ing treatment involving vincristine.[1-4] Itraconazole is presumed to potentiate the toxicity of vincristine either by inhibition of cytochrome P450 isoenzymes, thus reducing the clearance of vincristine,[1-4] or by inhibiting the P-glycoprotein efflux pump,[2,3] and increasing intracellular concentrations of vincristine. Nifedipine also decreases the clearance of vincristine, by similar mechanisms,[1,3,4] and can theoretically further potentiate toxicity.

1. Murphy JA, *et al.* Vincristine toxicity in five children with acute lymphoblastic leukaemia. *Lancet* 1995; **346:** 443.
2. Jeng MR, Feusner J. Itraconazole-enhanced vincristine neurotoxicity in a child with acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 2001; **18:** 137–42.
3. Sathiapalan RK, El-Solh H. Enhanced vincristine neurotoxicity from drug interactions: case report and review of literature. *Pediatr Hematol Oncol* 2001; **18:** 543–6.
4. Kamaluddin M, *et al.* Potentiation of vincristine toxicity by itraconazole in children with lymphoid malignancies. *Acta Paediatr* 2001; **90:** 1204–7.

Nifedipine. Vincristine toxicity may be potentiated by nifedipine, see Antifungals, above.

Pharmacokinetics

Vincristine is not reliably absorbed from the gastrointestinal tract. After intravenous injection it disappears rapidly from the blood. It is extensively protein bound and is reported to be concentrated in blood platelets. It is metabolised in the liver and excreted primarily in the bile; about 70 to 80% of a dose is found in faeces, as unchanged drug and metabolites, while 10 to 20% appears in the urine. The terminal half-life is reported to be about 85 hours but may range from about 19 to 155 hours. Vincristine does not appear to cross the blood-brain barrier in significant amounts.

Uses and Administration

Vincristine is an antineoplastic agent that may act similarly to vinblastine (p.786) by arresting mitosis at the metaphase. Significant cross-resistance with vinblastine has not been reported although pleiotropic resistance may occur.

Vincristine sulfate is used mainly in combination chemotherapy regimens for acute and chronic leukaemias, lymphomas, including Hodgkin's disease and non-Hodgkin's lymphomas, and multiple myeloma. It is also used for tumours of the breast, lung, head and neck, and soft-tissue sarcomas, as well as for paediatric solid tumours including Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma, Wilms' tumour, retinoblastoma, and medulloblastoma. Vincristine has also been used in idiopathic thrombocytopenic purpura refractory to other agents. See also the cross-references given below.

Vincristine sulfate is given by intravenous injection. It has been given as a solution containing 1 mg/mL. However, UK guidelines recommend that for patients over the age of 10 years, solutions of vincristine should generally be diluted to a maximum concentration of 100 micrograms/mL and to a volume of at least 10 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 injection may be given over 1 minute into a freely-running intravenous infusion (usually sodium chloride 0.9%) if preferred.

The usual adult intravenous dose of vincristine sulfate is 1.4 to 1.5 mg/m^2 once weekly, up to a maximum weekly dose of 2 mg (see also Administration, below). For children weighing over 10 kg, the suggested dose is 1.4 to 2 mg/m^2 once weekly, up to a maximum weekly dose of 2 mg. For those weighing less than 10 kg, the suggested initial dose is 50 micrograms/kg, once weekly.

Blood counts should be carried out before giving each dose. Dosage reduction is recommended in patients with hepatic impairment (see below).

A liposomal formulation of vincristine is under investigation for the treatment of acute lymphoblastic leukaemia.

Action. Results *in vitro* suggested[1] a selective action of vincristine against lymphocytes of patients with chronic lymphocytic leukaemia; lymphocytes of healthy subjects were not so affected. A further study[2] confirmed these findings, and also found marked variation in vincristine susceptibility among individual chronic lymphocytic leukaemic cells. This suggests that vincristine may have effects other than arrest of mitosis.

1. Vilpo J, Vilpo L. Selective toxicity of vincristine against chronic lymphocytic leukaemia in vitro. *Lancet* 1996; **347:** 1491–2.
2. Vilpo JA, *et al.* Selective toxicity of vincristine against chronic lymphocytic leukemia cells in vitro. *Eur J Haematol* 2000; **65:** 370–8.

