

1. Soubrane G, Bressler NM. Treatment of subfoveal choroidal neovascularisation in age related macular degeneration: focus on clinical application of verteporfin photodynamic therapy. *Br J Ophthalmol* 2001; **85:** 483–95.
2. NICE. Guidance on the use of photodynamic therapy for age-related macular degeneration: Technology Appraisal 68 (issued September 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/68_PDTGuidance.pdf (accessed 09/05/08)
3. El-Amir AN, *et al.* Age-related macular degeneration. *Br J Hosp Med* 2005; **66:** 677–81.
4. Messmer KJ, Abel SR. Verteporfin for age-related macular degeneration. *Ann Pharmacother* 2001; **35:** 1593–8.
5. Wormald R, *et al.* Photodynamic therapy for neovascular age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 01/08/08).
6. Cook HL, *et al.* Age-related macular degeneration: diagnosis and management. *Br Med Bull* 2008; **85:** 127–49.
7. Constable IJ. Age-related macular degeneration and its possible prevention. *Med J Aust* 2004; **181:** 471–2.
8. Fine SL, *et al.* Age-related macular degeneration. *N Engl J Med* 2000; **342:** 483–92.
9. Yang YC. Preserving vision with verteporfin photodynamic therapy. *Hosp Med* 2004; **65:** 39–43.
10. Comer GM, *et al.* Current and future treatment options for non-exudative and exudative age-related macular degeneration. *Drugs Aging* 2004; **21:** 967–92.
11. Bylsma GW, Guymer RH. Treatment of age-related macular degeneration. *Clin Exp Optom* 2005; **88:** 322–34.
12. Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials—TAP report 1. *Arch Ophthalmol* 1999; **117:** 1329–45.
13. Sun JK, Miller JW. Medical treatment of choroidal neovascularization secondary to age-related macular degeneration. *Int Ophthalmol Clin* 2005; **45:** 115–32.
14. Lois N. Neovascular age-related macular degeneration. *Compr Ophthalmol Update* 2004; **5:** 143–61.
15. Blumenkranz MS, *et al.* Verteporfin therapy for subfoveal choroidal neovascularization in age-related macular degeneration: three-year results of an open-label extension of 2 randomized clinical trials—TAP report no. 5. *Arch Ophthalmol* 2002; **120:** 1307–14.
16. Blinder KJ, *et al.* Verteporfin therapy of subfoveal choroidal neovascularization in pathologic myopia: 2-year results of a randomized clinical trial—VIP report no. 3. *Ophthalmology* 2003; **110:** 667–73.
17. Keam SJ, *et al.* Verteporfin: a review of its use in the management of subfoveal choroidal neovascularisation. *Drugs* 2003; **63:** 2521–54.
18. Wickens J, Blinder KJ. A preliminary benefit-risk assessment of verteporfin in age-related macular degeneration. *Drug Safety* 2006; **29:** 189–99.
19. Meads C, Hyde C. Photodynamic therapy with verteporfin is effective, but how big is its effect? Results of a systematic review. *Br J Ophthalmol* 2004; **88:** 212–17.
20. Verteporfin Roundtable Participants. Guidelines for using verteporfin (Visudyne) in photodynamic therapy for choroidal neovascularization due to age-related macular degeneration and other causes: update. *Retina* 2005; **25:** 119–34.
21. Sternberg P, Lewis H. Photodynamic therapy for age-related macular degeneration: a candid appraisal. *Am J Ophthalmol* 2004; **137:** 483–5.
22. Anonymous. A view on new drugs for macular degeneration. *Drug Ther Bull* 2007; **45:** 49–52.
23. Rosenfeld PJ, *et al.* MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006; **355:** 1419–31.
24. Brown DM, *et al.* ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006; **355:** 1432–44.
25. Takeda AL, *et al.* Pegaptanib and ranibizumab for neovascular age-related macular degeneration: a systematic review. *Br J Ophthalmol* 2007; **91:** 1177–82.
26. Vedula SS, Krzystolik MG. Antiangiogenic therapy with antivascular endothelial growth factor modalities for neovascular age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 09/05/08).
27. Wong TY, *et al.* Clinical update: new treatments for age-related macular degeneration. *Lancet* 2007; **370:** 204–6.
28. Liu M, Regillo CD. A review of treatments for macular degeneration: a synopsis of currently approved treatments and ongoing clinical trials. *Curr Opin Ophthalmol* 2004; **15:** 221–6.
29. Anonymous. Nutritional supplements for macular degeneration. *Drug Ther Bull* 2006; **44:** 9–11.
30. van Leeuwen R, *et al.* Dietary intake of antioxidants and risk of age-related macular degeneration. *JAMA* 2005; **294:** 3101–7.
31. Chong EW-T, *et al.* Dietary antioxidants and primary prevention of age related macular degeneration: systematic review and meta-analysis. *BMJ* 2007; **335:** 755–9.
32. Evans JR, Henshaw K. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 09/05/08).
33. Arjamaa O. Gene silencing in wet age-related macular degeneration. *Lancet* 2006; **368:** 630–1.

