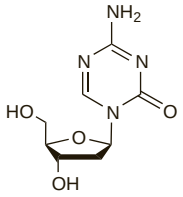
Decitabine *(BAN, USAN, rINN)*

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.

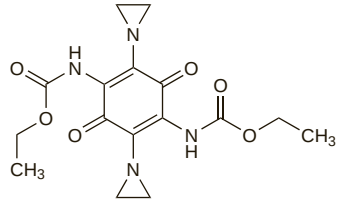
Diaziquone *(USAN, rINN)*

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

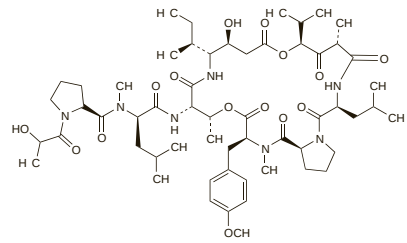
Diaziquone has been investigated as an antineoplastic in the treatment of malignant brain tumours and acute myeloid leukaemia. It is thought to act as an alkylating agent. Adverse effects include bone-marrow suppression, manifesting chiefly as leucopenia and thrombocytopenia, gastrointestinal disturbances,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

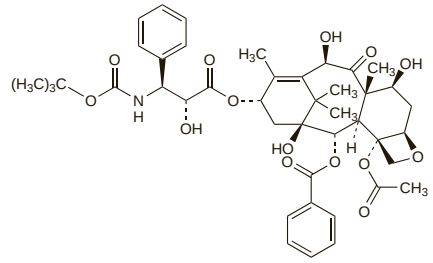
Доцетаксел

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

described as the mechanism for this effect, and docetaxel has been measured in tear fluid suggesting that irritation of the ocular surface and fibrosis of the tear drainage ducts may be caused by direct contact with docetaxel.[1] Epiphora and canalicular stenosis are more severe and occur more frequently in patients who receive weekly docetaxel than in those who receive the drug every 3 weeks.[2,3] The mean cumulative dose of docetaxel was found to be higher in those patients who developed stenosis.[2] Management of this adverse effect includes probing and irrigation of the lachrymal ducts and canalicular silicone tubing placement, or surgery followed by tube placement. The condition is generally reversible and tubing can be removed 4 to 6 weeks after stopping docetaxel therapy.[4] The use of topical tobramycin and dexamethasone on a tapering regimen can eliminate the need for silicone intubation or surgery in some patients.[3]

Very rare cases of transient visual disturbances such as flashing lights and scotomata have occurred during docetaxel infusion, and in association with hypersensitivity reactions. These were reversible upon stopping the infusion. For reference to a report of glaucoma possibly related to docetaxel, see Paclitaxel, p.759.

1. Esmaeli B, *et al.* Docetaxel secretion in tears: association with lacrimal drainage obstruction. *Arch Ophthalmol* 2002; **120:** 1180–2.
2. Esmaeli B, *et al.* Canalicular stenosis secondary to weekly versus every-3-weeks docetaxel in patients with metastatic breast cancer. *Ophthalmology* 2002; **109:** 1188–91.
3. Esmaeli B, *et al.* Prospective study of incidence and severity of epiphora and canalicular stenosis in patients with metastatic breast cancer receiving docetaxel. *J Clin Oncol* 2006; **24:** 3619–22.
4. Ahmadi MA, Esmaeli B. Surgical treatment of canalicular stenosis in patients receiving docetaxel weekly. *Arch Ophthalmol* 2001; **119:** 1802–4.

Effects on the gastrointestinal tract. Ischaemic colitis has occurred in patients treated with docetaxel.[1-3] Some patients also received vinorelbine, which may have exacerbated this complication.[1,2]

1. Ibrahim NK, *et al.* Colitis associated with docetaxel-based chemotherapy in patients with metastatic breast cancer. *Lancet* 2000; **355:** 281–3.
2. de Matteis A, *et al.* Intestinal side-effects of docetaxel/vinorelbine combination. *Lancet* 2000; **355:** 1098–9.
3. Hussein MAH, *et al.* Docetaxel-related ischemic colitis. *J Clin Oncol* 2005; **23:** 9424–5.

Effects on the heart. For comment on the increased risk of heart failure when docetaxel is given with trastuzumab and after anthracyclines, see under Interactions, below.

