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).

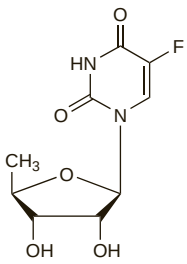
Preparations

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%.

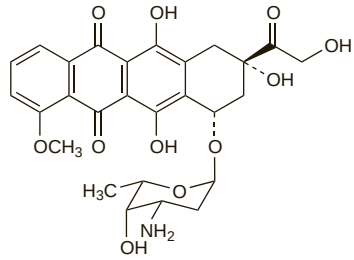
References.
1. Sommadossi J-P, *et al.* Kinetics and metabolism of a new fluoropyrimidine, 5′-deoxy-5-fluorouridine, in humans. *Cancer Res* 1983; **43:** 930–3.
2. Van Der Heyden SAM, *et al.* Pharmacokinetics and bioavailability of oral 5′-deoxy-5-fluorouridine in cancer patients. *Br J Clin Pharmacol*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

Combination therapy including doxorubicin has rarely been associated with secondary acute myeloid leukaemia (see also Carcinogenicity, p.635).

Formulations of liposomal doxorubicin may be associated with a reduced potential for local tissue necrosis, and possibly a reduced incidence of cardiotoxicity, although current clinical experience is limited, and such toxicity remains a possibility. Conversely, palmar-plantar erythrodysesthesia (p.639) appears to be more common, and may be dose-limiting. In addition, an acute pseudo-allergic reaction may be seen on initial infusion, but generally resolves on slowing or temporarily stopping the infusion.

Effects on the heart. Cardiotoxicity has been a major factor in limiting the use of the anthracyclines, doxorubicin and daunorubicin.[1-5] Toxicity is essentially of 2 kinds: acute, usually reversible ECG changes, including a wide range of arrhythmias, and a delayed, usually irreversible dose-related cardiomyopathy, resulting in congestive heart failure.[3-5] The latter may be further subdivided into chronic effects, occurring up to about a year afterwards, and late-onset toxicity occurring years after treatment.[4] Delayed toxicity may be fatal in as many as 60% of patients who develop it.[2]

The single most important determinant of cardiac toxicity appears to be the *cumulative dose*, with the risk of toxicity becoming ever greater at cumulative doxorubicin doses of 550 mg/m^2 or more,[2] and daunorubicin doses of 600 mg/m^2 or more.[1] However, patients vary widely in sensitivity,[4] and these values represent relatively arbitrary choices on a continuum of risk: there is no single safe dose.[2] Even at doses that produce no symptoms, subclinical myocardial damage may occur, and in children this may result in diminished cardiac reserve and heart disease in later life.[3,6,7] The *dosage schedule* also appears to be important; relatively high single doses on an infrequent schedule (presumably resulting in higher peak concentrations) appear to be more cardiotoxic than lower, weekly doses, or continuous infusion.[2,3,5,8-10] Cardiotoxicity is also reported to be more likely in *children and elderly* patients, and in those who have received prior *radiotherapy* to the chest.[1-5] There is reason to believe that previous *cardiovascular disease* may also increase the risk,[2-4] although such patients are commonly excluded from studies of anthracycline therapy.[2] *Females* may be at greater risk than males.[11] Use with cyclophosphamide, trastuzumab, or *other antineoplastics* with cardiotoxic potential may increase the likelihood of cardiomyopathy.

The late development of cardiac toxicity is of some concern: although in one study the mean time to development of symptoms was 33 days after a dose, with a range of 0 to 231 days,[2] several reports have indicated that late cardiac failure may occur up to 18 years after anthracycline therapy.[4,12,13]

Prevention. Given that doxorubicin-induced cardiac failure has been reported to occur in between 0.4 and 9% of all recipients, and that the fatality rate is high, much effort has gone into ways of predicting and preventing anthracycline-induced cardiotoxicity. Although ECG changes are commonly monitored, most of the changes are not predictive of cardiomyopathy and severe cardiac toxicity can occur without ECG changes. However, a persistent reduction in the voltage of the QRS wave is generally indicative of the need to perform further tests. Non-invasive cardiac monitoring, by means of echocardiography or radionuclide angiography, is useful in predicting the development of cardiomyopathy, but may give normal results until damage is quite advanced; sensitivity may be improved with exercise stress tests.[3-5] Endomyocardial biopsy is the most sensitive indicator of cardiomyopathy, but it is invasive and not widely available. The Childrens Cancer Study Group[14] has issued guidelines for monitoring using ECG, echocardiography, and radionuclide angiocardiography in patients receiving anthracyclines. The role of such techniques in predicting late-onset cardiotoxicity remains to be clarified.[4] There is some preliminary evidence to suggest that concentrations of cardiac troponins and natriuretic peptides could be used as predictive markers of myocardial damage.[15]

Dexrazoxane (p.1443) has shown some protective effect against the cardiotoxicity of doxorubicin and other anthracyclines, and is used to reduce cardiomyopathy in women receiving doxorubicin for metastatic breast cancer.