Preparations

USP 31: Verteporfin for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Visudyne; ***Austral.:*** Visudyne; ***Austria:*** Visudyne; ***Belg.:*** Visudyne; ***Braz.:*** Visudyne; ***Canad.:*** Visudyne; ***Chile:*** Visudyne; ***Cz.:*** Visudyne; ***Denm.:*** Visudyne; ***Fin.:*** Visudyne; ***Fr.:*** Visudyne; ***Ger.:*** Visudyne; ***Gr.:*** Visudine; ***Hong Kong:*** Visudyne; ***Hung.:*** Visudyne; ***Indon.:*** Visudyne; ***Israel:*** Visudyne; ***Ital.:*** Visudyne; ***Jpn:*** Visudyne; ***Malaysia:*** Visudyne; ***Neth.:*** Visudyne; ***Norw.:*** Visudyne; ***NZ:*** Visudyne; ***Philipp.:*** Visudyne; ***Pol.:*** Visudyne; ***Port.:*** Visudyne; ***Rus.:*** Visudyne (Визудин); ***S.Afr.:*** Visudyne; ***Singapore:*** Visudyne; ***Spain:*** Visudyne; ***Swed.:*** Visudyne; ***Switz.:*** Visudyne; ***Thai.:*** Visudyne; ***Turk.:*** Visudyne; ***UK:*** Visudyne; ***USA:*** Visudyne; ***Venez.:*** Visudyne.

Vinblastine Sulfate *(USAN, rINNM)*

29060-LE; NSC-49842; Sulfato de Vimblastina; Sulfato de vinblastina; Vinblastiinisulfaatti; Vinblastin Sülfat; Vinblastine, sulfate de; Vinblastine Sulphate *(BANM)*; Vinblastini sulfas; Vinblastino sulfatas; Vinblastinsulfat; Vinblastin-sulfát; Vinblasztin-szulfát; Vincaleukoblastine Sulphate; VLB (vinblastine); Winblastyny siarczan.

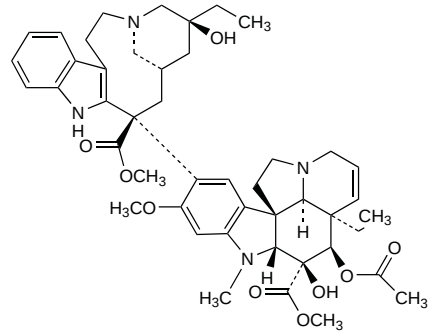
Винбластина Сульфат

$C_{46}H_{58}N_4O_9,H_2SO_4$ = 909.1.

CAS — 865-21-4 (vinblastine); 143-67-9 (vinblastine sulfate).

ATC — L01CA01.

ATC Vet — QL01CA01.



(vinblastine)

Description. Vinblastine sulfate is the sulfate of an alkaloid, vincaleukoblastine, extracted from *Catharanthus roseus* (*Vinca rosea*) (Apocynaceae).

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Vinblastine Sulphate). A white or slightly yellowish, very hygroscopic, crystalline powder. It loses not more than 15% of its weight on drying. Freely soluble in water; practically insoluble in alcohol. A 0.15% solution in water has a pH of 3.5 to 5.0. Store at a temperature not exceeding –20° in airtight glass containers. Protect from light.