Effects on the musculoskeletal system. For reference to cases of taxane-induced arthralgia and myalgia successfully treated with gabapentin, see Paclitaxel, p.759.

Effects on the skin and nails. Palmar-plantar erythrodysesthesia syndrome (p.639) has been reported with the use of docetaxel.[1] For reference to the use of vitamin E to alleviate palmar-plantar erythrodysesthesia syndrome caused by docetaxel and capecitabine, see Chemotherapy-induced Toxicity, under Uses of Vitamin E, p.1994. Cases of radiation recall dermatitis associated with docetaxel have also been reported.[2-4] There is a further report of recall dermatitis at sites previously treated with a laser.[5] A hyperpigmented eruption developed in a patient at the site of docetaxel injection after insufficient venous flushing; no eruption occurred after a second infusion with abundant venous flushing.[6] Licensed drug information states that very rare cases of bullous eruption such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with docetaxel, but that other factors may have contributed to the development of these reactions.

For further reference to reports of scleroderma and adverse effects on the nails after the use of docetaxel, see Paclitaxel, p.759.

In a multicentre study, patients given docetaxel wore a frozen glove on the right hand, leaving the left hand unprotected to serve as a control. The use of the glove significantly reduced skin and nail toxicity.[7]

1. Eich D, *et al.* Acral erythrodysesthesia syndrome caused by intravenous infusion of docetaxel in breast cancer. *Am J Clin Oncol* 2002; **25:** 599–602.
2. Piroth MD, *et al.* Radiation recall dermatitis from docetaxel. *Onkologie* 2002; **25:** 438–40.
3. Kandemir EG, *et al.* Docetaxel-induced radiation recall dermatitis. *Swiss Med Wkly* 2005; **135:** 34–5.
4. Borgia F, *et al.* Radiation recall dermatitis after docetaxel administration: absolute indication to replace the drug? *Br J Dermatol* 2005; **153:** 674–5.
5. Chu C-Y, Yang C-H. Docetaxel-induced recall dermatitis on previous laser treatment sites. *Br J Dermatol* 2005; **153:** 441–3.
6. Aydogan I, *et al.* Persistent serpentine supravenous hyperpigmented eruption associated with docetaxel. *J Eur Acad Dermatol Venereol* 2005; **19:** 345–7.
7. Scotté F, *et al.* Multicenter study of a frozen glove to prevent docetaxel-induced onycholysis and cutaneous toxicity of the hand. *J Clin Oncol* 2005; **23:** 4424–9.

Hypersensitivity. For a discussion of taxane-induced hypersensitivity, including references to desensitisation protocols, see under Paclitaxel, p.759.

Tumour lysis syndrome. Fatal cases of tumour lysis syndrome (p.639) have been reported after the second-line use of docetaxel.[1,2]

1. Sorscher SM. Tumor lysis syndrome following docetaxel therapy for extensive metastatic prostate cancer. *Cancer Chemother Pharmacol* 2004; **54:** 191–2.
2. Ajzensztejn D, *et al.* Tumor lysis syndrome after treatment with docetaxel for non-small-cell lung cancer. *J Clin Oncol* 2006; **24:** 2389–91.

Interactions

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

◊ Docetaxel is metabolised by cytochrome P450 isoenzyme CYP3A, and theoretically has the potential to interact with other drugs that are inhibitors or inducers of this enzyme.[1]

1. Royer I, *et al.* Metabolism of docetaxel by human cytochromes P450: interactions with paclitaxel and other antineoplastic drugs. *Cancer Res* 1996; **56:** 58–65.

Antifungals. In a pharmacokinetic study, no consistent effects on docetaxel concentrations were seen with the addition of *ketoconazole*. Significant inter- and intrapatient variability was observed and a potential interaction could not be excluded.[1] In another study in 7 patients, however, the clearance of docetaxel was significantly reduced by 49% when given with ketoconazole.[2]

1. Van Veldhuizen PJ, *et al.* Docetaxel and ketoconazole in advanced hormone-refractory prostate carcinoma: a phase I and pharmacokinetic study. *Cancer* 2003; **98:** 1855–62.
2. Engels FK, *et al.* Effect of cytochrome P450 3A4 inhibition on the pharmacokinetics of docetaxel. *Clin Pharmacol Ther* 2004; **75:** 448–54.

