5. Bisogno G, *et al.* Veno-occlusive disease of the liver in children treated for Wilms tumor. *Med Pediatr Oncol* 1997; **29:** 245–51.
6. Arndt C, *et al.* Age is a risk factor for chemotherapy-induced hepatopathy with vincristine, dactinomycin, and cyclophosphamide. *J Clin Oncol* 2004; **22:** 1894–1901. Correction [dosage error]. *ibid.*; 3434.
7. Tornesello A, *et al.* Veno-occlusive disease of the liver in right-sided Wilms' tumours. *Eur J Cancer* 1998; **34:** 1220–3.

Handling. Dactinomycin is irritant; avoid contact with skin and mucous membranes.

Interactions
For a general outline of antineoplastic drug interactions, see p.642.

Pharmacokinetics
Intravenous doses of dactinomycin are rapidly distributed with high concentrations in bone marrow and nucleated cells. It undergoes only minimal metabolism and is slowly excreted in urine and bile. The terminal plasma half-life is reported to be about 36 hours. It does not cross the blood-brain barrier but is thought to cross the placenta.

In children. A study[1] involving 31 patients aged between 1 and 20 years given dactinomycin in intravenous doses of 0.7 to 1.5 mg/m^2 found that the pharmacokinetics of the drug were variable, but could be described by a 3-compartment model. Peak plasma concentrations varied from 3.2 to 99.2 nanograms/mL, and both peak plasma concentration and exposure were inversely related to body-weight. Since there was evidence that exposure was also related to more severe toxicity, younger patients might be at greater risk with a regimen based on surface area; conversely the practice of capping the dose at 2 mg in older patients might result in underdosage.

For evidence that younger patients do experience more liver toxicity with dactinomycin, see Effects on the Liver, above.

1. Veal GJ, *et al.* Pharmacokinetics of dactinomycin in a pediatric patient population: a United Kingdom Children's Cancer Study Group Study. *Clin Cancer Res* 2005; **11:** 5893–9.

Uses and Administration
Dactinomycin is a highly toxic antibiotic with antineoplastic properties. It inhibits the proliferation of cells in a cell-cycle non-specific way by forming a stable complex with DNA and interfering with DNA-dependent RNA synthesis. It may enhance the cytotoxic effects of radiotherapy (see also Adverse Effects, above). Dactinomycin also has immunosuppressant properties.

It has been used, usually with other drugs or radiotherapy, in the treatment of Wilms' tumour (p.667), gestational trophoblastic tumours (p.650), nonseminomatous testicular cancer (p.673), and sarcomas such as rhabdomyosarcoma (p.676) and Ewing's sarcoma (p.675).

In the treatment of Wilms' tumour, childhood rhabdomyosarcoma, or Ewing's sarcoma, an intravenous dose of 15 micrograms/kg daily for 5 days has been used in combination regimens. In adults, gestational trophoblastic tumours have been treated with 12 micrograms/kg daily for 5 days as a single agent, or 500 micrograms on days 1 and 2 of combination regimens. Metastatic nonseminomatous testicular cancer has been treated with 1 mg/m^2 on day 1 of combination regimens. The dose intensity for adults or children should not exceed 15 micrograms/kg or 400 to 600 micrograms/m^2 daily for 5 days per 2-week cycle, and lower doses may need to be used in some chemotherapy combinations or with radiotherapy. Using a regional perfusion technique to localise the drug has permitted the use of higher doses, 50 micrograms/kg being suggested for an isolated lower extremity or pelvis and 35 micrograms/kg for an upper extremity.

Great care must be taken to avoid extravasation and it should be given, for preference, into the tubing of a fast-running intravenous infusion. Platelet and white cell counts should be performed frequently to detect bone-marrow depression; if either count shows a marked decrease the drug should be withheld until recovery occurs, which may take up to 3 weeks (see also Bone-marrow Depression, p.639).