USP 31 (Vinblastine Sulfate). A white or slightly yellow, odourless, hygroscopic, amorphous or crystalline powder. It loses not more than 15% of its weight on drying. Freely soluble in water. A 0.15% solution in water has a pH of 3.5 to 5.0. Store at a temperature between –25° and –10° in airtight containers. Protect from light.

Stability. Between about 5 and 20% of active drug was lost from solution when a solution of vinblastine sulfate 3 micrograms/mL in glucose 5% injection was stored for 48 hours in a range of intravenous burette giving sets, the highest loss being from cellulose propionate sets and the lowest from one made from methacrylate butadiene styrene.[1] Similarly, storage in PVC tubing led to a 42 to 44% loss from solution whereas only about 6% was lost over the 48 hours in polybutadiene tubing. The losses appeared to be due to drug sorption, and were therefore greater from the tubing which had a greater surface-area-to-volume ratio than the burettes.

1. McElnay JC, *et al.* Stability of methotrexate and vinblastine in burette administration sets. *Int J Pharmaceutics* 1988; **47:** 239–47.

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p.635, p.639, and p.641.

Bone-marrow depression, especially leucopenia, is the most common adverse effect with vinblastine and tends to be dose-limiting. Maximum depression occurs 5 to 10 days after a dose with recovery in a further 7 to 14 days. Leucopenia may be more severe in patients with cachexia or extensive skin ulceration: vinblastine should not be used in elderly patients with these conditions. Stomatitis and gastrointestinal bleeding may occur; nausea and vomiting respond to treatment with antiemetics.

The vinca alkaloids can produce central and peripheral (including autonomic) neurotoxicity, although these effects are less frequent with vinblastine. Symptoms include malaise, weakness, headache, depression, paraesthesia and numbness, loss of deep tendon reflexes, peripheral neuropathies, constipation and adynamic ileus, jaw pain, and convulsions. Damage to the eighth cranial nerve may result in vestibular and auditory toxicity leading to dizziness, nystagmus, vertigo, and partial or total deafness. A routine prophylactic regimen against constipation is recommended in patients receiving high doses of vinblastine. Overdosage has caused permanent damage to the CNS. Intrathecal use of the vinca alkaloids is contra-indicated because of the likelihood of fatal neurotoxicity (see Administration Error, below).

Other reported effects include skin reactions, alopecia, ischaemic cardiac toxicity, hypertension, dyspnoea and bronchospasm, and bone and tumour pain. A syndrome of inappropriate secretion of antidiuretic hormone has occurred at high doses, and may be relieved by fluid restriction and, if necessary, a suitable diuretic. Rare cases of anaphylaxis and anaphylactoid-type reactions have been reported with the vinca alkaloids.

Vinblastine is irritant to the skin and mucous membranes and extravasation may cause necrosis, cellulitis, and sloughing. The application of warmth and local injection of hyaluronidase may be of benefit in relieving the effects of extravasation. By analogy with its use in the management of vincristine overdosage (see p.787), folinic acid has been suggested for use in overdosage with vinblastine.

Vinblastine should not be injected into an extremity with impaired circulation because of an increased risk of thrombosis. It should be given with caution and at reduced dosage to patients with hepatic impairment (see under Uses, below).

Administration error. *Intrathecal doses of vinca alkaloids, including vinblastine, result in ascending paralysis and death.* For reference to the successful treatment of inadvertent intrathecal dosage of vincristine, and UK guidelines on dilution of vinca alkaloids to avoid intrathecal use, see p.787.

Handling and disposal. A method for the destruction of vincristine or vinblastine *wastes* using sulfuric acid and potassium permanganate.[1] Residues produced by degradation of either drug by this method showed no mutagenicity *in vitro*.

Urine and faeces produced for up to 4 and 7 days respectively after a dose of vinblastine should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73* Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Porphyria. Vinblastine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems, although there is conflicting evidence of porphyrinogenicity.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. Use with drugs that inhibit cytochromes of the CYP3A subfamily may result in decreased metabolism of vinblastine and increased toxicity. For a report of the possible contribution of vinblastine to reduced plasma concentrations of phenytoin, see p.499.

Analgesics. A report of enhanced hepatotoxicity in patients treated with interferon alfa and vinblastine who were given *paracetamol*.[1]

1. Kellokumpu-Lehtinen P, *et al.* Hepatotoxicity of paracetamol in combination with interferon and vinblastine. *Lancet* 1989; **i:** 1143.

