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.

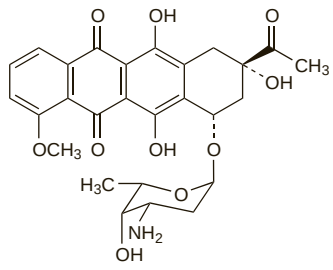
Дунорубицина Гидрохлорид

$C_{27}H_{29}NO_{10}$,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.

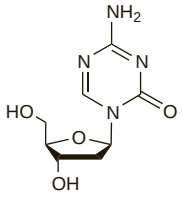
Decitabine *(BAN, USAN, rINN)*

5-Aza-2′-deoxycytidine; DAC; Decitabina; Décitabine; Decitabinum; NSC-127716. 4-Amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1,3,5-triazin-2(1*H*)-one.

Децитабин

$C_8H_{12}N_4O_4$ = 228.2.

CAS — 2353-33-5.



Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641. The most common adverse effect of decitabine is myelosuppression, which may be severe and dose-limiting. Fatalities have been reported. Other common adverse effects include fatigue, pyrexia, gastrointestinal disturbances, petechiae, and hyperglycaemia. Cardiorespiratory arrest, increased blood bilirubin, intracranial haemorrhage, abnormal liver function tests, pulmonary oedema, atrial fibrillation, central line infection, or febrile neutropenia may force treatment to be stopped or delayed. Other adverse effects which may be dose-limiting include lethargy, oedema, tachycardia, depression, or pharyngitis.

Pharmacokinetics

On intravenous dosage decitabine exhibits biphasic disposition. Plasma protein binding is negligible. The exact route of metabolism and excretion is not known; one pathway appears to be deamination by cytidine deaminase, which is found principally in the liver, but also in granulocytes, the intestinal epithelium, and whole blood. A terminal elimination half-life of about 0.5 hours has been reported after a 72-hour infusion.

Uses and Administration

Decitabine is an antineoplastic antimetabolite structurally related to cytarabine (p.705). It is reported to cause DNA hypomethylation by the inhibition of DNA methyltransferase, which has the potential to alter gene expression (re-activate silent genes) and limit disease progression and resistance. Decitabine is used in the treatment of myelodysplastic syndromes (p.654). It is given by intravenous infusion over 3 hours, diluted to a final concentration of 0.1 to 1 mg/mL in sodium chloride 0.9%, glucose 5%, or lactated Ringer's injection. The recommended dose is 15 mg/m^2 every 8 hours for 3 days; this 3-day cycle is repeated every 6 weeks, for a minimum of 4 cycles. Treatment may be continued as long as the patient continues to benefit. If haematological recovery from a cycle is incomplete, cycle length may be increased to as much as every 10 weeks and the dose reduced to 11 mg/m^2 every 8 hours upon restarting therapy; this dose may be maintained or increased in subsequent cycles as clinically indicated. Decitabine treatment should also be delayed if serum creatinine is 2 mg per 100 mL or greater, or if total bilirubin is 2 or more times the upper limit of normal, or if the patient has an active or uncontrolled infection.

Decitabine is also under investigation for the treatment of chronic myeloid leukaemia (p.653) and acute myeloid leukaemia (p.652). It is also reported to increase fetal haemoglobin in patients with sickle-cell disease (p.1044).

◊ References.