Preparations
USP 31: Dactinomycin for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Cosmegen; ***Austral.:*** Cosmegen; ***Austria:*** Cosmegen; ***Belg.:*** Lyovac Cosmegen; ***Braz.:*** Cosmegen; ***Canad.:*** Cosmegen; ***Fin.:*** Cosmegen; ***Fr.:*** Cosmegen; ***Ger.:*** Lyovac Cosmegen; ***Gr.:*** Cosmegen; ***Hong Kong:*** Cosmegen; ***India:*** Dacmozen; ***Irl.:*** Cosmegen; ***Ital.:*** Cosmegen; ***Malaysia:*** Cosmegen†; ***Mex.:*** Ac-De; ***Neth.:*** Lyovac Cosmegen; ***Norw.:*** Cosmegen; ***NZ:*** Cosmegen; ***Philipp.:*** Cosmegen; Trepar; ***Singapore:*** Cosmegen; ***Swed.:*** Cosmegen; ***Switz.:*** Cosmegen; ***Thai.:*** Cosmegen†; Lyovac Cosmegen; ***Turk.:*** Cosmegen; ***UK:*** Cosmegen; ***USA:*** Cosmegen.

Dasatinib *(USAN, rINN)*

BMS-354825; Dasatinibum. *N*-(2-Chloro-6-methylphenyl)-2-({6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl}amino)-5-thiazolecarboxamide.

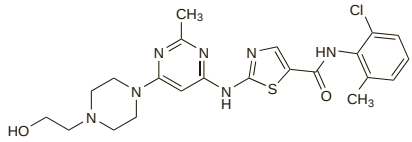
Дазатиниб

$C_{22}H_{26}ClN_7O_2S$ = 488.0.

CAS — 302962-49-8.

ATC — L01XE06.

ATC Vet — QL01XE06.



Adverse Effects, Treatment, and Precautions
The most common adverse effects of dasatinib include fluid retention, gastrointestinal disturbances, and bleeding. Fluid retention may be severe, and can result in pleural and pericardial effusion, pulmonary oedema, and ascites. Severe CNS haemorrhages, sometimes fatal, have been reported. Gastrointestinal haemorrhage may require interruption of therapy, and transfusions. Myelosuppression, manifest as neutropenia, thrombocytopenia, or anaemia, occurs more frequently in patients with advanced chronic myeloid leukaemia (CML) or acute lymphoblastic leukaemia than in patients in chronic phase. Recovery generally occurs after dose interruption and/or reduction, although treatment may need to be stopped. Febrile neutropenia has been reported. In patients with chronic phase CML, myelosuppression and fluid retention occur more often with twice daily dosing than once daily dosage. Other adverse effects include headache, pyrexia, musculoskeletal pain, fatigue, skin rashes, dyspnoea, cough, dizziness, chest pain, neuropathy, chills, and pruritus. Infections, including pneumonia, have been reported. Cardiac failure and arrhythmias can occur. Dasatinib has the potential to prolong the QT interval, and should be given with caution to patients at risk of this, such as those with hypokalaemia, hypomagnesaemia, or those on antiarrhythmic therapy, or receiving cumulative high doses of anthracyclines.

Effects on the skin. Panniculitis has been reported with the use of dasatinib, which resolved upon stopping therapy. In one case, dasatinib was restarted with prednisone, and no recurrence of panniculitis was noted. In another patient, however, a rash recurred on restarting therapy that was not sensitive to corticosteroid treatment.[1]

1. Assouline S, *et al.* Panniculitis during dasatinib therapy for imatinib-resistant chronic myelogenous leukemia. *N Engl J Med* 2006; **354:** 2623–4.

Interactions
Dasatinib is metabolised by the cytochrome P450 isoenzyme CYP3A4, and drugs that inhibit this enzyme, such as azole antifungals, macrolide antibacterials, HIV-protease inhibitors, and nefazodone may increase blood concentrations of dasatinib. Equally, inducers of CYP3A4 (such as carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampicin) may reduce blood concentrations of dasatinib. When use with such drugs cannot be avoided, dose adjustment of dasatinib may be necessary (see Uses and Administration, below). Since St John's wort may decrease dasatinib concentrations unpredictably, these drugs should not be given together.

