Aminoglycosides. Severe ototoxicity occurred when a short course of *gentamicin* was given to a patient who had recently completed a course of fludarabine.[1]

1. O'Brien RK, Sparling TG. Gentamicin and fludarabine ototoxicity. *Ann Pharmacother* 1995; **29:** 200–1.

Corticosteroids. For a suggestion that use of fludarabine with corticosteroids may increase the risk of infection, see Infection, above.

Pharmacokinetics

Intravenous fludarabine phosphate is rapidly dephosphorylated to fludarabine which is taken up by lymphocytes and rephosphorylated to the active triphosphate nucleotide. Peak intracellular concentrations of fludarabine triphosphate are seen about 4 hours after a dose. Fludarabine has a bioavailability of about 50 to 65% after oral doses of the phosphate.

Clearance of fludarabine from the plasma is triphasic with a terminal half-life of about 20 hours. Elimination is mostly via renal excretion: 60% of a dose is excreted in the urine. The pharmacokinetics of fludarabine exhibit considerable interindividual variation.

◊ References.

1. Johnson SA. Clinical pharmacokinetics of nucleoside analogues: focus on haematological malignancies. *Clin Pharmacokinet* 2000; **39:** 5–26.
2. Gandhi V, Plunkett W. Cellular and clinical pharmacology of fludarabine. *Clin Pharmacokinet* 2002; **41:** 93–103.

Uses and Administration

Fludarabine is a fluorinated nucleotide analogue of the antiviral vidarabine (p.912); it acts as a purine antagonist antimetabolite. It is used for its antineoplastic properties in the treatment of chronic lymphocytic leukaemia. Fludarabine phosphate is given by bolus injection or by intravenous infusion over 30 minutes in a usual dose of 25 mg/m^2 daily for 5 consecutive days. Alternatively it may be given orally in a dose of 40 mg/m^2 daily for 5 consecutive days. Courses may be repeated every 28 days, usually for up to 6 cycles.

Haematological function should be monitored regularly; the dosage may need to be reduced, or further courses delayed, if blood counts indicate severe or persistent myelosuppression (see also Bone-marrow Depression, p.639). Doses should be reduced in renal impairment (see below).

◊ General references.

1. Adkins JC, *et al.* Fludarabine: an update of its pharmacology and use in the treatment of haematological malignancies. *Drugs* 1997; **53:** 1005–37.
2. Plosker GL, Figgitt DP. Oral fludarabine. *Drugs* 2003; **63:** 2317–23.

Administration in renal impairment. Doses of fludarabine phosphate should be reduced by up to 50% in patients with mild to moderate renal impairment (creatinine clearance between 30 and 70 mL/minute); the drug should not be given in more severe renal impairment.

Malignant neoplasms. Fludarabine is the preferred second-line therapy for chronic lymphocytic leukaemia once initial alkylating agent therapy fails,[1] and may also be used for initial therapy (see p.653). It has also been tried in other malignancies. Listed below are some references to the use of fludarabine phosphate for the treatment of chronic lymphocytic leukaemia,[2,3] and its potential activity against a variety of other malignancies, including indolent low-grade non-Hodgkin's lymphoma[4,5] (p.656), mycosis fungoides,[6] heavy chain disease,[7] prolymphocytic leukaemia,[8,9] hairy cell leukaemia,[10] and Waldenström's macroglobulinaemia.[11,12]

1. NICE. Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia (issued September 2001). Available at: http://www.nice.org.uk/nicemedia/pdf/NICEfludarab_E_29guidance.pdf (accessed 31/07/08)
2. Zhu Q, *et al.* Fludarabine in comparison to alkylator-based regimen as induction therapy for chronic lymphocytic leukemia: a systematic review and meta-analysis. *Leuk Lymphoma* 2004; **45:** 2239–45.
3. Richards S. Fludarabine increases complete response but not survival compared with conventional alkylator-based regimens for previously untreated chronic lymphocytic leukaemia. *Cancer Treat Rev* 2005; **31:** 332–5.
4. Hiddemann W, Pott-Hoeck C. Fludarabine in the management of malignant lymphomas. *Drugs* 1994; **47** (suppl 6): 50–6.
5. Anderson VR, Perry CM. Fludarabine: a review of its use in non-Hodgkin's lymphoma. *Drugs* 2007; **67:** 1633–55.
6. Scarisbrick JJ, *et al.* A trial of fludarabine and cyclophosphamide combination chemotherapy in the treatment of advanced refractory primary cutaneous T-cell lymphoma. *Br J Dermatol* 2001; **144:** 1010–15.
7. Agrawal S, *et al.* First report of fludarabine in gamma-heavy chain disease. *Br J Haematol* 1994; **88:** 653–5.
8. Smith OP, Mehta AB. Fludarabine monophosphate for prolymphocytic leukaemia. *Lancet* 1990; **336:** 820.
9. Kantarjian HM, *et al.* Efficacy of fludarabine, a new adenine nucleoside analogue, in patients with prolymphocytic leukemia and the prolymphocytoid variant of chronic lymphocytic leukemia. *Am J Med* 1991; **90:** 223–8.
10. Kantarjian HM, *et al.* Fludarabine therapy in hairy cell leukemia. *Cancer* 1991; **67:** 1291–3.
11. Dhodapkar MV, *et al.* Prognostic factors and response to fludarabine therapy in patients with Waldenström macroglobulinemia: results of United States intergroup trial (Southwest Oncology Group S9003). *Blood* 2001; **98:** 41–8.
12. Leblond V, *et al.* Multicenter, randomized comparative trial of fludarabine and the combination of cyclophosphamide-doxorubicin-prednisone in 92 patients with Waldenström macroglobulinemia in first relapse or with primary refractory disease. *Blood* 2001; **98:** 2640–4.