Alteration of the dosage schedule to weekly rather than three-weekly dosage, or the use of continuous infusion, has also been advocated as a way of reducing doxorubicin cardiotoxicity,[8-10] as has giving anthracyclines formulated in liposomes.[4]

Several anthracycline derivatives have been developed with the aim of reducing the inherent cardiotoxicity of this class of compounds, including aclarubicin (p.676), epirubicin (p.716), and mitoxantrone (p.754). However, although this strategy has met with some success, almost all these compounds exhibit some degree of cardiotoxicity.

Treatment. The result of treatment for such cardiotoxicity has generally been poor. Options have included digoxin, diuretics, low-salt diet, and bed rest. However, beta blockers may be useful, and results in patients with epirubicin-induced cardiotoxicity[16] have indicated that treatment with an ACE inhibitor can improve cardiac function and survival. Study is underway to determine whether ACE inhibitors can also prevent the initial toxicity if given immediately after an anthracycline.[17] Heart transplantation has been used.[5]

1. Von Hoff DD, *et al.* Daunomycin-induced cardiotoxicity in children and adults: a review of 110 cases. *Am J Med* 1977; **62:** 200–8.
2. Von Hoff DD, *et al.* Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med* 1979; **91:** 710–17.
3. Hale JP, Lewis IJ. Anthracyclines: cardiotoxicity and its prevention. *Arch Dis Child* 1994; **71:** 457–62.
4. Shan K, *et al.* Anthracycline-induced cardiotoxicity. *Ann Intern Med* 1996; **125:** 47–58.
5. Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. *N Engl J Med* 1998; **339:** 900–905.
6. Yeung ST, *et al.* Functional myocardial impairment in children treated with anthracyclines for cancer. *Lancet* 1991; **337:** 816–18.
7. Lipschultz SE, *et al.* Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. *N Engl J Med* 1991; **324:** 808–15.
8. Legha SS, *et al.* Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. *Ann Intern Med* 1982; **96:** 133–9.
9. Torti FM, *et al.* Reduced cardiotoxicity of doxorubicin delivered on a weekly schedule: assessment by endomyocardial biopsy. *Ann Intern Med* 1983; **99:** 745–9.
10. Lum BL, *et al.* Doxorubicin: alteration of dose scheduling as a means of reducing cardiotoxicity. *Drug Intell Clin Pharm* 1985; **19:** 259–64.
11. Lipshultz SE, *et al.* Female sex and higher drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. *N Engl J Med* 1995; **332:** 1738–43.
12. Goorin AM, *et al.* Initial congestive heart failure, six to ten years after doxorubicin chemotherapy for childhood cancer. *J Pediatr* 1990; **116:** 144–7.
13. Steinherz LJ, *et al.* Cardiac toxicity 4 to 20 years after completing anthracycline therapy. *JAMA* 1991; **266:** 1672–7.
14. Steinherz LJ, *et al.* Guidelines for cardiac monitoring of children during and after anthracycline therapy: report of the Cardiology Committee of the Childrens Cancer Study Group. *Pediatrics* 1992; **89:** 942–9.
15. Sparano JA, *et al.* Predicting cancer therapy-induced cardiotoxicity: the role of troponins and other markers. *Drug Safety* 2002; **25:** 301–11.
16. Jensen BV, *et al.* Treatment with angiotensin-converting-enzyme inhibitor for epirubicin-induced dilated cardiomyopathy. *Lancet* 1996; **347:** 297–9.
17. Jensen BV, *et al.* Angiotensin-converting enzyme inhibitor for epirubicin-induced dilated cardiomyopathy. *Lancet* 1996; **347:** 1485.

Effects on the liver. Hepatitis and non-specific hepatocellular damage has been reported in patients receiving doxorubicin as part of combination therapy.[1] A characteristic hepatotoxicity can also be produced by the combination of radiotherapy with doxorubicin.[2]

1. Avilés A, *et al.* Hepatic injury during doxorubicin therapy. *Arch Pathol Lab Med* 1984; **108:** 912–13.
2. Price LA. Surviving malignant disease: medical and oncological aspects. *Br J Hosp Med* 1983; **30:** 8–12.

Effects on the skin and nails. Hyperpigmentation has occurred in patients given daunorubicin, doxorubicin, or idarubicin.[1-6] Reports described pigmentation of the skin and transverse hyperpigmented bands of the nails. Effects on the skin resolved over several weeks, and bands on the nails moved with normal nail growth. Dark-skinned patients appear to be more susceptible to this adverse effect. Biopsy has found an increase in melanin granules in the affected tissues. An unusual blue-grey pigmentation of the face was reported in a patient given doxorubicin.[7]

For specific reference to treatment of alopecia caused by doxorubicin, and for extravasation, see p.639.

1. Kelly TM, *et al.* Hyperpigmentation with daunorubicin therapy. *Arch Dermatol* 1984; **120:** 262–3.
2. Kumar L, Kochupillai V. Doxorubicin induced hyperpigmentation. *N Z Med J* 1990; **103:** 165.
3. Curran CF. Doxorubicin-associated hyperpigmentation. *N Z Med J* 1990; **103:** 517.
4. Anderson LL, *et al.* Cutaneous pigmentation after daunorubicin chemotherapy. *J Am Acad Dermatol* 1992; **26:** 255–6.
5. Borecky DJ, *et al.* Idarubicin-induced pigmentary changes of the nails. *Cutis* 1997; **59:** 203–4.
6. Kroumpouzos G, *et al.* Generalized hyperpigmentation with daunorubicin chemotherapy. *J Am Acad Dermatol* 2002; **46** (suppl): S1–S3.
7. Konohana A. Blue-gray pigmentation in a patient receiving doxorubicin. *J Dermatol* 1992; **19:** 250–2.