Administration. Although a maximum single dose of 2 mg is recommended for vincristine sulfate to reduce neurotoxicity, a review[1] has suggested that this guideline is overly rigid, since it does not take into account interindividual variations in pharmacokinetics and susceptibility to toxicity, which may be considerable. Furthermore the authors considered the evidence for effectiveness of this dosage limitation to be equivocal. They suggested beginning therapy at 1.4 mg/m^2 and adjusting subsequent doses according to toxicity.

For UK recommendations on dilution of intravenous vinca alkaloids see Administration Error, under Adverse Effects, above.

1. McCune JS, Lindley C. Appropriateness of maximum-dose guidelines for vincristine. *Am J Health-Syst Pharm* 1997; **54:** 1755–8.

Administration in hepatic impairment. Licensed product information states that the dose of vincristine should be reduced by 50% in patients having a serum bilirubin value above 3 mg per 100 mL (51 micromoles/litre).

Amyloidosis. For mention of regimens including vincristine used in the management of amyloidosis, see p.743.

Blood disorders, non-malignant. Vincristine may be employed in the treatment of various auto-immune blood disorders, see under Vinblastine, p.786.

Malignant neoplasms. Vincristine is widely used in the treatment of malignant neoplasms. It is a fundamental part of potentially curative regimens for acute lymphoblastic leukaemia, Hodgkin's disease and aggressive non-Hodgkins lymphomas (see p.651, p.655 and p.656). It has also been used in chronic lymphocytic leukaemia (p.653) and in other non-Hodgkin's lymphomas including AIDS-related lymphoma (p.657), Burkitt's lymphoma (p.657) and mycosis fungoides (p.657). Other haematological malignancies in which it may be tried include multiple myeloma (p.658). Among the solid neoplasms, vincristine is used in regimens to treat gestational trophoblastic tumours (p.650), tumours of the brain (p.660), head and neck (p.666), Wilms' tumour (p.667), small-cell lung cancer (p.668), and thymoma (p.674). It is also employed in regimens for neuroblastoma (p.674), retinoblastoma (p.675), and some sarcomas including sarcomas of bone, Kaposi's sarcoma, and rhabdomyosarcoma (see p.675, p.675, and p.676).

Preparations

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

Proprietary Preparations (details are given in Part 3)
Arg.: Vinces; ***Austral.:*** Oncovin; ***Austria:*** Oncovin; ***Belg.:*** Oncovin; Vincrisin; ***Braz.:*** Biocrist†; Oncovin†; Tecnocris; Vincizina; Vincrifil†; Vincristex†; Vinracine†; ***Chile:*** Citomid; Oncovin†; ***Cz.:*** Citomid†; ***Denm.:*** Oncovin; ***Fin.:*** Oncovin†; ***Fr.:*** Oncovin; ***Ger.:*** Cellcristin; Farmistin†; Onkocristin; ***Gr.:*** Oncovin; ***India:*** Biocristine; Cytocristin; Neocristin; ***Malaysia:*** Vinracine; ***Mex.:*** Citomid; Ifavin†; Oncovin; Vinblax†; Vincasar†; Vintec; ***Norw.:*** Oncovin†; ***Philipp.:*** Alcavixin; Nevexitin; ***Port.:*** Faulcris†; Oncovin†; ***Rus.:*** Citomid (Цитомид)†; ***S.Afr.:*** Oncovin†; ***Spain:*** Vincrisul; ***Swed.:*** Oncovin; ***Switz.:*** Oncovin; ***Thai.:*** Citomid; ***UK:*** Oncovin; ***USA:*** Oncovin; Vincasar PFS; ***Venez.:*** Oncovin†.

Vindesine Sulfate *(USAN, rINNM)*

Compound 112531 (vindesine); Desacetyl Vinblastine Amide Sulfate; LY-099094; NSC-245467 (vindesine or vindesine sulfate); Sulfato de vindesina; Vindesiinisulfaatti; Vindésine, sulfate de; Vindesine Sulphate *(BANM)*; Vindesini sulfas; Vindesinsulfat; Vindesin-sulfát; Vindezino sulfatas; Vindezin-szulfát. 3-Carbamoyl-4-*O*-deacetyl-3-de(methoxycarbonyl)vincaleukoblastine sulfate.