Dasatinib is a substrate of the cytochrome P450 isoenzyme CYP3A4, and may alter blood concentrations of other drugs that are substrates of this enzyme.

Since the solubility of dasatinib is dependent on pH, use with antacids should be avoided. If antacid therapy is needed, it should be given at least 2 hours before or 2 hours after the dose of dasatinib. Similarly, histamine H_2-receptor antagonists or proton pump inhibitors such as famotidine or omeprazole should not be given with dasatinib as long-term suppression of gastric acid secretion is likely to reduce dasatinib exposure.

Pharmacokinetics
Maximum plasma concentrations of dasatinib are achieved between 0.5 and 6 hours after an oral dose. The mean terminal half-life is about 5 hours. Consumption of a high-fat meal may increase exposure to dasatinib, but this effect is not considered to be of clinical significance. Dasatinib is extensively distributed and metabolised. Metabolism occurs primarily by the cytochrome P450 isoenzyme CYP3A4, forming an active metabolite. Plasma protein binding of dasatinib and its active metabolite is about 96% and 93%, respectively. Elimination is mainly via the faeces; about 4% is recovered in the urine.

Uses and Administration
Dasatinib is a tyrosine kinase inhibitor that is used for the treatment of adults with all phases of chronic myeloid leukaemia (CML; p.653) who have resistance or intolerance to previous therapy, including imatinib. It is also used for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukaemia (ALL; p.651) who are resistant to or intolerant of prior therapy.

A recommended oral starting dose of dasatinib in chronic phase CML is 100 mg once daily: tablets, which should be swallowed whole, not crushed or chewed, should be taken consistently either in the morning or the evening. The recommended starting dose for accelerated, myeloid, or lymphoid blast phase CML or Philadelphia chromosome-positive ALL is 70 mg twice daily. Dosage may be adjusted according to response and tolerability; doses of up to 140 mg once daily have been used in patients with chronic phase CML, and up to 100 mg twice daily in those with advanced phase, or with ALL. Treatment is continued until disease progression or unacceptable toxicity occurs.

If concurrent use of potent inhibitors or inducers of cytochrome P450 isoenzyme CYP3A4 cannot be avoided, dose adjustments are considered necessary. A dose increase should be considered in those patients given strong CYP3A4 inducers, and the patient should be monitored for toxicity. For those given a strong CYP3A4 inhibitor, the dose of dasatinib should be reduced to 20 mg daily. If this is not tolerated, then either drug should be stopped; if the inhibitor is stopped, a washout period of about 1 week should be allowed before the dose of dasatinib is increased.

◊ References.

1. Talpaz M, *et al.* Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N Engl J Med* 2006; **354:** 2531–41.
2. Hochhaus A, *et al.* Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. *Blood* 2007; **109:** 2303–9. Correction. *ibid.*; **110:** 1438.
3. Cortes J, *et al.* Dasatinib induces complete hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in blast crisis. *Blood* 2007; **109:** 3207–13.
4. Guilhot F, *et al.* Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase. *Blood* 2007; **109:** 4143–50.
5. Ottmann O, *et al.* Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a phase 2 study. *Blood* 2007; **110:** 2309–15.

6. Anonymous. Dasatinib (Sprycel) for CML and Ph+ALL. *Med Lett Drugs Ther* 2007; **49:** 6–7.
7. Olivieri A, Manzione L. Dasatinib: a new step in molecular target therapy. *Ann Oncol* 2007; **18** (suppl): vi42–vi46.
8. Keam SJ. Dasatinib: in chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia. *BioDrugs* 2008; **22:** 59–69.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Sprycel; ***Austral.:*** Sprycel; ***Cz.:*** Sprycel; ***Fr.:*** Sprycel; ***Gr.:*** Sprycel; ***Hung.:*** Sprycel; ***Indon.:*** Sprycel; ***Malaysia:*** Sprycel; ***NZ:*** Sprycel; ***UK:*** Sprycel; ***USA:*** Sprycel.