Antibacterials. There is a report of severe vinblastine toxicity in 3 patients who received vinblastine and ciclosporin with *erythromycin*.[1] Adverse effects resolved on stopping erythromycin and recurred in 1 patient who was rechallenged with erythromycin.

1. Tobe SW, *et al.* Vinblastine and erythromycin: an unrecognised serious drug interaction. *Cancer Chemother Pharmacol* 1995; **35:** 188–90.

Antineoplastics. Acute bronchospastic reactions after injection of a vinca alkaloid have been reported, usually in patients who have also received *mitomycin*,[1] and presenting as acute respiratory distress, cyanosis, and dyspnoea, often with the development of pulmonary infiltrates and pneumonitis.[2,3] A number of fatalities due to respiratory complications have occurred. For reports of vascular toxicity and Raynauds syndrome associated with the use of vinca alkaloids with *bleomycin* and other drugs, see Effects on the Cardiovascular System, p.636.

1. Dyke RW. Acute bronchospasm after a vinca alkaloid in patients previously treated with mitomycin. *N Engl J Med* 1984; **310:** 389.
2. Konits PH, *et al.* Possible pulmonary toxicity secondary to vinblastine. *Cancer* 1982; **50:** 2771–4.
3. Ozols RF, *et al.* MVP (mitomycin, vinblastine, and progesterone): a second-line regimen in ovarian cancer with a high incidence of pulmonary toxicity. *Cancer Treat Rep* 1983; **67:** 721–2.

Antivirals. Severe myelosuppression has occurred in patients given relatively high doses of vinblastine with *interferon alfa-n1*.

A patient who had been given vinblastine 6 mg/m^2 every 3 weeks had severe gastrointestinal and haematological toxicity and moderate renal failure when *HAART* with zidovudine, lamivudine, abacavir, nevirapine, and lopinavir with ritonavir was reintroduced.[1] The vinblastine dosage was eventually stabilised at 2 mg/m^2 during HAART without toxicity.

1. Kotb R, *et al.* Life-threatening interaction between antiretroviral therapy and vinblastine in HIV-associated multicentric Castleman's disease. *Eur J Haematol* 2006; **76:** 269–71.

Pharmacokinetics

Vinblastine is not reliably absorbed from the gastrointestinal tract. After intravenous use it is rapidly cleared from the blood and distributed to tissues; it is reported to be concentrated in blood platelets. It is extensively protein bound. Vinblastine is metabolised in the liver, by cytochrome P450 isoenzymes of the CYP3A subfamily, to an active metabolite desacetylvinblastine, and is excreted in faeces via the bile, and in urine; some is excreted as unchanged drug. The terminal half-life is reported to be about 25 hours. It does not cross the blood-brain barrier in significant amounts.

◊ References.

1. Levêque D, Jehl F. Molecular pharmacokinetics of catharanthus (vinca) alkaloids. *J Clin Pharmacol* 2007; **47:** 579–88.

Uses and Administration

Vinblastine sulfate is an antineoplastic agent that apparently acts by binding to the microtubular proteins of the spindle and arresting mitosis at the metaphase; it is thus specific for the M phase of the cell cycle. It also interferes with glutamate metabolism and possibly nucleic acid synthesis, and has some immunosuppressant activity. Significant cross-resistance with vincristine has not been reported although pleiotropic resistance may occur.

Vinblastine sulfate is used, usually with other antineoplastics, in the treatment of Hodgkin's disease and other lymphomas, for some inoperable malignant neoplasms including those of the breast, bladder, and kidney, and in non-small cell lung cancer, choriocarcinoma, and Kaposi's sarcoma; vinblastine has also been employed in the management of Langerhans-cell histiocytosis. It was formerly used with bleomycin and cisplatin (PVB) for testicular cancer, but other regimens are now preferred. The management of these conditions is discussed under Choice of Antineoplastic, as indicated by the cross-references given below.