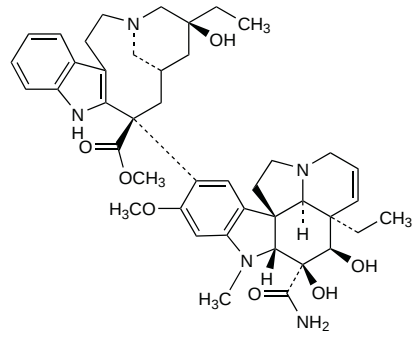
Виндезина Сульфат

$C_{43}H_{55}N_5O_7,H_2SO_4$ = 852.0.

CAS — 53643-48-4 (vindesine); 59917-39-4 (vindesine sulfate).

ATC — L01CA03.

ATC Vet — QL01CA03.



(vindesine)

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Vindesine Sulphate). A white or almost white, hygroscopic, amorphous substance. Freely soluble in water and in methyl alcohol; practically insoluble in cyclohexane. The pH of a 0.5% solution in water is 3.5 to 5.5. Store in airtight polypropylene containers with a polypropylene cap, at a temperature not exceeding –50°.

Adverse Effects, Treatment, and Precautions

As for Vinblastine Sulfate, p.786.

The main dose-limiting effect of vindesine is granulocytopenia, with the nadir of the white cell count usually occurring 3 to 5 days after a dose and recovery after a further 4 to 5 days. Although neurotoxicity occurs it may be less severe than that seen with vincristine (see p.787). Alopecia is the most common adverse effect.

Folinic acid has been suggested for the treatment of overdosage by analogy with vincristine.

Vindesine should not be given by the intrathecal route, as this may produce fatal toxicity. Care should be taken if acute abdominal pain occurs: further doses may result in paralytic ileus.

Administration error. *Inadvertent intrathecal doses of vinca alkaloids result in ascending paralysis and death.* In a 10-year-old child accidentally given an intrathecal injection of vindesine, treatment with folinic acid and dexamethasone produced transient recovery but symptoms subsequently recurred and the patient died of progressive ascending paralysis.[1] The CNS showed changes at necropsy similar to those seen after intrathecal vincristine. Other fatal cases[2] have subsequently been reported. 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.

1. Robbins G. Accidental intrathecal injection of vindesine. *BMJ* 1985; **291:** 1094.
2. Nisse P, *et al.* Administration accidentelle intrathécale de vindésine: à propos de 2 cas mortels. *Therapie* 2007; **62:** 360–1.

Interactions

As for Vinblastine Sulfate, p.786.

Pharmacokinetics

The pharmacokinetics of vindesine are similar to those of the other vinca alkaloids. After intravenous doses elimination from the blood is triphasic; the drug is rapidly distributed to body tissues. The terminal half-life is reported to be about 20 hours. It is metabolised primarily in the liver and excreted in bile and urine.

Uses and Administration

Vindesine sulfate is an antineoplastic agent derived from vinblastine (see p.785); like the other vinca alkaloids it causes mitotic arrest in metaphase by binding to microtubular protein. It is used in the treatment of refractory acute lymphoblastic or chronic myeloid leukaemias, and malignant melanoma. It has also been tried in malignant neoplasms of the breast, and lung. See also the cross references given below.

Vindesine sulfate is given weekly by intravenous injection. It may be given as a solution containing 1 mg/mL in sodium chloride injection 0.9%. However, UK guidelines recommend that for patients over the age of 10 years, solutions of vindesine should generally be di-

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.

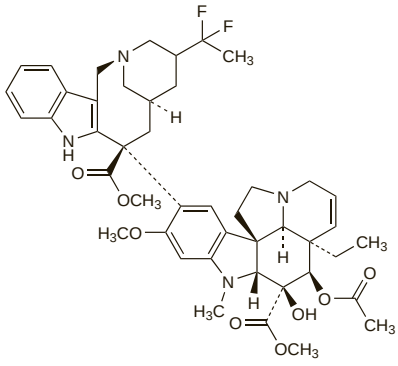
Vinflunine *(rINN)*

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.

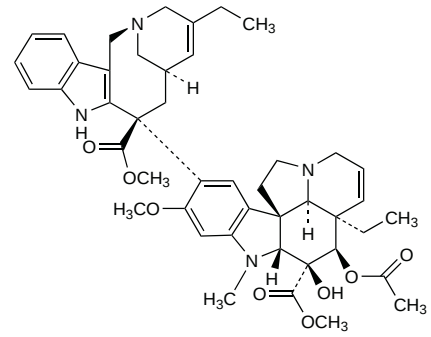
Винорелбина Тартрат

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