Palmar-plantar erythrodysesthesia syndrome. Discussion of palmar-plantar erythrodysesthesia syndrome (p.639) associated with the use of liposomal doxorubicin, and recommendations for its management.[1] The most effective way of preventing the syndrome was to maintain doses at not more than 10 mg/m^2 weekly (typically as a single infusion of 40 mg/m^2 every 4 weeks). At such doses, the syndrome, if it occurred was typically mild and easily managed. Dose-intensity modification was also thought likely to be beneficial in managing the syndrome if it developed, although evidence to support this was lacking.

1. von Moos R, *et al.* Pegylated liposomal doxorubicin-associated hand-foot syndrome: recommendations of an international panel of experts. *Eur J Cancer* 2008; **44:** 781–90.

Precautions

For a general discussion see Antineoplastics, p.641.

Doxorubicin and other anthracyclines are generally contra-indicated in patients with heart disease. The total cumulative dose should be limited, and cardiac function should be monitored during treatment (see Effects on the Heart, above). Blood counts should be monitored and doses should not be repeated while there is bone-marrow depression or ulceration of the mouth. Doxorubicin should be given with great care in reduced doses to patients with hepatic impairment; dosage reduction may also be necessary in children and the elderly. Extravasation results in severe tissue damage and doxorubicin and other anthracyclines should not be given by intramuscular or subcutaneous injection. The adverse effects of irradiation may be enhanced by doxorubicin and skin reactions previously induced by radiotherapy may recur; the maximum cumulative dose should be reduced to no more than 400 mg/m^2 in patients who have received radiotherapy to the chest or heart. Different liposomal formulations may not be interchangeable with conventional formulations, or with each other.

Breast feeding. Doxorubicin and its metabolites have been detected in breast milk.[1] The American Academy of Pediatrics considers[2] that doxorubicin is concentrated in breast milk, that it may possibly cause immune suppression in the infant, has unknown effects on growth, and an association with carcinogenesis.

1. Egan PC, *et al.* Doxorubicin and cisplatin excretion into human milk. *Cancer Treat Rep* 1985; **69:** 1387–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 29/06/04)

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

A method for the destruction of doxorubicin or daunorubicin *wastes* using sulfuric acid and potassium permanganate.[1] Residues produced by degradation of daunorubicin by this method showed no mutagenicity *in vitro*; some mutagenicity was seen with high concentrations of residues from doxorubicin.

Urine and faeces produced for up to 7 days after a dose of doxorubicin should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes; some antineoplastic agents. *IARC Scientific Publications 73*. Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Pregnancy. Although doxorubicin has been reported to be undetectable in amniotic fluid[1,2] it has been found in fetal tissue (liver, kidney, and lungs) at concentrations several times those in maternal plasma,[2] indicating that it does cross the placenta. The effect of anthracyclines on the outcome of 160 pregnancies has been analysed.[3] Most women had received combination chemotherapy that included doxorubicin or daunorubicin, for haematological malignancies or breast cancer. Most outcomes (73%) were normal. There were 5 malformations, most often associated with regimens that also included antimetabolites or alkylating agents; the malformations were highly variable. Fetal toxicity was associated with chemotherapy use for solid tumours during the first trimester, and the risk of severe fetal toxicity was significantly increased with doxorubicin doses above 70 mg/m^2 per cycle. Fetal cardiac toxicity occurred in 2 cases and was associated with anthracycline use during the second and third trimesters. It has been suggested that the use of epirubicin may reduce the risk of fetal myocardiopathy. Fetal death was more frequent in women with acute leukaemia; it was associated with disease progression and the authors recommended that chemotherapy should not be postponed.

1. Roboz J, *et al.* Does doxorubicin cross the placenta? *Lancet* 1979; **ii:** 1382–3.
2. D'Incalci M, *et al.* Transplacental passage of doxorubicin. *Lancet* 1983; **i:** 75.
3. Germann N, *et al.* Anthracyclines during pregnancy: embryo–fetal outcome in 160 patients. *Ann Oncol* 2004; **15:** 146–50.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. The cumulative dose of doxorubicin should be reduced in patients who have received other cardiotoxic drugs such as daunorubicin or cyclophosphamide. Doxorubicin is reported to inhibit the intracellular activation of stavudine and hence its antiviral effect.

Antibacterials. Hypersensitivity reactions to doxorubicin or daunorubicin have been reported in 2 patients with recent exposure to *clindamycin*, one of whom had exhibited hypersensitivity to that antibiotic.[1] The possibility of cross-sensitivity between anthracyclines and clindamycin should be considered.