Daunorubicin Hydrochloride

(BANM, USAN, rINNM)

Cloridrato de Daunorrubicina; Daunomycin Hydrochloride; Daunoribisin Hidroklorür; Daunorubicin hydrochlorid; Daunorubicine, chlorhydrate de; Daunorubicin-hidroklorid; Daunorubicinhydroklorid; Daunorubicini hydrochloridum; Daunorubicino hidrochloridas; Daunorubisiinihydrokloridi; FI-6339 (daunorubicin); Hidrocloruro de daunorubicina; NDC-0082-4155; NSC-82151; RP-13057 (daunorubicin); Rubidomycin Hydrochloride. (1*S*,3*S*)-3-Acetyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxonaphthacen-1-yl 3-amino-2,3,6-trideoxy-α-L-*lyxo*-pyranoside hydrochloride; (8*S*-*cis*)-8-Acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)]oxy-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride.

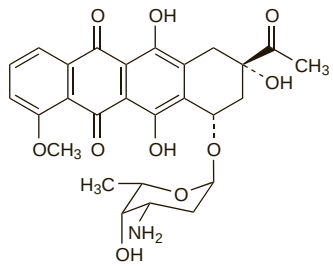
Дунорубицина Гидрохлорид

$C_{27}H_{29}NO_{10}$,HCl = 564.0.

CAS — 20830-81-3 (daunorubicin); 23541-50-6 (daunorubicin hydrochloride).

ATC — L01DB02.

ATC Vet — QL01DB02.



(daunorubicin)

NOTE. Daunorubicin citrate is used in the preparation of liposomal preparations (see Uses and Administration, below).

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

Ph. Eur. 6.2 (Daunorubicin Hydrochloride). The hydrochloride of a substance produced by certain strains of *Streptomyces coeruleorubidus* or *S. peucetius* or obtained by any other means. It is manufactured by methods designed to minimise or eliminate the presence of histamine. An orange-red, hygroscopic, crystalline powder. It contains between 95 and 102% of the hydrochloride (anhydrous and solvent-free basis). Freely soluble in water and in methyl alcohol; slightly soluble in alcohol; practically insoluble in acetone. A 0.5% solution in water has a pH of 4.5 to 6.5. Store in airtight containers. Protect from light.

USP 31 (Daunorubicin Hydrochloride). An orange-red, hygroscopic, crystalline powder. It has a potency equivalent to not less than 842 and not more than 1030 micrograms of the base per mg. Freely soluble in water and in methyl alcohol; slightly soluble in alcohol; practically insoluble in acetone; very slightly soluble in chloroform. A 0.5% solution in water has a pH of 4.5 to 6.5. Store at a temperature not exceeding 40° in airtight containers. Protect from light.

Incompatibility. Daunorubicin is incompatible with heparin sodium,[1] and has also been reported to be incompatible with a solution of dexamethasone sodium phosphate.

1. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; **17:** 532–8.

Stability. In a study[1] of the stability of anthracycline antineoplastic agents in 4 infusion fluids (glucose 5%, sodium chloride 0.9%, lactated Ringer's injection, and a commercial infusion fluid) daunorubicin hydrochloride was stable in all 4, the percentage remaining after 24 hours being 98.5%, 97.4%, 94.7%, and 95.4% respectively. Stability appeared to be partly related to pH; daunorubicin was more stable as the pH of the mixture became more acidic, with the best stability in glucose 5% with a pH of 4.5. Although daunorubicin solutions are degraded by light, the effect is reported not to be significant at concentrations of 500 micrograms/mL or above; however, below this concentration precautions should be taken to protect solutions from light, and storage should be in polyethylene or polypropylene containers to minimise adsorptive losses.[2] It has been suggested that formulation with the food colouring Scarlet GN, which absorbs light over the same spectral region as daunorubicin, would stabilise daunorubicin solutions to light.[3]

Liposomal daunorubicin should be diluted with glucose 5% solution as aggregation of the liposomes may result with sodium chloride. In addition, licensed product information advises that liposomal daunorubicin should not be mixed with substances containing benzyl alcohol or other detergent-like molecules, which can lead to premature rupture of the liposomes.

