luted 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 it may be given into a fast-running infusion of sodium chloride, glucose 5%, or glucose-saline injection. The usual starting dose for adults is 3 mg/m^2 which may be raised by increments of 500 micrograms/m^2 weekly providing that the granulocyte and platelet counts do not fall below acceptable levels (see also Bone-marrow Depression, p.639), and acute abdominal pain is not experienced; weekly doses are usually between 3 and 4 mg/m^2. Children may be given 4 mg/m^2 initially, with weekly doses usually ranging between 4 and 5 mg/m^2. An alternative regimen for children with leukaemia is 2 mg/m^2 daily for 2 consecutive days, repeated after an interval of 5 to 7 days. Blood counts should be made before each injection. It may be necessary to reduce initial doses in patients with significantly impaired hepatic function.

Malignant neoplasms. Vindesine has been tried in refractory metastatic melanoma (p.673), childhood acute lymphoblastic leukaemia (p.651), chronic myeloid leukaemia in blastic crisis (p.653), and neuroblastoma (p.674). It is also under investigation in lung cancer, particularly non-small cell lung cancer (p.668) and responses have been reported in advanced breast cancer (p.661).

Preparations

BP 2008: Vindesine Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Eldisine†; ***Austral.:*** Eldisine†; ***Austria:*** Eldisin; ***Belg.:*** Eldisine; ***Cz.:*** Eldisine†; ***Fin.:*** Eldisine†; ***Fr.:*** Eldisine; ***Ger.:*** Eldisine; ***Gr.:*** Eldisine; Enison; Gesidine; ***Irl.:*** Eldisine; ***Ital.:*** Eldisine; ***Neth.:*** Eldisine; ***Port.:*** Gesidine; ***S.Afr.:*** Eldisine†; ***Spain:*** Enison; ***Swed.:*** Eldisine; ***Switz.:*** Eldisine; ***UK:*** Eldisine.

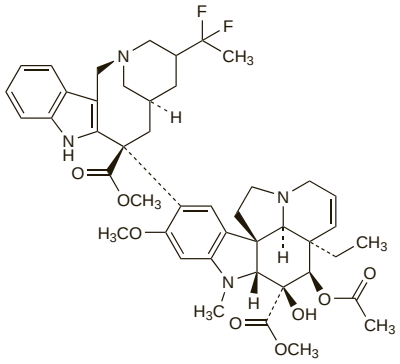
Vinflunine *(rINN)*

F-12158; F-13840; L-0070; Vinflunina; Vinfluninum. 4′-Deoxy-20′,20′-difluoro-8′-norvincaleukoblastine.

Винфлунин

$C_{45}H_{54}F_2N_4O_8$ = 816.9.

CAS — 162652-95-1 (vinflunine); 194468-36-5 (vinflunine tartrate).



Profile

Vinflunine is a vinca alkaloid derived from vinorelbine (p.789) that is under investigation for the treatment of bladder cancer and non-small cell lung cancer.

Vinorelbine Tartrate *(BANM, USAN, rINNM)*

5′-Nor-anhydrovinblastine Tartrate; Tartrato de vinorelbina; Vinorelbiinitartraatti; Vinorelbin Bitartrat; Vinorelbin-ditartarát; Vinorelbine Ditartrate; Vinorelbine, tartrate de; Vinorelbini Ditartras; Vinorelbini tartras; Vinorelbino tartratas; Vinorelbintartrat. 3′,4′-Didehydro-4′-deoxy-8′-norvincaleukoblastine ditartrate.

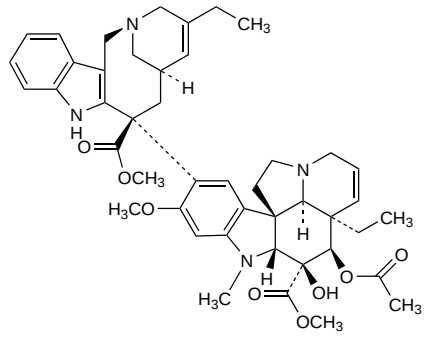
Винорелбина Тартрат

$C_{45}H_{54}N_4O_8,2C_4H_6O_6$ = 1079.1.

CAS — 71486-22-1 (vinorelbine); 125317-39-7 (vinorelbine tartrate).

ATC — L01CA04.