1. Arena FP, Sherlock S. Doxorubicin hypersensitivity and clindamycin. *Ann Intern Med* 1990; **112:** 150.

Antineoplastics. Giving doxorubicin with or after drugs, such as *streptozocin*[1] or *methotrexate*,[2] that can impair hepatic function, has resulted in increased doxorubicin toxicity, possibly due to reduced hepatic clearance. A high incidence of cardiotoxicity (manifest as congestive heart failure) has been reported in patients given doxorubicin with *paclitaxel* (which also has cardiotoxic effects).[3] Any interaction may be schedule dependent.[4] Similarly an increased incidence of cardiotoxicity has been seen when *trastuzumab* was given with or after anthracyclines (see Effects on the Heart under Trastuzumab, p.782).

Valspodar inhibits P-glycoprotein, and a pharmacokinetic study[5] found that it decreased clearance of doxorubicin and prolonged the terminal half-life, increasing exposure to doxorubicin and myelosuppressive effects. The authors suggested that the dose of doxorubicin might need to be reduced by about 60%.

Sorafenib may increase systemic exposure to doxorubicin.

For a suggestion that doxorubicin might enhance the hepatotoxicity of *mercaptopurine*, see under Daunorubicin Hydrochloride, p.709.

For a report of an increased incidence of febrile neutropenia and gastrointestinal complications when doxorubicin is used with *docetaxel*, see Antineoplastics, under Docetaxel, p.711.

In a pharmacokinetic study, both paclitaxel and docetaxel increased exposure to liposomal doxorubicin, although the effect was less pronounced with docetaxel.[6]

1. Anonymous. Two drugs may not be better than one. *JAMA* 1976; **236:** 913.
2. Robertson JH, *et al.* Toxicity of doxorubicin and methotrexate in osteogenic sarcoma. *BMJ* 1976; **1:** 23.
3. Gianni L, *et al.* Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. *J Clin Oncol* 1995; **13:** 2688–99.
4. Danesi R, *et al.* Pharmacokinetic optimisation of treatment schedules for anthracyclines and paclitaxel in patients with cancer. *Clin Pharmacokinet* 1999; **37:** 195–211.
5. Advani R, *et al.* A phase I trial of doxorubicin, paclitaxel, and valspodar (PSC 833), a modulator of multidrug resistance. *Clin Cancer Res* 2001; **7:** 1221–9.
6. Briasoulis E, *et al.* Interaction pharmacokinetics of pegylated liposomal doxorubicin (Caelyx) on coadministration with paclitaxel or docetaxel. *Cancer Chemother Pharmacol* 2004; **53:** 452–7.

Immunosuppressants. Increased plasma-doxorubicin concentrations and myelotoxicity have occurred when *ciclosporin* was used to modulate tumour resistance.[1] Severe neurological toxicity occurred in another patient given doxorubicin after long-term ciclosporin therapy.[2] It has been suggested that the use of ciclosporin or its analogues (see Antineoplastics, above for the effect of valspodar) to modulate doxorubicin resistance should be undertaken with caution.[3]

1. Rushing DA, *et al.* The effects of cyclosporine on the pharmacokinetics of doxorubicin in patients with small cell lung cancer. *Cancer* 1994; **74:** 834–41.
2. Barbui T, *et al.* Neurological symptoms and coma associated with doxorubicin administration during chronic cyclosporin therapy. *Lancet* 1992; **339:** 1421.
3. Beck WT, Kuttesch JF. Neurological symptoms associated with cyclosporin plus doxorubicin. *Lancet* 1992; **340:** 496.

Thalidomide. In a comparison of two treatment regimens for multiple myeloma (thalidomide, dexamethasone, cisplatin, cyclophosphamide, and etoposide, with or without doxorubicin), there was an increased risk of deep-vein thrombosis in those patients who received the combination that included doxorubicin.[1] The authors cited a previous study[2] in which the addition of thalidomide to an antineoplastic regimen increased the risk of deep-vein thrombosis, and concluded that patients with multiple myeloma treated with the combination of doxorubicin and thalidomide are at increased risk.

1. Zangari M, *et al.* Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy. *Blood* 2002; **100:** 1168–71.
2. Zangari M, *et al.* Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. *Blood* 2001; **98:** 1614–15.

Pharmacokinetics

After intravenous injection, doxorubicin is rapidly cleared from the blood, and distributed into tissues including lungs, liver, heart, spleen, and kidneys. It undergoes rapid metabolism in the liver to metabolites including the active metabolite doxorubicinol (adriamycinol). About 40 to 50% of a dose is stated to be excreted in bile within 7 days, of which about half is as unchanged drug. Only about 5% of a dose is excreted in urine within 5 days. It does not cross the blood-brain barrier but may cross the placenta and is distributed into breast milk. The disappearance of doxorubicin from the blood is triphasic: mean half-lives are 12 minutes, 3.3 hours and about 30 hours.

The pharmacokinetics of liposomal formulations are somewhat different from the conventional drug. The use of macrogols in the surface layer of the liposomes (pegylation) reduces removal of liposomes by macrophages. This results in prolonged circulation in the plasma, with relatively little tissue distribution, but tumour neovasculature is reported to permit penetration of liposomes into tumour tissue. Pharmacokinetics are reported to be biphasic with mean half-lives of 5 hours and 55 to 75 hours respectively. A non-pegylated liposomal formulation also exists and is reported to produce higher peak plasma concentrations of total doxorubicin than conventional formulations, but lower free (not liposome-encapsulated) concentrations. Clearance is reduced, and peak plasma concentrations of doxorubicinol delayed.