Vinblastine sulfate may be given by intravenous injection as a solution containing 1 mg/mL in sodium chloride 0.9%. However, UK guidelines recommend that for patients over the age of 10 years, solutions of vinblastine should generally be diluted to a volume of at least 20 mL to avoid inadvertent intrathecal use; higher concentrations can be used for children under 10 years of age. Care should be taken to avoid extravasation and the intravenous injection may be given into a freely running infusion of sodium chloride injection if preferred. The usual dose is about 6 mg/m^2, not more often than every 7 days, although doses starting at 3.7 mg/m^2 and increasing to 18.5 mg/m^2 have been given as a single agent. If a maintenance dose is required, it may be given every 7 days provided white cell counts permit (see below), and should be the maximum dose that the patient is able to tolerate without serious leucopenia occurring.

Children may be given vinblastine sulfate in a usual maximum weekly dose of 7.5 mg/m^2. Doses of up to 12.5 mg/m^2 weekly as a single agent have been given.

White cell counts should be made before each injection and some sources suggest a repeat dose should not be given unless the count has risen to at least 4000 cells/mm^3 (but see also Bone-marrow Depression, p.639). A dosage reduction is advised in patients with hepatic impairment (see below).

Administration in hepatic impairment. UK licensed product information recommends that the dose of vinblastine be reduced by 50% in patients having a serum bilirubin value above 3 mg per 100 mL.

Blood disorders, non-malignant. The vinca alkaloids vinblastine and vincristine have been used experimentally in the treatment of auto-immune blood disorders such as idiopathic thrombocytopenic purpura (p.1505). There are also reports of the haemolytic-uraemic syndrome/thrombotic thrombocytopenic purpura responding to treatment with intravenous injection of vincristine.[1-3] For further details on the treatment of thrombotic microangiopathies, see under Plasma, p.1076. Vincristine has been given with normal immunoglobulin in the management of a patient with life-threatening thrombocytopenia due to sarcoidosis.[4] Vincristine has also been used for life-threatening haemangioma (p.1505).

1. Gutterman LA, *et al.* The hemolytic-uremic syndrome: recovery after treatment with vincristine. *Ann Intern Med* 1983; **98:** 612–13.
2. Ferrara F, *et al.* Vincristine as salvage treatment for refractory thrombotic thrombocytopenic purpura. *Ann Hematol* 1999; **78:** 521–3.
3. Ferrara F, *et al.* Vincristine as treatment for recurrent episodes of thrombotic thrombocytopenic purpura. *Ann Hematol* 2002; **81:** 7–10.
4. Larner AJ. Life threatening thrombocytopenia in sarcoidosis. *BMJ* 1990; **300:** 317–19.

Histiocytic syndromes. The value of systemic chemotherapy in patients with Langerhans-cell histiocytosis (p.650) is uncertain; however, it is certainly widely used in extensive disease, vinblastine being one of the drugs often employed.[1,2]

1. The French Langerhans' Cell Histiocytosis Study Group. A multicentre retrospective survey of Langerhans' cell histiocytosis: 348 cases observed between 1983 and 1993. *Arch Dis Child* 1996; **75:** 17–24.
2. Gadner H, *et al.* A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. *J Pediatr* 2001; **138:** 728–34. Correction. *ibid.*; **139:** 170.

Malignant neoplasms. Vinblastine plays an important role in the ABVD regimen in patients with Hodgkin's disease (p.655). It also formed part of the effective, if toxic, PVB regimen used to treat germ cell (ovarian or testicular) cancer, p.670 and p.673 respectively, although other regimens tend now to be preferred. The vinca alkaloids are also active in gestational trophoblastic tumours (p.650), and vinblastine is also used in the therapy of invasive bladder cancer (p.659); it may be used in the adjuvant or palliative treatment of non-small-cell lung cancer (p.668) and in the palliative care of advanced breast cancer (p.661) and mycosis fungoides (p.657). It has been used in malignancies of the kidney (p.667). Vinca alkaloids are also used to treat Kaposi's sarcoma (p.675).