ATC Vet — QL01CA04.



(vinorelbine)

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

Ph. Eur. 6.2 (Vinorelbine Tartrate). A white or almost white, hygroscopic powder. Freely soluble in water and in methyl alcohol; practically insoluble in hexane. A 1.4% solution in water has a pH of 3.3 to 3.8. Store under an inert gas at a temperature not exceeding –15°. Protect from light.

USP 31 (Vinorelbine Tartrate). A white to yellow or light brown amorphous powder. Freely soluble in water. pH of a 1% solution in water is between 3.3 and 3.8. Store at a temperature between –25° and –10° in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Vinblastine Sulfate, p.786. The main dose-limiting effect of vinorelbine is granulocytopenia. The nadir of the granulocyte count occurs 5 to 10 days after a dose, with recovery usually after a further 7 to 14 days. The drug should be stopped if moderate or severe neurotoxicity develops. Local pain and thrombophlebitis may be seen with repeated injection of vinorelbine. Gastrointestinal effects such as nausea and vomiting are common with the oral formulation.

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

Effects on the gastrointestinal tract. For reference to a report of vinorelbine possibly exacerbating ischaemic colitis in patients receiving docetaxel, see p.711.

Interactions

As for Vinblastine Sulfate, p.786.

Pharmacokinetics

As with the other vinca alkaloids, vinorelbine exhibits triphasic pharmacokinetics after intravenous injection, and has a terminal half-life of between about 28 and 44 hours. It is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations achieved between 1.5 and 3 hours after oral doses. It is metabolised in the liver; deacetylvinorelbine has antineoplastic activity. Vinorelbine and its metabolites are excreted primarily in faeces via the bile but also in urine.

◊ References.

1. Levêque D, Jehl F. Clinical pharmacokinetics of vinorelbine. *Clin Pharmacokinet* 1996; **31:** 184–97.
2. Marty M, *et al.* Oral vinorelbine pharmacokinetics and absolute bioavailability study in patients with solid tumors. *Ann Oncol* 2001; **12:** 1643–9.
3. Bugat R, *et al.* The effects of food on the pharmacokinetic profile of oral vinorelbine. *Cancer Chemother Pharmacol* 2002; **50:** 285–90.
4. Variol P, *et al.* A simultaneous oral/intravenous population pharmacokinetic model for vinorelbine. *Eur J Clin Pharmacol* 2002; **58:** 467–76.
5. Wong M, *et al.* Predictors of vinorelbine pharmacokinetics and pharmacodynamics in patients with cancer. *J Clin Oncol* 2006; **24:** 2448–55.

Uses and Administration

Vinorelbine is a semisynthetic derivative of vinblastine (p.786) with similar general properties. It is used in the treatment of advanced breast cancer and non-small cell lung cancers (see p.661 and p.668 respectively), and has been tried in other malignancies including lymphomas and tumours of ovary and prostate.

Vinorelbine is given as the tartrate but doses are calculated in terms of vinorelbine: vinorelbine tartrate 1.385 mg is equivalent to about 1 mg of vinorelbine. It may be given by intravenous injection over 5 to 10 minutes, as a solution containing the equivalent of vinorelbine 1.5 to 3 mg/mL in glucose 5% or sodium chloride 0.9% injection, directly or into a freely-running intravenous infusion. However, UK guidelines recommend that for patients over the age of 10 years, solutions of vinorelbine 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. It may also be given by intravenous infusion over 20 to 30 minutes after dilution in 125 mL of glucose 5% or sodium chloride 0.9%.

The usual initial intravenous dose in the treatment of breast cancer or non-small cell lung cancer is the equivalent of vinorelbine 25 to 30 mg/m^2 weekly. In the UK, the manufacturers recommend that if the neutrophil count falls below 2000 cells/mm^3 subsequent doses should be delayed until recovery. In the USA it is suggested that subsequent doses should be halved if granulocyte counts fall to between 1000 and 1500 cells/mm^3; treatment should be interrupted if counts are below 1000 cells/mm^3 and stopped if granulocytopenia persists for more than 2 weeks (see also Bone-marrow Depression, p.639). Doses should also be reduced in hepatic impairment and in patients with massive liver metastases (but see also below).

