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).

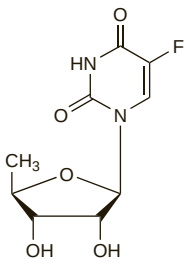
Preparations

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%.

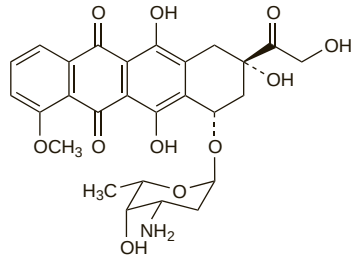
References.
1. Sommadossi J-P, *et al.* Kinetics and metabolism of a new fluoropyrimidine, 5′-deoxy-5-fluorouridine, in humans. *Cancer Res* 1983; **43:** 930–3.
2. Van Der Heyden SAM, *et al.* Pharmacokinetics and bioavailability of oral 5′-deoxy-5-fluorouridine in cancer patients. *Br J Clin Pharmacol*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