Preparations

BP 2008: Vinblastine Injection;
USP 31: Vinblastine Sulfate for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Blastovin; Velbe†; Xintoprost†; ***Austral.:*** Velbe; ***Austria:*** Velbe; ***Belg.:*** Velbe; Vinblasin; ***Braz.:*** Rabinefil†; Velban†; ***Chile:*** Lemblastine; Velbe†; ***Denm.:*** Velbe; ***Fin.:*** Velbe†; ***Fr.:*** Velbe; ***Ger.:*** Cellblastin†; Velbe†; ***Gr.:*** Velbe; ***Hong Kong:*** Velbe†; ***India:*** Cytoblastin; ***Israel:*** Blastovin; ***Ital.:*** Velbe; ***Mex.:*** Ifabla†; Lemblastine; Velbe†; ***Neth.:*** Blastivin; Velbe; ***Norw.:*** Velbe; ***Philipp.:*** Velbastine; ***Port.:*** Solblastin; Velbe†; ***Swed.:*** Velbe; ***Switz.:*** Velbe; ***UK:*** Velbe; ***USA:*** Velban; ***Venez.:*** Velbe†.

Vincristine Sulfate *(USAN, rINNM)*

Compound 37231; Leurocristine Sulphate; NSC-67574; 22-Oxovincaleukoblastine Sulphate; Sulfato de vincristina; Vincristine, sulfate de; Vincristine Sulphate *(BANM)*; Vincristini sulfas; Vinkristiinisulfaatti; Vinkristin Sülfat; Vinkristino sulfatas; Vinkristinsulfat; Vinkristin-sulfát; Vinkrisztin-szulfát; Winkrystyny siarczan.

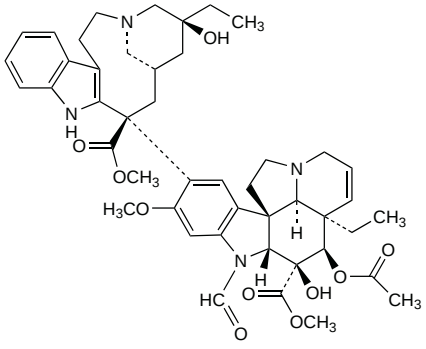
Винкристина Сульфат

$C_{46}H_{56}N_4O_{10},H_2SO_4$ = 923.0.

CAS — 57-22-7 (vincristine); 2068-78-2 (vincristine sulfate).

ATC — L01CA02.

ATC Vet — QL01CA02.



(vincristine)

Description. Vincristine sulfate is the sulfate of an alkaloid, 22-oxovincaleukoblastine, obtained from *Catharanthus roseus* (*Vinca rosea*) (Apocynaceae).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Vincristine Sulphate). A white or slightly yellowish, very hygroscopic, crystalline powder. It loses not more than 12% of its weight on drying. Freely soluble in water; slightly soluble in alcohol. A 0.1% solution in water has a pH of 3.5 to 4.5. Store at a temperature not exceeding –20° in airtight glass containers. Protect from light.

USP 31 (Vincristine Sulfate). A white to slightly yellow, odourless, hygroscopic, amorphous or crystalline powder. It loses not more than 12% of its weight on drying. Freely soluble in water; slightly soluble in alcohol; soluble in methyl alcohol. A 0.1% solution in water has a pH of 3.5 to 4.5. Store at a temperature between –25° and –20° in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Vinblastine Sulfate, p.786.

Bone-marrow depression occurs less commonly than with vinblastine but neurological and neuromuscular effects are more severe with vincristine and are dose-limiting. Walking may be impaired and the neurological effects may not be reversed for several months after the drug is stopped. Convulsions, often with hypertension, have occurred. Constipation is common and there may be abdominal pain. Urinary disturbances have occurred and alopecia is frequent.

Folinic acid has been given for the treatment of overdosage: suggested doses are as much as 100 mg of folinic acid intravenously every 3 hours for 24 hours, then every 6 hours for at least 48 hours. However, this is unlikely to be of benefit in reversing neuromuscular toxicity. For mention of the use of glutamic acid in managing the usually fatal consequences of inadvertent intrathecal dosage, see below.

Because severe constipation and impaction of faeces often occur with vincristine, laxatives or enemas may be necessary to ensure regular bowel function. Vincristine should be given with caution to patients with pre-existing neuromuscular disease and is contra-indicated in patients with the demyelinating form of Charcot-Marie-Tooth syndrome (see under Effects on the Nervous System, below). Doses may need to be adjusted in patients with hepatic impairment. Care should also be taken in elderly patients, who may be more susceptible to neurotoxicity.