◊ References.

1. Speth PAJ, *et al.* Clinical pharmacokinetics of doxorubicin. *Clin Pharmacokinet* 1988; **15:** 15–31.
2. Rushing DA, *et al.* The disposition of doxorubicin on repeated dosing. *J Clin Pharmacol* 1993; **33:** 698–702.
3. Piscitelli SC, *et al.* Pharmacokinetics and pharmacodynamics of doxorubicin in patients with small cell lung cancer. *Clin Pharmacol Ther* 1993; **53:** 555–61.
4. Amantea MA, *et al.* Population pharmacokinetics and pharmacodynamics of pegylated-liposomal doxorubicin in patients with AIDS-related Kaposi's sarcoma. *Clin Pharmacol Ther* 1997; **61:** 301–11.
5. Danesi R, *et al.* Pharmacokinetic-pharmacodynamic relationships of the anthracycline anticancer drugs. *Clin Pharmacokinet* 2002; **41:** 431–44.
6. Swenson CE, *et al.* Pharmacokinetics of doxorubicin administered i.v. as Myocet (TLC D-99; liposome-encapsulated doxorubicin citrate) compared with conventional doxorubicin when given in combination with cyclophosphamide in patients with metastatic breast cancer. *Anticancer Drugs* 2003; **14:** 239–46.
7. Gabizon A, *et al.* Pharmacokinetics of pegylated liposomal doxorubicin : review of animal and human studies. *Clin Pharmacokinet* 2003 **42:** 419–36.

Uses and Administration

Doxorubicin is an anthracycline antineoplastic antibiotic. It is thought to have multiple modes of action including intercalation of DNA leading to an inhibition of DNA and RNA synthesis, inhibition of topoisomerase II, free radical formation, and alterations in cell membranes. Doxorubicin is a cell-cycle non-specific agent. It also has antibacterial and immunosuppressant properties.

Doxorubicin is effective against a wide range of tumours as indicated by the cross-references given below. Doxorubicin is used, often with other antineoplastics, in the treatment of Hodgkin's disease, non-Hodgkin's lymphomas, acute leukaemias, bone and soft-tissue sarcomas, neuroblastoma, Wilms' tumour, and malignant neoplasms of the bladder, breast, lung, ovary, and stomach. It has also been used in other tumours. Liposomal doxorubicin is used in the management of Kaposi's sarcoma in patients with AIDS, for the treatment of metastatic breast and ovarian cancers, and with bortezomib for the treatment of multiple myeloma.

Doxorubicin hydrochloride is given by intravenous injection into a fast-running infusion of sodium chloride 0.9% or glucose 5% over 3 minutes or more. When used as a single agent, the dose is 60 to 75 mg/m^2, or 1.2 to 2.4 mg/kg, once every 3 weeks. Alternatively, doses of 20 to 25 mg/m^2 have been given daily for 3 days every 3 weeks, although dividing the dose in this way may increase the incidence of mucositis. A regimen of 20 mg/m^2 as a single weekly dose may be used, and is reported to be associated with a lower incidence of cardiotoxicity.

Doses may need to be reduced if doxorubicin is given with other antineoplastics: a dose of 30 to 60 mg/m^2 every 3 weeks has been suggested. Doses should also be reduced in patients with liver dysfunction (see below).

The maximum total dose should not exceed 450 to 550 mg/m^2; in patients who have received radiotherapy to the chest, or other cardiotoxic drugs, it may be advisable to further limit the total dose.

In the management of AIDS-related Kaposi's sarcoma *pegylated liposomal* doxorubicin hydrochloride is given in an intravenous dose of 20 mg/m^2 infused over 30 minutes once every 2 to 3 weeks. For the treatment of breast and ovarian cancers, the suggested dose of this liposomal formulation is 50 mg/m^2 infused over 1 hour once every 4 weeks. In the treatment of multiple myeloma, liposomal doxorubicin hydrochloride is given at a dose of 30 mg/m^2 on day 4 of the bortezomib regimen (see p.689); it is given as an infusion over 1 hour immediately after the bortezomib infusion. In all these conditions, treatment should be continued for as long as the patient responds satisfactorily and tolerates treatment. The pegylated liposomal formulation should be diluted only with glucose 5%; generally, doses below 90 mg are diluted in 250 mL, and doses over 90 mg are diluted in 500 mL.

A *non-pegylated liposomal* formulation is also available and contains a doxorubicin citrate complex prepared with the aid of doxorubicin hydrochloride. It is given in the treatment of metastatic breast cancer in doses equivalent to doxorubicin hydrochloride 60 to 75 mg/m^2 every 3 weeks, with cyclophosphamide 600 mg/m^2. Doses are given by intravenous infusion over 1 hour, diluted in sodium chloride 0.9% or glucose 5% to a final concentration of 0.4 to 1.2 mg/mL doxorubicin.