Antineoplastics. The clearance of a dose of docetaxel was markedly reduced[1] when it was given after 4 days of treatment with *topotecan*, rather than on day 1; this resulted in worsened neutropenia.

Sorafenib may increase systemic exposure to docetaxel.

An increased incidence of febrile neutropenia and gastrointestinal disorders, including 2 fatalities, was reported in patients given docetaxel with *doxorubicin*,[2] although others[3] considered this high incidence unrepresentative of usual toxicity rates with this combination.

Heart failure has been reported in patients given docetaxel with other cytotoxic drugs, especially *trastuzumab*, and particularly after anthracycline-containing therapy. UK licensed drug information therefore recommends that patients given docetaxel with trastuzumab should undergo baseline cardiac assessment and cardiac function should be monitored during treatment.

1. Zamboni WC, *et al.* Pharmacokinetic and pharmacodynamic study of the combination of docetaxel and topotecan in patients with solid tumors. *J Clin Oncol* 2000; **18:** 3288–94.
2. Brain EGC, *et al.* Life-threatening sepsis associated with adjuvant doxorubicin plus docetaxel for intermediate-risk breast cancer. *JAMA* 2005; **293:** 2367–71.
3. Martin M, *et al.* Life-threatening complications from doxorubicin-docetaxel chemotherapy for breast cancer. *JAMA* 2005; **294:** 2166.

Pharmacokinetics

On intravenous dosage docetaxel is rapidly distributed to body tissues. Docetaxel is more than 95% bound to plasma proteins. It is extensively metabolised via hepatic cytochrome P450 isoenzyme CYP3A4 and excreted chiefly in the faeces as metabolites. Only about 6% of a dose is excreted in urine. The terminal elimination half-life is about 11 hours. Clearance is reduced in hepatic impairment.

◊ References.

1. Rudek MA, *et al.* Factors affecting pharmacokinetic variability following doxorubicin and docetaxel-based therapy. *Eur J Cancer* 2004; **40:** 1170–8.
2. Baker SD, *et al.* Clinical pharmacokinetics of docetaxel: recent developments. *Clin Pharmacokinet* 2006; **45:** 235–52.
3. Tran A, *et al.* Pharmacokinetics and toxicity of docetaxel: role of CYP3A, MDR1, and GST polymorphisms. *Clin Pharmacol Ther* 2006; **79:** 570–80.
4. Charles KA, *et al.* Predicting the toxicity of weekly docetaxel in advanced cancer. *Clin Pharmacokinet* 2006; **45:** 611–22.

Uses and Administration

Docetaxel is a semisynthetic taxane similar to paclitaxel (see p.760). It is manufactured from a taxane precursor derived from the needles of the European yew tree *Taxus baccata*. Docetaxel is used for locally advanced or metastatic breast cancer (p.661). It may be used as first-line treatment with doxorubicin; in the treatment of refractory disease, it is used alone or with capecitabine. In the treatment of metastatic breast cancer that overexpresses HER2 (human epidermal growth receptor 2), docetaxel may be used with trastuzumab as initial therapy. For adjuvant treatment of operable, node-positive breast cancer, docetaxel is given with doxorubicin and cyclophosphamide. Docetaxel is also indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (p.668), either with cisplatin for initial treatment of unresectable disease, or after failure of previous platinum-based chemotherapy. It is used with prednisone or prednisolone in hormone-refractory metastatic prostate cancer (p.671). Docetaxel is given with cisplatin and fluorouracil in the first-line treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastro-oesophageal junction (p.664); it is also used in this combination for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (p.666).

Docetaxel is given by intravenous infusion in glucose 5% or sodium chloride 0.9% at a concentration not exceeding 0.74 mg/mL. Infusion is normally over 1 hour. Premedication with an oral corticosteroid, such as dexamethasone 16 mg daily, for 3 days starting 1 day before docetaxel is recommended with many regimens.

The licensed dose for docetaxel as a single agent in the treatment of **breast cancer** after failure of previous chemotherapy is 60 to 100 mg/m^2 once every 3 weeks. A dose of 75 mg/m^2 once every 3 weeks is given in combination therapy with doxorubicin, or capecitabine, or when used as adjuvant therapy with doxorubicin and cyclophosphamide. When used with trastuzumab, docetaxel is given at a dose of 100 mg/m^2 once every 3 weeks.