Administration error. *Inadvertent intrathecal doses of vincristine result in ascending paralysis and death.*[1,2] However, in one case[1] treatment immediately after the error, and consisting of removal of contaminated spinal fluid and flushing with lactated Ringer's solution and fresh frozen plasma diluted in lactated Ringer's solution, plus intravenous and oral glutamic acid, was reported successful in stabilising neurological dysfunction and preventing death. A similar case of successful treatment has subsequently been reported,[3] in which immediate CSF aspiration and irrigation (with lactated Ringer's solution containing fresh frozen plasma to bind vincristine) for 6 days was combined with intravenous folate, glutamic acid, and pyridoxine. The role of neuroprotectant drugs in these cases is uncertain, although a study involving 84 patients found that glutamic acid 1.5 g daily given orally in divided doses during a 6-week induction chemotherapy course decreased vincristine-induced neurotoxicity.[4] One manufacturer (*Lilly*) has stated that the roles of glutamic acid, folinic acid, and pyridoxine remain unclear.

While early recognition and immediate treatment with cerebrospinal fluid drainage and exchange may improve survival,[5] fatalities still occur despite these measures.[5,6] Recommendations[2,6] have been made in order to prevent further errors occurring, including restrictions on the prescription, administration, and storage of intrathecal drugs. In the UK, recommendations state that vinca alkaloids for intravenous use in adults or children over 10 years should be diluted to a maximum concentration of 100 micrograms/mL (vincristine) or a volume of at least 20 mL (vinblastine, vindesine, or vinorelbine) and labelled with a clear warning of the consequences of use by other routes. Higher concentrations may be used in children under 10 years, and in certain specialised centres.[2]

1. Dyke RW. Treatment of inadvertent intrathecal injection of vincristine. *N Engl J Med* 1989; **321:** 1270–1.
2. Department of Health. Updated national guidance on the safe administration of intrathecal chemotherapy (HSC 2003/010, 2 October 2003). Available at: http://www.dh.gov.uk/assetRoot/04/06/43/17/04064317.pdf (accessed 01/07/04)
3. Qweider M, *et al.* Inadvertent intrathecal vincristine administration: a neurosurgical emergency. Case report. *J Neurosurg Spine* 2007; **6:** 280–3.
4. Jackson DV, *et al.* Amelioration of vincristine neurotoxicity by glutamic acid. *Am J Med* 1988; **84:** 1016–22.
5. Alcaraz A, *et al.* Intrathecal vincristine: fatal myeloencephalopathy despite cerebrospinal fluid perfusion. *J Toxicol Clin Toxicol* 2002; **40:** 557–61.
6. Fernandez CV, *et al.* Intrathecal vincristine: an analysis of reasons for recurrent fatal chemotherapeutic error with recommendations for prevention. *J Pediatr Hematol Oncol* 1998; **20:** 587–90.

Effects on the nervous system. In its most typical form, vincristine neurotoxicity[1] manifests as a mixed sensorimotor neuropathy of the distal type. The earliest symptoms are sensory changes in the form of paraesthesias, accompanied by impairment and ultimately loss of deep tendon reflexes. In more severe forms, impairment of motor function occurs with wrist drop and foot drop, ataxia and gait abnormalities, and occasionally progressive quadriparesis.

In contrast to these peripheral neuropathies, which are usually associated with long-term usage, there may be short-term autonomic neuropathy resulting in constipation and occasionally ileus, abdominal pain, atony of the urinary bladder (which may lead to urinary retention), orthostatic hypotension, and rarely, impotence. Effects on the cranial nerves may result in ptosis, hoarseness (due to laryngeal nerve paralysis), or optic neuropathies. Effects on the CNS are rare, probably in part because of poor penetration into CSF, but include excessive release of antidiuretic hormone and consequent hyponatraemia.