Blood counts should be made routinely during treatment with doxorubicin (see also Bone-marrow Depression, p.639) and cardiac function should be monitored at regular intervals for early signs of cardiotoxicity.

Doxorubicin hydrochloride has also been instilled into the bladder in the local treatment of malignant neoplasms. For this purpose 50 mL of a 1 mg/mL solution may be instilled into the bladder for about one hour; treatment may be given at weekly to monthly intervals. Doxorubicin has also been given intra-arterially.

Various novel formulations of doxorubicin have been investigated. Doxorubicin with carbon/iron carrier particles (MTC-DOX) is a magnetically targeted treatment, using an external magnet to keep the drug at the tumour site, that has been investigated for hepatocellular carcinoma. A polymer of doxorubicin and polyisohexylcyanoacrylate in nanoparticle form is under investigation for the treatment of hepatocellular carcinoma. Doxorubicin-eluting beads, for injection directly into the brain, are under investigation for the treatment of glioma.

◊ Reviews of liposomal formulations.

1. Working PK, Dayan AD. CPMP Preclinical Expert Report: Caelyx (Stealth liposomal doxorubicin HCL). *Hum Exp Toxicol* 1996; **15:** 752–85.
2. Sharpe M, *et al.* Polyethylene glycol-liposomal doxorubicin: a review of its use in the management of solid and haematological malignancies and AIDS-related Kaposi's sarcoma. *Drugs* 2002; **62:** 2089–2126.
3. Forbes C, *et al.* A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer. *Health Technol Assess* 2002; **6:** 1–119.
4. O'Shaughnessy JA. Pegylated liposomal doxorubicin in the treatment of breast cancer. *Clin Breast Cancer* 2003; **4:** 318–28.
5. Orditura M, *et al.* Pegylated liposomal doxorubicin: pharmacologic and clinical evidence of potent antitumor activity with reduced anthracycline-induced cardiotoxicity. *Oncol Rep* 2004; **12:** 549–56.
6. Thigpen JT, *et al.* Role of pegylated liposomal doxorubicin in ovarian cancer. *Gynecol Oncol* 2005; **96:** 10–18.
7. Soloman R, Gabizon AA. Clinical pharmacology of liposomal anthracyclines: focus on pegylated liposomal doxorubicin. *Clin Lymphoma Myeloma* 2008; **8:** 21–32.
8. Patil RR, *et al.* Engineered nanocarriers of doxorubicin: a current update. *Crit Rev Ther Drug Carrier Syst* 2008; **25:** 1–61.

Administration in hepatic impairment. Doses of doxorubicin should be adjusted as follows in patients with liver dysfunction:

- serum-bilirubin concentrations of 12 to 30 micrograms/mL: half the normal dose
- serum-bilirubin greater than 30 micrograms/mL: quarter of the usual dose.

Slightly different schedules may apply to liposomal products but may vary between preparations.

Amyloidosis. For mention of the use of doxorubicin in patients with amyloidosis (and of the increased risk this may carry in cardiac amyloidosis) see p.743.

Malignant neoplasms. Doxorubicin plays a major role in combination regimens for chemotherapy of solid malignancies; it is often employed for tumours of the breast and lung (see p.661 and p.668) and for Wilms' tumour and neuroblastoma or retinoblastoma in children (see p.667, p.674, and p.675) and has been used for malignancies of the bladder (p.659); for various gynaecological cancers including those of the endometrium, and ovary (see p.663, and p.670); for cancer of the liver, stomach, and pancreas (p.667, p.664, p.671); and for neoplasms of prostate, and thymus (p.671 and p.674). It is also used in the treatment of sarcomas of bone and soft-tissue (see p.675 and p.676) and liposomal doxorubicin is used in patients with Kaposi's sarcoma (see p.675).

In addition, doxorubicin is a component of the ABVD regimen used to treat Hodgkin's disease (see p.655) and is part of the CHOP regimen used for non-Hodgkin's lymphoma (p.656). Doxorubicin is also used in Burkitt's lymphoma (p.657), mycosis fungoides (p.657), and the lymphomas associated with AIDS (see p.657). It has been employed in acute lymphoblastic leukaemia (p.651), in chronic lymphocytic leukaemia as part of the CHOP regimen (though with uncertain benefit—see p.653), and in multiple myeloma (p.658).

Preparations

BP 2008: Doxorubicin Injection;
USP 31: Doxorubicin Hydrochloride for Injection; Doxorubicin Hydrochloride Injection.