1. Poochikian GK, *et al*. Stability of anthracycline antitumor agents in four infusion fluids. *Am J Hosp Pharm* 1981; **38:** 483–6.
2. Wood MJ, *et al*. Photodegradation of doxorubicin, daunorubicin and epirubicin measured by high-performance liquid chromatography. *J Clin Pharm Ther* 1990; **15:** 291–300.
3. Thoma K, Klimek R. Photostabilization of drugs in dosage forms without protection from packaging materials. *Int J Pharmaceutics* 1991; **67:** 169–75.

Adverse Effects, Treatment, and Precautions

As for Doxorubicin, p.712 and p.713.

Cardiotoxicity is more likely when the total cumulative dose of daunorubicin exceeds 550 to 600 mg/m^2 in adults, 300 mg/m^2 in children, or in children aged under 2 years, 10 mg/kg. The cumulative dose should be limited to 400 mg/m^2 in patients who have had previous radiation therapy to the mediastinum. Product information for liposomal daunorubicin recommends determining ventricular ejection fraction after cumulative doses of 320 mg/m^2, and every 160 mg/m^2 thereafter. Daunorubicin should be used in reduced doses in hepatic and renal impairment.

Liposomal formulations of daunorubicin may be associated with a reduced potential for local tissue necrosis although current clinical experience is limited and such toxicity remains a possibility. An acute syndrome of back pain, flushing, and chest tightness may occur during infusion, but generally resolves on slowing or temporarily stopping the infusion.

Effects on the heart. For a discussion of the cardiotoxicity of anthracyclines, and its management, see Effects on the Heart, under Doxorubicin, p.713.

Effects on the skin and nails. For reports of hyperpigmentation in patients given daunorubicin, see under Doxorubicin, p.713.

Handling and disposal. Daunorubicin hydrochloride is irritant; avoid contact with skin and mucous membranes.

For a method for the destruction of daunorubicin in wastes see under Doxorubicin, p.713.

Interactions

As for Doxorubicin, p.713.

Antineoplastics. Hepatic dysfunction was reported[1] in 13 patients given daunorubicin 180 to 450 mg/m^2. Ten of them had also received *tioguanine* or *cytarabine*, or a combination of these. The authors also noted that other studies had suggested that the related drug doxorubicin might enhance the hepatotoxicity of *mercaptopurine*, and thought that a similar interaction could occur between daunorubicin and tioguanine.

1. Penta JS, *et al*. Hepatotoxicity of combination chemotherapy for acute myelocytic leukemia. *Ann Intern Med* 1977; **87:** 247–8.

Pharmacokinetics

After intravenous injection, daunorubicin is rapidly distributed into body tissues, particularly the liver, lungs, kidneys, spleen, and heart with an initial distribution half-life of about 45 minutes. It is rapidly metabolised in the liver, and is excreted in bile and urine as unchanged drug and metabolites. The major metabolite, daunorubicinol, has antineoplastic activity. Up to 25% of a dose is excreted in urine in an active form over several days (the terminal plasma elimination half-lives of daunorubicin and its major metabolite are reported to be 18.5 and 26.7 hours respectively); an estimated 40% is excreted in bile. Daunorubicin does not appear to cross the blood-brain barrier, but crosses the placenta.

The pharmacokinetics of liposomal doxorubicin are significantly different from those of the conventional drug formulation, with a decreased uptake by normal tissues (although tumour neovasculature is reported to have increased permeability to the liposomes), and a terminal half-life of 4 to 5 hours.

Uses and Administration

Daunorubicin is an antineoplastic anthracycline antibiotic with actions similar to those of doxorubicin (p.714), to which it is closely related. It is used with other antineoplastics to induce remissions in acute leukaemias. Daunorubicin is given in combination regimens for acute lymphoblastic leukaemia (see p.651) and acute myeloid leukaemias (see p.652). It has also been tried in some other malignancies. A liposomal formulation of daunorubicin has been developed for use in the management of Kaposi's sarcoma in patients with AIDS (see also p.675).