The dose for **non-small cell lung cancer** is 75 mg/m^2 once every 3 weeks, for both first-line combination therapy and monotherapy after failure of previous chemotherapy.

For **gastric adenocarcinoma** docetaxel 75 mg/m^2 is given before cisplatin and fluorouracil; treatment is repeated every 3 weeks.

In the induction treatment of **head and neck cancer**, the recommended dose of docetaxel is 75 mg/m^2, given before cisplatin and fluorouracil; treatment is given every 3 weeks for 3 cycles, followed by chemoradiotherapy, or for 4 cycles when followed by radiotherapy alone.

For **prostate cancer**, the dose of docetaxel is 75 mg/m^2 once every 3 weeks, with prednisone or prednisolone 5 mg orally twice daily given continuously. The use of prednisone or prednisolone reduces the need for a premedication corticosteroid; dexamethasone 8 mg may be given at 12 hours, 3 hours, and 1 hour before docetaxel.

Regular blood counts are required, and dosage in subsequent courses should be reduced in patients who experience severe or febrile neutropenia (see also Bone-marrow Depression, p.639), or severe cutaneous reactions or peripheral neuropathy. The dose of docetaxel should be reduced in hepatic impairment, see below.

◊ References. For references to taxanes as a class, see Paclitaxel, p.760.

1. Comer AM, Goa KL. Docetaxel: a review of its use in non-small cell lung cancer. *Drugs Aging* 2000; **17:** 53–80.
2. Shepherd FA, *et al.* Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000; **18:** 2095–2103.
3. Beer TM, *et al.* Docetaxel (Taxotere) in the treatment of prostate cancer. *Expert Rev Anticancer Ther* 2003; **3:** 261–8.
4. Herbst RS, Khuri FR. Mode of action of docetaxel–a basis for combination with novel anticancer agents. *Cancer Treat Rev* 2003; **29:** 407–15.
5. Maenpaa JU. Docetaxel: promising and novel combinations in ovarian cancer. *Br J Cancer* 2003; **89** (suppl): S29–S34.
6. Tannock IF, *et al.* Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004; **351:** 1502–12.
7. Petrylak DP, *et al.* Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004; **351:** 1513–20.
8. Montero A, *et al.* Docetaxel for treatment of solid tumours: a systematic review of clinical data. *Lancet Oncol* 2005; **6:** 229–39.
9. Martin M, *et al.* Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med* 2005; **352:** 2302–13.
10. Engels FK, *et al.* Potential for improvement of docetaxel-based chemotherapy: a pharmacological review. *Br J Cancer* 2005; **93:** 173–7.

11. McKeage K, Keam SJ. Docetaxel: in hormone-refractory metastatic prostate cancer. *Drugs* 2005; **65:** 2287–94.
12. Lyseng-Williamson KA, Fenton C. Docetaxel: a review of its use in metastatic breast cancer. *Drugs* 2005; **65:** 2513–31.
13. Ajani JA. Chemotherapy for advanced gastric or gastroesophageal cancer: defining the contributions of docetaxel. *Expert Opin Pharmacother* 2006; **7:** 1627–31.
14. Thuss-Patience PC, *et al.* Docetaxel in the treatment of gastric cancer. *Future Oncol* 2006; **2:** 603–20.
15. Deeks ED, Scott LJ. Docetaxel: in gastric cancer. *Drugs* 2007; **67:** 1893–1901.

Administration. Docetaxel has been investigated as a low-dose weekly infusion, in patient groups such as the elderly, those with poor performance status, or refractory disease.[1-6] Weekly doses of 30 to 40 mg/m^2 are considered to be of similar efficacy to the standard three-weekly dosage regimen.[7] A pharmacokinetic study in 20 elderly patients suggested that a suitable starting dose might be 26 mg/m^2, increased provided there was no toxicity.[8]