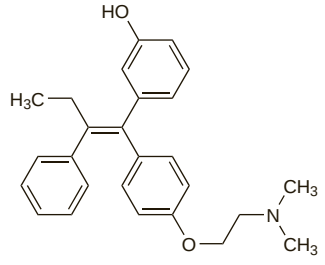
Proprietary Preparations (details are given in Part 3)
Arg.: Adriblastina; Caelyx†; Colhidrol; Dicladox; Doxocris; Doxokebir; Doxopeg; Doxorbin†; Doxtie; Flavicina†; Nagun; Onkostatil; Ranxas†; Roxorin; Varidoxo; ***Austral.:*** Caelyx; ***Austria:*** Adriblastin; Caelyx; DOXO-Cell; Doxolem; Doxorubin; Myocet; ***Belg.:*** Adriblastina; Caelyx; Doxorubin; Myocet; ***Braz.:*** Adriblastina; Biorrub; Caelyx; Doxofil†; Doxolem; Neoxane†; Rubex; Rubidox; ***Canad.:*** Caelyx; Myocet; ***Chile:*** Adriblastina; Caelyx; Daxotel; ***Cz.:*** Adriblastina; Caelyx; Doxolem; Myocet; Rastocin†; ***Denm.:*** Caelyx; ***Fin.:*** Caelyx; ***Fr.:*** Adriblastine; Caelyx; Myocet; ***Ger.:*** Adriblastin; Adrimedac; Caelyx; DOXO-Cell; Myocet; Onkodox; Ribodoxo-L; ***Gr.:*** Adriblastina; Caelyx; Doxorubin; Doxotil; Myocet; Rubidox; ***Hong Kong:*** Caelyx; ***Hung.:*** Adriblastina; Caelyx; Myocet; Pallagicin†; ***India:*** Adrim†; Cadria; Duxocin; Oncodox; ***Indon.:*** Caelyx; Pallagicin; Rubidox; ***Irl.:*** Caelyx; Myocet; ***Israel:*** Adriblastina; Caelyx†; Doxil; ***Ital.:*** Adriblastina; Caelyx; Myocet; ***Jpn:*** Adriacin; ***Malaysia:*** Caelyx; Doxorubin; ***Mex.:*** Adriblastina; Caelyx; Doxolem; Doxotec; Ifadox; Oxocina†; ***Neth.:*** Adriblastina; Caelyx; Doxorubin; Myocet; ***Norw.:*** Caelyx; ***NZ:*** Caelyx; Doxorubin; ***Philipp.:*** Adriblastina; Adrim; Axibin; Caelyx; Rubidox; ***Pol.:*** Adriblastina; Adrimedac; Biorubina; Caelyx; Rastocin; ***Port.:*** Adriblastina†; DOXO-cell; Fauldoxo; Myocet; ***Rus.:*** Caelyx (Келикс); Doxolem (Докселем)†; Rastocin (Растоцин); ***S.Afr.:*** Adriblastina; Caelyx; ***Singapore:*** Adriblastina; Caelyx; Doxorubin†; ***Spain:*** Caelyx; Farmiblastina; Myocet; ***Swed.:*** Caelyx; ***Switz.:*** Adriblastin; Caelyx; ***Thai.:*** AD Mycin; Adriblastina; Adrim; Caelyx; Doxolem; Doxorubin; Lipo-Dox; ***Turk.:*** Adriblastina; Caelyx; ***UK:*** Caelyx; Myocet; ***USA:*** Doxil; Rubex†; ***Venez.:*** Adriblastina; Adrim; Caelyx; Doxonolver.

Droloxifene *(USAN, rINN)* ⊗

Droloxifène; Droloxifeno; Droloxifenum; 3-Hydroxytamoxifen; K-21060E. (*E*)-α-{*p*-[2-(Dimethylamino)ethoxy]phenyl}-α′-ethyl-3-stilbenol.

Дролоксифен

$C_{26}H_{29}NO_2$ = 387.5.
CAS — 82413-20-5.



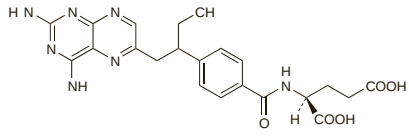
Profile
Droloxifene is a selective oestrogen receptor modulator related to tamoxifen (p.772) and with similar general properties. It has been investigated in the hormonal treatment and prophylaxis of breast cancer and is under study for osteoporosis.

Edatrexate *(USAN, rINN)*

CGP-30694; Édatrexate; Edatrexato; Edatrexatum. *N*-(*p*-{1-[(2,4-Diamino-6-pteridinyl)methyl]propyl}benzoyl)-L-glutamic acid.

Эдатрексат

$C_{22}H_{25}N_7O_5$ = 467.5.
CAS — 80576-83-6.



Profile
Edatrexate is an analogue of methotrexate (p.745) and has similar general properties. It has been investigated as an antineoplastic in the treatment of various malignant neoplasms. Mucositis may be dose limiting.

Edrecolomab *(USAN, rINN)*

17-1A Antibody; C1; Édrécolomab; Edrecolomabum; Monoclonal Antibody 17-1A. Immunoglobulin G2a (mouse monoclonal 17-1A γ-chain anti-human colon cancer tumor-associated antigen), disulfide with mouse monoclonal 17-1A light chain, dimer.

Эдреколомаб

CAS — 156586-89-9.
ATC — L01XC01.
ATC Vet — QL01XC01.

Profile
Edrecolomab is a monoclonal antibody of murine origin directed at epithelial cell surface glycoproteins that has been used as adjuvant therapy after surgery in patients with colorectal cancer (p.665), although reports of improved survival do not seem to have been borne out. It has been given by intravenous infusion over 2 hours, in an initial dose of 500 mg, followed by 4 further doses of 100 mg at monthly intervals. The drug is of murine origin and most patients develop antibodies after use. Hypersensitivity reactions, including anaphylactic reactions, have occurred.