1. DeSimone J, *et al.* Maintenance of elevated fetal hemoglobin levels by decitabine during dose interval treatment of sickle cell anemia. *Blood* 2002; **99:** 3905–8.
2. Momparler RL. Pharmacology of 5-aza-2′-deoxycytidine (decitabine). *Semin Hematol* 2005; **42** (suppl 2): S9–S16.
3. Kantarjian HM, Issa JP. Decitabine dosing schedules. *Semin Hematol* 2005; **42** (suppl 2): S17–S22. Correction. *ibid.*; 274.
4. Lubbert M, Minden M. Decitabine in acute myeloid leukemia. *Semin Hematol* 2005; **42** (suppl 2): S38–S42.
5. Issa JP, Byrd JC. Decitabine in chronic leukemias. *Semin Hematol* 2005; **42** (suppl 2): S43–S49.
6. Kuykendall JR. 5-Azacytidine and decitabine monotherapies of myelodysplastic disorders. *Ann Pharmacother* 2005; **39:** 1700–9.
7. Momparler RL. Epigenetic therapy of cancer with 5-aza-2′-deoxycytidine (decitabine). *Semin Oncol* 2005; **32:** 443–51.
8. Kantarjian H, *et al.* Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer* 2006; **106:** 1794–1803.
9. McKeage K, Croom KF. Decitabine in myelodysplastic syndromes. *Drugs* 2006; **66:** 951–8.
10. Jabbour E, *et al.* Evolution of decitabine development: accomplishments, ongoing investigations, and future strategies. *Cancer* 2008; **112:** 2341–51.

Preparations

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

Denileukin Diftitox *(USAN, rINN)*

DAB_{389}IL2; Denileucina diftitox; Denileukin Difitox *(BAN)*; Dénileukine Diftitox; Denileukinum Diftitoxum; LY-335348.

Денилейкин Дифтитокс

CAS — 173146-27-5.

ATC — L01XX29.

ATC Vet — QL01XX29.

Adverse Effects and Precautions

Denileukin diftitox can cause an acute hypersensitivity reaction within 24 hours of infusion with symptoms reminiscent of a cytokine release syndrome. Anaphylaxis and death have also been reported. A more delayed flu-like syndrome may also occur up to several days after infusion. Vascular leak syndrome, characterised by hypotension, oedema, or hypoalbuminaemia, may also be delayed. Gastrointestinal disturbances, chills, fever, and asthenia are common. Other adverse effects include rash, predisposition to cutaneous infections, and thrombotic events. Visual loss has been reported; although recovery was reported in some patients, in most cases impairment persisted.

Uses and Administration

Denileukin diftitox is a recombinant interleukin fusion toxin comprised of interleukin-2 linked to the A and B fragments of diphtheria toxin. It is given by intravenous infusion for the management of persistent or recurrent cutaneous T-cell lymphoma (see Mycosis Fungoides, p.657), in patients whose malignant cells express the CD25 interleukin-2 receptor. The concentration of denileukin diftitox must be at least 15 micrograms/mL during all steps in the preparation of the solution for infusion. The recommended dose is 9 or 18 micrograms/kg daily, given over 15 minutes or more, for 5 consecutive days every 3 weeks.

◊ References.

1. Olsen E, *et al.* Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. *J Clin Oncol* 2001; **19:** 376–88.
2. Martin A, *et al.* A multicenter dose-escalation trial with denileukin diftitox (ONTAK, DAB(389)IL-2) in patients with severe psoriasis. *J Am Acad Dermatol* 2001; **45:** 871–81.
3. Talpur R, *et al.* Treatment of refractory peripheral T-cell lymphoma with denileukin diftitox (ONTAK). *Leuk Lymphoma* 2002; **43:** 121–6.
4. Frankel AE, *et al.* A phase II study of DT fusion protein denileukin diftitox in patients with fludarabine-refractory chronic lymphocytic leukemia. *Clin Cancer Res* 2003; **9:** 3555–61.
5. Eklund JW, Kuzel TM. Denileukin diftitox: a concise clinical review. *Expert Rev Anticancer Ther* 2005; **5:** 33–8.
6. Foss F. Clinical experience with denileukin diftitox (ONTAK). *Semin Oncol* 2006; **33** (suppl 3): 11–16.

Preparations

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

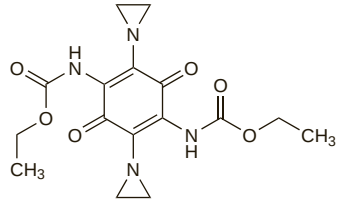
Diaziquone *(USAN, rINN)*

Aziridinylbenzoquinone; AZQ; CI-904; Diazicuona; Diaziquonum; NSC-182986. Diethyl 2,5-bis-(1-aziridinyl)-3,6-dioxo-1,4-cyclohexadiene-1,4-dicarbamate.