Daunorubicin is usually given as the hydrochloride, but doses are expressed in terms of the base. Daunorubicin hydrochloride 21.4 mg is equivalent to about 20 mg daunorubicin.

In combination treatment regimens for adult acute leukaemia, the usual dose is 30 to 45 mg/m^2 daily on days 1 to 3 of the first course, and days 1 and 2 of subsequent courses. Daunorubicin is given as a solution in sodium chloride 0.9% into a fast-running infusion of sodium chloride or glucose. Courses may be repeated after 3 to 6 weeks. A dose of 25 mg/m^2 has been given intravenously once a week, in combination regimens, to children with acute lymphoblastic leukaemia. For children less than 2 years of age, or less than 0.5 m^2, a dose of 1 mg/kg has been used instead.

The total cumulative dose in adults should not exceed 550 to 600 mg/m^2; in patients who have received radiotherapy to the chest it may be advisable to limit the total dose to about 400 mg/m^2. Lower limits apply in children: a total cumulative dose of no more than 300 mg/m^2, or in children aged under 2 years 10 mg/kg, is recommended. Dosage should be reduced in patients with impaired hepatic or renal function (see below), and elderly patients with inadequate bone marrow reserves.

In the treatment of Kaposi's sarcoma, liposomal daunorubicin is given intravenously every 2 weeks starting with a dose of 40 mg/m^2, and continued for as long as disease control can be maintained. It is diluted with glucose 5% (sodium chloride 0.9% should not be used) to a concentration between 0.2 and 1 mg/mL, and given over 30 to 60 minutes.

Blood counts should be determined frequently during treatment as daunorubicin has a potent effect on bone-marrow function (see also Bone-marrow Depression, p.639). Cardiac function should be monitored at regular intervals to detect signs of cardiotoxicity.

Administration in hepatic impairment. Doses of daunorubicin should be reduced in hepatic impairment. Some licensed product information recommends that patients with serum-bilirubin concentrations of 12 to 30 micrograms/mL should receive 75% of the usual dose, and those with concentrations greater than 30 micrograms/mL should be given 50% of the usual dose.

Administration in renal impairment. Doses of daunorubicin should be reduced in renal impairment. Some licensed product information recommends that patients with serum-creatinine concentrations of 105 to 265 micromoles/litre should receive 75% of the usual dose, and those with concentrations greater than 265 micromoles/litre should be given 50% of the usual dose.

Preparations

USP 31: Daunorubicin Hydrochloride for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Daunoblastina; Maxidauno; ***Austral.:*** DaunoXome; ***Austria:*** Daunoblastin; DaunoXome; ***Belg.:*** Cerubidine; ***Braz.:*** Daunoblastina; Daunocin†; DaunoXome†; ***Canad.:*** Cerubidine; ***Chile:*** Cerubidine; Daurocina; Oncodaunotec; ***Cz.:*** Cerubidine†; ***Denm.:*** Cerubidin; DaunoXome; ***Fin.:*** DaunoXome; ***Fr.:*** Cerubidine; DaunoXome; ***Ger.:*** Daunoblastin; DaunoXome; ***Gr.:*** Cerubidine; DaunoXome; ***Hong Kong:*** Daunoblastina†; ***Hung.:*** Daunoblastina; ***India:*** Daunotec; Norubin; ***Irl.:*** Cerubidin; DaunoXome; ***Israel:*** Cerubidine; ***Ital.:*** Daunoblastina; DaunoXome; ***Mex.:*** Rubilem; ***Neth.:*** Cerubidine; DaunoXome; ***Norw.:*** Cerubidin; ***Port.:*** Daunoblastina†; DaunoXome; ***Rus.:*** DaunoXome (Дауноэом); ***S.Afr.:*** Cerubidin†; Daunoblastin; ***Singapore:*** Daunoblastina; ***Spain:*** Daunoblastina; DaunoXome†; ***Swed.:*** Cerubidin†; DaunoXome; ***Switz.:*** Cerubidine; DaunoXome†; ***UK:*** DaunoXome; ***USA:*** Cerubidine; DaunoXome; ***Venez.:*** Daunoblastina.