In the treatment of non-small cell lung cancer, vinorelbine is also given orally at a dose of 60 mg/m^2 once weekly for 3 weeks. Subsequent doses may be increased to 80 mg/m^2, unless the neutrophil count falls below 500 cells/mm^3, or to between 500 and 1000 cells/mm^3 on two separate occasions, in which case the dose is kept at 60 mg/m^2 for the next 3 doses.

◊ References.

1. Gregory RK, Smith IE. Vinorelbine—a clinical review. *Br J Cancer* 2000; **82:** 1907–13.
2. Sarris AH, *et al.* Infusional vinorelbine in relapsed or refractory lymphomas. *Leuk Lymphoma* 2000; **39:** 291–9.
3. Sorensen P, *et al.* Phase II study of vinorelbine in the treatment of platinum-resistant ovarian carcinoma. *Gynecol Oncol* 2001; **81:** 58–62.
4. Oudard S, *et al.* Phase II study of vinorelbine in patients with androgen-independent prostate cancer. *Ann Oncol* 2001; **12:** 847–52.
5. Domenech GH, Vogel CL. A review of vinorelbine in the treatment of breast cancer. *Clin Breast Cancer* 2001; **2:** 113–28.
6. Aapro MS, *et al.* Developments in cytotoxic chemotherapy: advances in treatment utilising vinorelbine. *Crit Rev Oncol Hematol* 2001; **40:** 251–63.
7. Gridelli C, De Vivo R. Vinorelbine in the treatment of non-small cell lung cancer. *Curr Med Chem* 2002; **9:** 879–91.
8. Freyer G, *et al.* Phase II study of oral vinorelbine in first-line advanced breast cancer chemotherapy. *J Clin Oncol* 2003; **21:** 35–40.
9. Gebbia V, Puozzo C. Oral versus intravenous vinorelbine: clinical safety profile. *Expert Opin Drug Saf* 2005; **4:** 915–28.
10. Aapro MS, *et al.* Oral vinorelbine: role in the management of metastatic breast cancer. *Drugs* 2007; **67:** 657–67.
11. Gralla RJ, *et al.* Oral vinorelbine in the treatment of non-small cell lung cancer: rationale and implications for patient management. *Drugs* 2007; **67:** 1403–10.

Administration in hepatic impairment. Clearance of vinorelbine was markedly reduced in patients with diffuse liver metastases and hence severely altered hepatic function: a 50% dose reduction was probably appropriate in such patients even if hyperbilirubinaemia was not marked.[1] However, reduced doses were not necessary in patients with moderate liver involvement in whom liver function, as measured by lidocaine metabolism, was not markedly reduced. Licensed product information in the UK suggests that the intravenous dose be reduced by one-third in patients with massive liver metastases (more than 75% of liver volume replaced by tumour cells).

In the USA, licensed information recommends that the intravenous dose of vinorelbine be reduced by 50% in patients with bilirubin values of 2.1 to 3 mg per 100 mL and by 75% in those with bilirubin greater than 3 mg per 100 mL.

1. Robieux I, *et al.* Pharmacokinetics of vinorelbine in patients with liver metastases. *Clin Pharmacol Ther* 1996; **59:** 32–40.

Preparations

USP 31: Vinorelbine Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Filcrin; Navelbine; Neocitec; Sulcoline; Vilbine†; Vilne; Vinarine; Vinkebir; Vinorel; Vinorgen; ***Austral.:*** Navelbine; ***Austria:*** Navelbine; ***Belg.:*** Navelbine; ***Braz.:*** Navelbine; Neocitec; Norelbin; ***Canad.:*** Navelbine; ***Chile:*** Navelbine; ***Cz.:*** Navelbine; Navirel; Nibrevin; ***Denm.:*** Navelbine; Navirel; ***Fin.:*** Navelbine; ***Fr.:*** Navelbine; ***Ger.:*** Navelbine; ***Gr.:*** Navelbine; ***Hong Kong:*** Navelbine; ***Hung.:*** Navelbin; ***India:*** Vinelbine; ***Israel:*** Navelbine; ***Ital.:*** Navelbine; ***Jpn:*** Navelbine; ***Malaysia:*** Navelbine; ***Mex.:*** Navelbine;

Viessia; Vinilex; ***Neth.:*** Navelbine; ***Norw.:*** Navelbine; ***NZ:*** Navelbine; ***Philipp.:*** Navelbine; Vinotel; ***Pol.:*** Navelbine; Navirel; ***Port.:*** Navelbine; Vinorel; ***Rus.:*** Maverex (Маверекс); Navelbine (Навельбин); ***S.Afr.:*** Navelbine; ***Singapore:*** Navelbine; ***Spain:*** Navelbine; ***Swed.:*** Navelbine; ***Switz.:*** Navelbine; ***Thai.:*** Navelbine; Vinelbine; ***Turk.:*** Navelbine; ***UK:*** Navelbine; ***USA:*** Navelbine.