Диазихон

$C_{16}H_{20}N_4O_6$ = 364.4.

CAS — 57998-68-2.



Profile

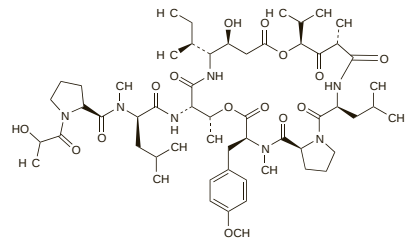
Diaziquone has been investigated as an antineoplastic in the treatment of malignant brain tumours and acute myeloid leukaemia. It is thought to act as an alkylating agent. Adverse effects include bone-marrow suppression, manifesting chiefly as leucopenia and thrombocytopenia, gastrointestinal disturbances, and alopecia. Anaphylactoid reactions have occurred.

Didemnin B

Didemnina B; NSC-325319.

$C_{57}H_{89}N_7O_{15}$ = 1112.4.

CAS — 77327-05-0.



Profile

The didemnins are biologically active peptides extracted from a marine sea squirt of the genus *Tridemnum*. They possess antineoplastic and antiviral properties; didemnin B is reported to be more active than didemnin A or didemnin C and has been investigated as an antineoplastic, although results have not generally been favourable. Nausea and vomiting are dose-limiting; myelosuppression, cardiac and renal toxicity, liver dysfunction, other gastrointestinal disturbances, myalgia, fatigue, and phlebitis may occur. Hypersensitivity reactions, possibly due to the polyoxyl castor oil vehicle, are common.

Docetaxel *(BAN, USAN, rINN)*

Docétaxel; Docetaxelum; Docetaxol; Docetaxolum; Dosetaksel; Dosetaksoli; NSC-628503; RP-56976. (2*R*,3*S*)-*N*-Carboxy-3-phenylisoserine, *N*-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate; *tert*-Butyl {(1*S*,2*S*)-2-[(2*S*,5*R*,7*S*,10*R*,13*S*)-4-acetoxy-2-benzoyloxy-1,7,10-trihydroxy-9-oxo-5,20-epoxytax-11-en-13-yloxycarbonyl]-2-hydroxy-1-phenylethyl}carbamate.

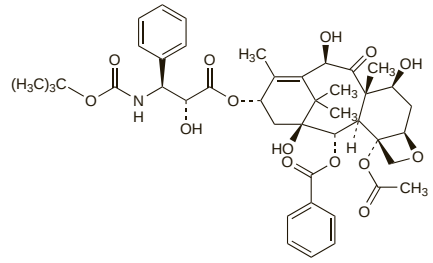
Доцетаксел

$C_{43}H_{53}NO_{14}$ = 807.9.

CAS — 114977-28-5 (anhydrous docetaxel); 148408-66-6 (docetaxel trihydrate).

ATC — L01CD02.

ATC Vet — QL01CD02.



Adverse Effects, Treatment, and Precautions

As for Paclitaxel, p.759. Neutropenia, anaemia and skin reactions are common with docetaxel and may be severe. Fluid retention, resulting in oedema, ascites, pleural and pericardial effusion, and weight gain, is also common, and may be cumulative; premedication with a corticosteroid can reduce fluid retention as well as the severity of hypersensitivity reactions. Asthenia and fatigue have also been reported. Rare cases of ototoxicity, hearing impairment or loss have occurred. Very rare cases of acute myeloid leukaemia and myelodysplastic syndrome have been reported with combination chemotherapy regimens containing docetaxel; haematological follow-up may be required.

Docetaxel should not be used in patients hypersensitive to polysorbate 80, which is contained in the formulation. Patients with hepatic impairment show increased sensitivity to toxic effects of docetaxel, and should be given the drug with great care and in reduced doses, if at all.

Effects on the eyes. Excessive tear formation (epiphora) severe enough to interfere with reading and driving has been reported in patients given docetaxel. Canalicular stenosis has been