It has also been tried for other malignant neoplasms including pancreatic cancer and advanced breast cancer.

◊ References.

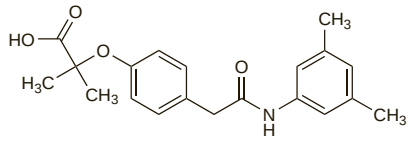
1. Riethmüller G, *et al.* Randomised trial of monoclonal antibody for adjuvant therapy of resected Dukes' C colorectal carcinoma. *Lancet* 1994; **343:** 1177–83.
2. Riethmüller G, *et al.* Monoclonal antibody therapy for resected Dukes' C colorectal cancer: seven-year outcome of a multicenter randomized trial. *J Clin Oncol* 1998; **16:** 1788–94.
3. Adkins JC, Spencer CM. Edrecolomab (monoclonal antibody 17-1A). *Drugs* 1998; **56:** 619–26.
4. Punt CJA, *et al.* Edrecolomab alone or in combination with fluorouracil and folinic acid in the adjuvant treatment of stage III colon cancer: a randomised study. *Lancet* 2002; **360:** 671–7.
5. Hartung G, *et al.* Adjuvant therapy with edrecolomab versus observation in stage II colon cancer: a multicenter randomized phase III study. *Onkologie* 2005; **28:** 347–50.

Efaproxiral *(USAN, rINN)* ⊗

Éfaproxiral; Efaproxiralum; RSR-13. 2-(4-{2-[(3,5-Dimethylphenyl)amino]-2-oxoethyl}phenoxy)-2-methyl propanoic acid.

Эфапроксирал

$C_{20}H_{23}NO_4$ = 341.4.
CAS — 131179-95-8.
ATC — L01XD06.
ATC Vet — QL01XD06.



Efaproxiral Sodium *(USAN, rINNM)* ⊗

Efaproxiral sódico; Éfaproxiral Sodique; Natrii Efaproxiralum.

Натрий Эфапроксирал

$C_{20}H_{22}NNaO_4$ = 363.4.
CAS — 170787-99-2.
ATC — L01XD06.
ATC Vet — QL01XD06.

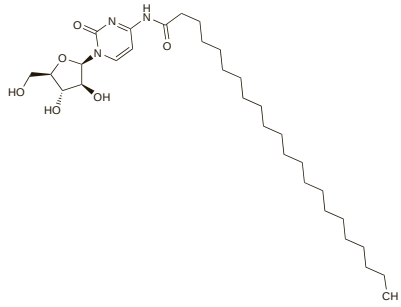
Profile
Efaproxiral is an allosteric modifier of haemoglobin that enhances the diffusion of oxygen to hypoxic tumour tissue, making it more sensitive to radiotherapy. It has been investigated in the treatment of brain metastases from solid tumours.

Enocitabine *(rINN)*

Behenoyl Cytarabine; Behenoylcytosine Arabinoside; BH-AC; Enocitabina; Énocitabine; Enocitabinum; NSC-239336. *N*-(1-β-D-Arabinofuranosyl-1,2-dihydro-2-oxo-4-pyrimidinyl)docosanamide.

Эноцитабин

$C_{31}H_{55}N_3O_6$ = 565.8.
CAS — 55726-47-1.



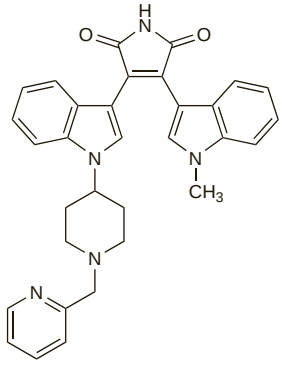
Profile
Enocitabine is an antineoplastic that is converted in the body to cytarabine (p.705). It has been used similarly in the treatment of acute leukaemias.

Enzastaurin Hydrochloride *(USAN, rINNM)*

Enzastaurine, Chlorhydrate d'; Enzastaurini Hydrochloridum; Hidrocloruro de enzastaurina; LY-317615. 3-(1-Methyl-1*H*-indol-3-yl)-4-{1-[1-(pyridin-2-ylmethyl)piperidin-4-yl]-1*H*-indol-3-yl}-1*H*pyrrole-2,5-dione hydrochloride.

Энзастаурина Гидрохлорид

$C_{32}H_{29}N_5O_2$,HCl = 552.1.
CAS — 359017-79-1.



(enzastaurin)

Profile
Enzastaurin hydrochloride is a protein kinase C inhibitor that is under investigation for the treatment of gliomas and non-Hodgkin's lymphoma.

◊ References.

1. Sorbera LA, *et al.* Enzastaurin hydrochloride. *Drugs Of The Future* 2007; **32:** 297–309. Correction. *ibid.*; 751.
2. Ma S, Rosen ST. Enzastaurin. *Curr Opin Oncol* 2007; **19:** 590–5.
3. Chen YB, LaCasce AS. Enzastaurin. *Expert Opin Invest Drugs* 2008; **17:** 939–44.