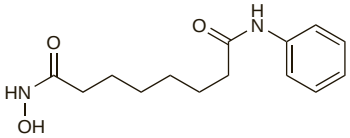
Vorinostat *(USAN, rINN)*

SAHA; Suberoylanilide Hydroxamic Acid; Vorinostatum. *N*-Hydroxy-*N′*-phenyl octanediamide.

Вориностат

$C_{14}H_{20}N_2O_3$ = 264.3.

CAS — 149647-78-9.



Adverse Effects, Treatment, and Precautions

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

The most common adverse effects of vorinostat are gastrointestinal disturbances, fatigue, chills, dry mouth and taste disorders. Thrombocytopenia and anaemia also occur commonly, and are dose-related; dose reductions may be necessary and in some instances, therapy may need to be stopped. Pulmonary embolism has occurred. Other adverse effects include muscle spasms, alopecia, dizziness, peripheral oedema, headache, pruritus, cough, upper respiratory-tract infection, and pyrexia. Hypokalaemia and hyperglycaemia have been reported, as has prolongation of the QT interval. Blood cell counts, electrolytes, glucose, and serum creatinine should be monitored every 2 weeks during the first 2 months of therapy and monthly thereafter. Baseline and periodic ECG monitoring should be performed.

Interactions

Severe thrombocytopenia and gastrointestinal bleeding have been reported when vorinostat has been given with other histone deacetylase inhibitors such as valproic acid; platelet counts should be monitored every 2 weeks for the first 2 months of therapy. Vorinostat may prolong prothrombin time and affect the INR in patients receiving coumarin anticoagulants.

Pharmacokinetics

After an oral dose of vorinostat with a high-fat meal, mean time to maximum plasma concentration was about 4 hours; this was reduced to 1.5 hours after fasting. Aside from this decrease in the rate of absorption, a high-fat meal also increased the extent of absorption. While these results were stated not to be clinically significant, licensed product information recommends that vorinostat be taken with food. Plasma protein binding is about 71%. Vorinostat is metabolised by glucuronidation and hydrolysis followed by oxidation; metabolites are pharmacologically inactive. Less than 1% of a dose is recovered in the urine as unchanged drug. The mean terminal half-life is about 2 hours for vorinostat.

◊ References.

1. Rubin EH, *et al*. A study to determine the effects of food and multiple dosing on the pharmacokinetics of vorinostat given orally to patients with advanced cancer. *Clin Cancer Res* 2006; **12:** 7039–45.

Uses and Administration

Vorinostat is a histone deacetylase inhibitor used for the treatment of cutaneous T-cell lymphoma (see Non-Hodgkin's Lymphomas, p.656). The recommended dose is 400 mg orally, given once daily with food. This may be reduced to 300 mg once daily, with a further reduction to 300 mg once daily for 5 consecutive days of each week, if needed. Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

Vorinostat is also under investigation for the treatment of multiple myeloma and mesothelioma.

◊ References.

1. O'Connor OA. Clinical experience with intravenous and oral formulations of the novel histone deacetylase inhibitor suberoylanilide hydroxamic acid in patients with advanced hematologic malignancies. *J Clin Oncol* 2006; **24:** 166–73.
2. Krug LM, *et al*. Potential role of histone deacetylase inhibitors in mesothelioma: clinical experience with suberoylanilide hydroxamic acid. *Clin Lung Cancer* 2006; **7:** 257–61.
3. Richon VM. Cancer biology: mechanism of antitumour action of vorinostat (suberoylanilide hydroxamic acid), a novel histone deacetylase inhibitor. *Br J Cancer* 2006; **95** (suppl): S2–S6.
4. O'Connor OA. Clinical experience with the novel histone deacetylase inhibitor vorinostat (suberoylanilide hydroxamic acid) in patients with relapsed lymphoma. *Br J Cancer* 2006; **95** (suppl): S7–S12.
5. Duvic M, Zhang C. Clinical and laboratory experience of vorinostat (suberoylanilide hydroxamic acid) in the treatment of cutaneous T-cell lymphoma. *Br J Cancer* 2006; **95** (suppl): S13–S19.
6. Anonymous. Vorinostat (Zolinza) for cutaneous T-Cell lymphoma. *Med Lett Drugs Ther* 2007; **49:** 23–4.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Zolinza.