1. Hainsworth JD, *et al.* Weekly docetaxel in the treatment of elderly patients with advanced breast cancer: a Minnie Pearl Cancer Research Network phase II trial. *J Clin Oncol* 2001; **19:** 3500–5.
2. Mekhail T, *et al.* Phase I trial of weekly docetaxel and gemcitabine in patients with refractory malignancies. *Cancer* 2003; **97:** 170–8.
3. Petrioli R, *et al.* Weekly low-dose docetaxel in advanced non-small cell lung cancer previously treated with two chemotherapy regimens. *Lung Cancer* 2003; **39:** 85–9.
4. Di Maio M, *et al.* Individual patient data meta-analysis of docetaxel administered once every 3 weeks compared with once every week second-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol* 2007; **25:** 1377–82.
5. Abbrederis K, *et al.* Weekly docetaxel monotherapy for advanced gastric or esophagogastric junction cancer: results of a phase II study in elderly patients or patients with impaired performance status. *Crit Rev Oncol Hematol* 2008; **66:** 84–90.
6. Rivera E, *et al.* Phase 3 study comparing the use of docetaxel on an every-3-week versus weekly schedule in the treatment of metastatic breast cancer. *Cancer* 2008; **112:** 1455–61.
7. Hainsworth JD. Practical aspects of weekly docetaxel administration schedules. *Oncologist* 2004; **9:** 538–45.
8. Hurria A, *et al.* Pharmacokinetics and toxicity of weekly docetaxel in older patients. *Clin Cancer Res* 2006; **12:** 6100–5.

Administration in hepatic impairment. UK licensed product information recommends that doses of docetaxel monotherapy should be reduced from 100 mg/m^2 to 75 mg/m^2 in mild to moderate hepatic impairment, defined as alanine aminotransferase (ALT/SGPT) and/or aspartate aminotransferase (AST/SGOT) more than 1.5 times the upper limit of normal (ULN), and alkaline phosphatase more than 2.5 times the ULN. Hepatic function should be monitored; use should be avoided if possible in severe hepatic impairment. US licensed information advises against the use of docetaxel in patients with bilirubin above ULN, or in those with mild to moderate hepatic impairment (defined as for the UK, above).

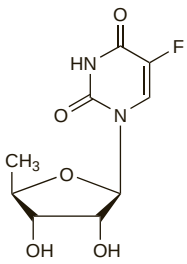
Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Asodocel; Docekebir; Dolectran; Donataxel; Doxetal; Doxmil†; Eriox; Neocel†; Plustaxano; Taxotere; Texot; Trazoteva; Trixotene†; ***Austral.:*** Taxotere; ***Austria:*** Taxotere; ***Belg.:*** Taxotere; ***Braz.:*** Taxotere; ***Canad.:*** Taxotere; ***Chile:*** Taxotere; ***Cz.:*** Taxotere; ***Denm.:*** Taxotere; ***Fin.:*** Taxotere; ***Fr.:*** Taxotere; ***Ger.:*** Taxotere; ***Gr.:*** Taxotere; ***Hong Kong:*** Taxotere; ***Hung.:*** Taxotere; ***India:*** Daxotel; Docetax; ***Indon.:*** Taxotere; ***Irl.:*** Taxotere; ***Israel:*** Taxotere; ***Ital.:*** Taxotere; ***Jpn:*** Taxotere; ***Malaysia:*** Taxotere; ***Mex.:*** Taxotere; ***Neth.:*** Taxotere; ***Norw.:*** Taxotere; ***NZ:*** Taxotere; ***Philipp.:*** Taxotere; ***Pol.:*** Taxotere; ***Port.:*** Taxotere; ***Rus.:*** Tautax (Таутакс); Taxotere (Таксотер); ***S.Afr.:*** Taxotere; ***Singapore:*** Taxotere; ***Spain:*** Taxotere; ***Swed.:*** Taxotere; ***Switz.:*** Taxotere; ***Thai.:*** Daxotel†; Taxotere; ***Turk.:*** Taxotere; ***UK:*** Taxotere; ***USA:*** Taxotere; ***Venez.:*** Daxotel; Taxotere.

Doxifluridine *(rINN)*

5′-Deoxy-5-fluorouridine; 5-DFUR; Doxifluridina; Doxifluridinum; FUDR; Ro-21-9738.

Доксифлуридин
$C_9H_{11}FN_2O_5$ = 246.2.
CAS — 3094-09-5.