Hallucinations have occurred[2] and effects on the special senses have been reported: both bilateral optic atrophy and blindness,[3] and profound neurological deafness (which was largely reversible on drug withdrawal)[4] have occurred. Convulsions associated with hypertension are another feature of vincristine toxicity.[5]

Toxicity is related to both the cumulative and the individual dose.[1] It usually begins in adults after receiving a total of 5 to 6 mg, and is significant by the time a cumulative dose of 15 to 20 mg is reached. If individual doses are low (less than 2 mg) or intervals between doses are longer than the usual week, patients can tolerate higher cumulative doses. Children tolerate vincristine better than adults, but the elderly are particularly prone to neurotoxicity. Patients with existing neurological disorders such as poliomyelitis or the Charcot-Marie-Tooth syndrome may be at increased risk of neurotoxicity.[6-9] It has been suggested that increased neurotoxicity may be associated with the use of ready-to-use solutions rather than reconstituted lyophilised preparations but this has not been proved.[10-14]

There is no good treatment for the effects of vincristine on the nervous system: symptoms are largely reversible once dosage is interrupted, and should be managed with appropriate symptomatic care.[1] However, there is some suggestion that glutamic acid may be of benefit in treating neurotoxicity—see Administration Error, above. For the use of dinoprost to alleviate ileus induced by vinca alkaloids, see p.2007.

1. Legha SS. Vincristine neurotoxicity: pathophysiology and management. *Med Toxicol* 1986; **1:** 421–7.
2. Holland JF, *et al.* Vincristine treatment of advanced cancer: a cooperative study of 392 cases. *Cancer Res* 1973; **33:** 1258–64.
3. Awidi AS. Blindness and vincristine. *Ann Intern Med* 1980; **93:** 781.
4. Yousif H, *et al.* Partially reversible nerve deafness due to vincristine. *Postgrad Med J* 1990; **66:** 688–9.
5. Ito S, *et al.* Seizures and hypertension complicating vincristine therapy in children. *Clin Pharmacol Ther* 1995; **57:** 208.
6. Hogan-Dann CM, *et al.* Polyneuropathy following vincristine therapy in two patients with Charcot-Marie-Tooth syndrome. *JAMA* 1984; **252:** 2862–3.
7. Miller BR. Neurotoxicity and vincristine. *JAMA* 1985; **253:** 2045.
8. Chauncey TR, *et al.* Vincristine neurotoxicity. *JAMA* 1985; **254:** 507.
9. Griffiths JD, *et al.* Vincristine neurotoxicity in Charcot-Marie-Tooth syndrome. *Med J Aust* 1985; **143:** 305–6.
10. Arnold AM, *et al.* Acute vincristine neurotoxicity. *Lancet* 1985; **i:** 346.
11. Jalihal S, Roebuck N. Acute vincristine neurotoxicity. *Lancet* 1985; **i:** 637.
12. Davies CE, *et al.* Acute vincristine neurotoxicity. *Lancet* 1985; **i:** 637–8.
13. Warrier RP, Ducos R. Acute vincristine neurotoxicity. *Lancet* 1985; **i:** 980.
14. Gennery BA. Vincristine neurotoxicity. *Lancet* 1985; **ii:** 385.

Handling and disposal. For a method for the destruction of vincristine *wastes*, see under Vinblastine Sulfate, p.786.

Urine and faeces produced for up to 4 and 7 days respectively after a dose of vincristine 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.

Porphyria. Vincristine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems, although there is conflicting evidence of porphyrinogenicity.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. Use of vincristine with drugs that inhibit cytochromes of the CYP3A subfamily may result in decreased metabolism of vincristine and increased toxicity. If vincristine is used with asparaginase it should be given 12 to 24 hours before the enzyme: giving asparaginase with or before vincristine may reduce vincristine clearance and increase toxicity. For reports of vascular toxicity and Raynaud's syndrome associated with the use of vinca alkaloids with bleomycin and other drugs see Effects on the Cardiovascular System, p.636.

Antibacterials. Severe neurotoxicity has occurred when *isoniazid* was added to the regimen of a patient receiving vincristine.[1]

1. Carrión C, *et al.* Possible vincristine-isoniazid interaction. *Ann Pharmacother* 1995; **29:** 201.

Antiepileptics. A pharmacokinetic study showed that systemic clearance of vincristine was 63% higher when it was given with *phenytoin* or *carbamazepine*, two inducers of the cytochrome P450 isoenzyme CYP3A4. The clinical significance of this finding is unknown.[1]

1. Villikka K, *et al.* Cytochrome P450-inducing antiepileptics increase the clearance of vincristine in patients with brain tumours. *Clin Pharmacol Ther* 1999; **66:** 589–93.

Antifungals. Toxicity has been reported to be increased in children who received *itraconazole* with or without nifedipine dur-