Vorozole *(BAN, USAN, rINN)* ⊗

R-83842; Vorozol; Vorozolum. (+)-6-[4-Chloro-α-(1,2,4-triazol-1-yl)benzyl]-1-methyl-1*H*-benzotriazole.

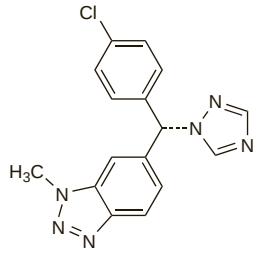
Ворозол

$C_{16}H_{13}ClN_6$ = 324.8.

CAS — 129731-10-8.

ATC — L02BG05.

ATC Vet — QL02BG05.



Profile

Vorozole is a selective nonsteroidal inhibitor of the aromatase (oestrogen synthetase) system. It has been investigated in the treatment of breast cancer.

◊ References.

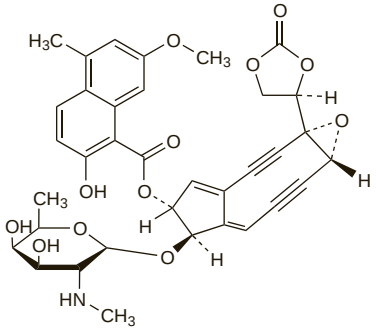
1. Goss PE, *et al*. Randomized phase III trial comparing the new potent and selective third-generation aromatase inhibitor vorozole with megestrol acetate in postmenopausal advanced breast cancer patients. *J Clin Oncol* 1999; **17:** 52–63.
2. Harper-Wynne CL, *et al*. Comparison of the systemic and intratumoral effects of tamoxifen and the aromatase inhibitor vorozole in postmenopausal patients with primary breast cancer. *J Clin Oncol* 2002; **20:** 1026–35.

Zinostatin *(USAN, rINN)*

Neocarzinostatin; NSC-69856; NSC-157365; Zinostatina; Zinostatine; Zinostatinum.

Зиностатин

CAS — 9014-02-2.



Description. Zinostatin is an antineoplastic antibiotic obtained from *Streptomyces carzinostaticus*.

Pharmacopoeias. *Jpn* includes zinostatin stimalamer.

Profile

Zinostatin is an antibiotic with antineoplastic activity and has been used in the treatment of malignant neoplasms.

Zinostatin stimalamer (SMANCS), a conjugate of zinostatin with a styrene-maleic acid polymer, is used for the treatment of liver cancer.

Zorubicin Hydrochloride *(USAN, rINNM)*

Hidrocloruro de zorubicina; NSC-164011; RP-22050 (zorubicin); Zorubicine, Chlorhydrate de; Zorubicini Hydrochloridum. Benzoic acid (2*S*-*cis*)-{1-[4-(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyloxy)-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxonaphthacen-2-yl]ethylidene}hydrazide hydrochloride.

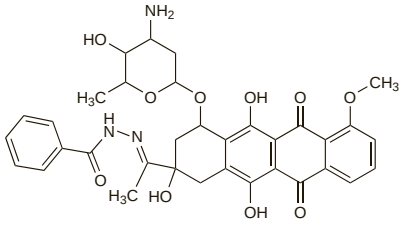
Зорубицина Гидрохлорид

$C_{34}H_{35}N_3O_{10}$,HCl = 682.1.

CAS — 54083-22-6 (zorubicin); 36508-71-1 (zorubicin hydrochloride).

ATC — L01DB05.

ATC Vet — QL01DB05.



(zorubicin)

Profile

Zorubicin is an anthracycline antibiotic with antineoplastic actions similar to those of doxorubicin (see p.712). It has been used as the hydrochloride in the treatment of acute leukaemias.