Pharmacopoeias. In *Jpn.*

Profile
Doxifluridine is an antineoplastic that probably acts through its conversion in the body to fluorouracil (p.722). It is given orally in the management of malignant neoplasms of the breast (p.661) and gastrointestinal tract (p.664), and of other solid tumours, in doses of 0.8 to 1.2 g daily in divided doses. It has also been given by the intravenous route.

Pharmacokinetics. Doxifluridine is metabolised to fluorouracil and 5,6-dihydrofluorouracil. It is orally active with a bioavailability of 34 to 47%.

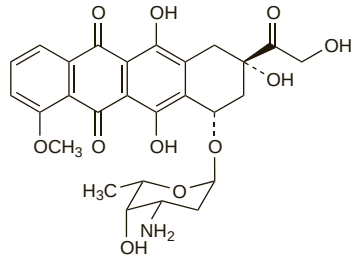
References.
1. Sommadossi J-P, *et al.* Kinetics and metabolism of a new fluoropyrimidine, 5′-deoxy-5-fluorouridine, in humans. *Cancer Res* 1983; **43:** 930–3.
2. Van Der Heyden SAM, *et al.* Pharmacokinetics and bioavailability of oral 5′-deoxy-5-fluorouridine in cancer patients. *Br J Clin Pharmacol* 1999; **47:** 351–6.

Preparations
Proprietary Preparations (details are given in Part 3)
Jpn: Furtulon.

Doxorubicin *(BAN, USAN, rINN)*

Adriamycin; Doksorubisiini; Doxorubicina; Doxorubicine; Doxorubicinum; FI-106; 3-Hydroxyacetyldaunorubicin; 14-Hydroxydaunomycin. 8-Hydroxyacetyl (8*S*,10*S*)-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-6,8,11-trihydroxy-1-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione.

Доксорубицин
$C_{27}H_{29}NO_{11}$ = 543.5.
CAS — 23214-92-8.
ATC — L01DB01.
ATC Vet — QL01DB01.



NOTE. In many countries the name Adriamycin is a trademark.

Doxorubicin Citrate *(BANM, rINNM)*

Citrato de doxorubicina; Doxorubicine, Citrate de; Doxorubicini Citras.

Доксорубицина Цитрат
$C_{27}H_{29}NO_{11}$,$xC_6H_8O_7$.
CAS — 111266-55-8.
ATC — L01DB01.
ATC Vet — QL01DB01.

NOTE. Doxorubicin citrate complex is a constituent of some liposomal products. It is prepared from doxorubicin hydrochloride (below).

Doxorubicin Hydrochloride *(BANM, rINNM)*

Cloridrato de Doxorrubicina; Doksorubicino hidrochloridas; Doksorubicyny chlorowodorek; Doksorubisiinihydrokloridi; Doksorubisin Hidroklorür; Doxorubicine, chlorhydrate de; Doxorubicin-hidroklorid; Doxorubicin-hydrochlorid; Doxorubicinhydroklorid; Doxorubicini hydrochloridum; Hidrocloruro de doxorubicina; NSC-123127.

Доксорубицина Гидрохлорид
$C_{27}H_{29}NO_{11}$,HCl = 580.0.
CAS — 25316-40-9.
ATC — L01DB01.
ATC Vet — QL01DB01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Doxorubicin Hydrochloride). The hydrochloride of a substance isolated from certain strains of *Streptomyces coeruleorubidus* or *S. peucetius* or obtained by any other means. It contains between 98 and 102% of the hydrochloride, calculated on the anhydrous substance. An orange-red, hygroscopic, crystalline powder. Soluble in water; slightly soluble in methyl alcohol. A 0.5% solution in water has a pH of 4.0 to 5.5. Store in airtight containers.
USP 31 (Doxorubicin Hydrochloride). A red-orange, hygroscopic, crystalline or amorphous powder. It contains not less than 98% and not more than 102% of $C_{27}H_{29}NO_{11}$,HCl, calculated on the anhydrous, solvent-free basis. Soluble in water, in sodium chloride 0.9%, and in methyl alcohol; practically insoluble in chloroform, in ether, and in other organic solvents. A 0.5% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. It may exist in an amorphous form, which should be stored at –25° to –10°.

Incompatibility. Admixture of doxorubicin hydrochloride with cefalotin sodium, dexamethasone, diazepam, or hydrocortisone sodium succinate is reported to result in immediate precipitation;[1] similarly precipitation has occurred when doxorubicin hydrochloride was mixed with furosemide or heparin sodium.[2] A mixture of fluorouracil or aminophylline with doxorubicin hydrochloride is reported to darken in colour from red to purple, indicating degradation of doxorubicin.[1] For mention of the compatibility of doxorubicin with paclitaxel, see p.759.

Liposomal doxorubicin differs in its incompatibilities from conventional formulations: whereas the latter are reportedly incompatible with allopurinol, cefepime, and ganciclovir, there was no visual evidence of this with the liposomal formulation. However, it was incompatible with a number of drug solutions including amphotericin B, docetaxel, gallium nitrate, hydroxyzine hydrochloride, metoclopramide hydrochloride, miconazole, mitoxantrone hydrochloride, morphine sulfate and some other opioids, paclitaxel, sodium bicarbonate, and some antibacterials.[3]

1. Dorr RT. Incompatibilities with parenteral anticancer drugs. *Am J Intravenous Ther* 1979; **6:** 42–52.
2. Cohen MH, *et al.* Drug precipitation within IV tubing: a potential hazard of chemotherapy administration. *Cancer Treat Rep* 1985; **69:** 1325–6.
3. Trissel LA, *et al.* Compatibility of doxorubicin hydrochloride liposome injection with selected other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 2708–13.

Stability. Although sensitive to light at low concentrations, doxorubicin is not subject to significant photodegradation at clinical concentrations and special precautions to protect solutions from light during administration do not appear to be necessary.[1,2] Solutions in sodium chloride solution 0.9% were reported[3] to be stable for 24 days when stored in PVC minibags at 25° and for even longer if stored in minibags or polypropylene syringes at 4°. Stability in solution seems to be partly related to pH, with doxorubicin becoming more stable[3-5] at acid pH. A fall in pH of the solution also significantly decreases the loss of doxorubicin by adsorption and precipitation onto the surface of a positively-charged in-line filter.[6]

Some liposomal doxorubicin formulations should be diluted only with glucose 5%. If not used immediately, they may be stored for 24 hours at 2° to 8°.

1. Tavoloni N, *et al.* Photolytic degradation of adriamycin. *J Pharm Pharmacol* 1980; **32:** 860–2.
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. Wood MJ, *et al.* Stability of doxorubicin, daunorubicin and epirubicin in plastic syringes and minibags. *J Clin Pharm Ther* 1990; **15:** 279–89.
4. Poochikian GK, *et al.* Stability of anthracycline antitumor agents in four infusion fluids. *Am J Hosp Pharm* 1981; **38:** 483–6.
5. Beijnen JH, *et al.* Stability of anthracycline antitumour agents in infusion fluids. *J Parenter Sci Technol* 1985; **39:** 220–2.
6. Francomb MM, *et al.* Effect of pH on the adsorption of cytotoxic drugs to a 96 hour intravenous filter. *Pharm J* 1991; **247:** R26.

Adverse Effects and Treatment

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

Doxorubicin and other anthracyclines cause pronounced bone-marrow depression, which may be dose-limiting. White cell count reaches a nadir 10 to 15 days after a dose and usually recovers by about 21 days.

The anthracyclines may produce cardiac toxicity, both as an acute, usually transient disturbance of cardiac function marked by ECG abnormalities and, sometimes, arrhythmias; and as a delayed, sometimes fatal, irreversible congestive heart failure, which may occur suddenly. Severe cardiotoxicity is more likely in adults receiving total cumulative doses of doxorubicin greater than 450 to 550 mg/m^2, and may occur months or even years after use.

Gastrointestinal disturbances include moderate or sometimes severe nausea and vomiting; stomatitis and oesophagitis may progress to ulceration. More rarely, facial flushing, conjunctivitis, and lachrymation may occur. Alopecia occurs in the majority of patients. The urine may be coloured red. Occasional hypersensitivity reactions may occur. Hyperuricaemia may occur due to tumour lysis syndrome.

Doxorubicin and other anthracyclines are very irritant and thrombophlebitis and streaking of the skin over the vein used for injection has been reported; extravasation is serious and may produce extensive local necrosis and ulceration. Intravesical instillation can cause bladder and urethral irritation, haematuria, and haemorrhagic cystitis.