Preparations

USP 31: Fludarabine Phosphate for Injection; Fludarabine Phosphate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Fludakebir; Fludara; Fluradosa; Forclina; ***Austral.:*** Fludara; ***Austria:*** Fludara; ***Belg.:*** Fludara; ***Braz.:*** Fludara; ***Canad.:*** Fludara; ***Chile:*** Fludara; ***Cz.:*** Fludara; Tazumara; ***Denm.:*** Fludara; ***Fin.:*** Fludara; ***Fr.:*** Fludara; ***Ger.:*** Fludara; ***Gr.:*** Fludara; ***Hong Kong:*** Fludara; ***Hung.:*** Fludara; ***India:*** Fludara; ***Indon.:*** Fludara; ***Irl.:*** Fludara; ***Israel:*** Fludara; ***Ital.:*** Fludara; ***Malaysia:*** Fludara; ***Mex.:*** Beneflur; Fludara; ***Neth.:*** Fludara; ***Norw.:*** Fludara; ***NZ:*** Fludara; ***Philipp.:*** Fludara; ***Pol.:*** Fludara; ***Port.:*** Fludara; ***Rus.:*** Fludara (Флудара); ***S.Afr.:*** Fludara; ***Singapore:*** Fludara; ***Spain:*** Beneflur; ***Swed.:*** Fludara; ***Switz.:*** Fludara; ***Thai.:*** Fludara; ***Turk.:*** Fludara; ***UK:*** Fludara; ***USA:*** Fludara; ***Venez.:*** Fludara.

Fluorouracil *(BAN, USAN, rINN)*

5-Fluorouracil; Fluorouracilas; Fluorouracile; Fluorouracilo; Fluorouracilum; Fluorouracyl; Fluorourasiili; Fluorourasil; 5-Fluorourasil; Fluoruracil; 5-FU; NSC-19893; Ro-2-9757; WR-69596. 5-Fluoropyrimidine-2,4(1*H*,3*H*)-dione.

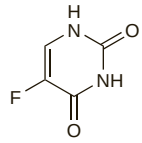
Флуороурацил

$C_4H_3FN_2O_2$ = 130.1.

CAS — 51-21-8.

ATC — L01BC02.

ATC Vet — QL01BC02.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
Ph. Eur. 6.2 (Fluorouracil). A white or almost white, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. A 1% solution in water has a pH of 4.5 to 5.0. Protect from light.
USP 31 (Fluorouracil). A white to practically white, practically odourless, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Incompatibility. Preparations of fluorouracil are alkaline, and compatibility problems may be expected with acidic drugs and preparations, or those which are unstable in the presence of alkali. Fluorouracil is reported to be incompatible with cytarabine,[1] diazepam,[2] doxorubicin[2] (and presumably other anthracyclines that are unstable at alkaline pH), and calcium folinate.[3] Although fluorouracil has been stated to be incompatible with methotrexate[1] a study of the long-term stability of an admixture of the 2 drugs in sodium chloride 0.9% injection suggests otherwise.[4]

1. McRae MP, King JC. Compatibility of antineoplastic, antibiotic and corticosteroid drugs in intravenous admixtures. *Am J Hosp Pharm* 1976; **33:** 1010–13.
2. Dorr RT. Incompatibilities with parenteral anticancer drugs. *Am J Intravenous Ther* 1979; **6:** 42–52.
3. Trissel LA, *et al.* Incompatibility of fluorouracil with leucovorin calcium or levoleucovorin calcium. *Am J Health-Syst Pharm* 1995; **52:** 710–15.
4. Vincké BJ, *et al.* Extended stability of 5-fluorouracil and methotrexate solutions in PVC containers. *Int J Pharmaceutics* 1989; **54:** 181–9.

Stability. Despite one report[1] that fluorouracil had limited stability when dissolved in glucose 5% at room temperature (10% loss from solution in 43 hours when stored in PVC and in only 7 hours when stored in glass), others[2] found such a solution to be stable for at least 16 weeks when stored in PVC at 5°. When stored at room temperature in PVC, solutions of fluorouracil may lose water by evaporation, which slowly increases their concentration.[2,3] Results of a study of fluorouracil and methotrexate admixtures in sodium chloride 0.9% suggest that extended stability (up to 13 weeks) is possible in this diluent at 5° in PVC bags.[3] Commercial solutions of fluorouracil for injection have been reported to be stable for 7 days at 37° in a portable infusion pump, although at 25° one brand showed evidence of precipitation.[4] Fluorouracil solutions may be incompatible with synthetic elastomers: microscopic precipitation has been reported as soon as 4 hours after placement into polyisoprene reservoirs of elastomeric infusers and in polypropylene syringes with an elastomeric joint.[5] Some have questioned the validity of this finding.[6,7]

1. Benvenuto JA, *et al.* Stability and compatibility of antitumor agents in glass and plastic containers. *Am J Hosp Pharm* 1981; **38:** 1914–18.
2. Quebbeman EJ, *et al.* Stability of fluorouracil in plastic containers used for continuous infusion at home. *Am J Hosp Pharm* 1984; **41:** 1153–6.
3. Vincké B, *et al.* Extended stability of 5-fluorouracil and methotrexate solutions in PVC containers. *Int J Pharmaceutics* 1989; **54:** 181–9.
4. Stiles ML, *et al.* Stability of fluorouracil administered through four portable infusion pumps. *Am J Hosp Pharm* 1989; **46:** 2036–40.
5. Corbrion V, *et al.* Precipitation of fluorouracil in elastomeric infusers with a polyisoprene reservoir and in polypropylene syringes with an elastomeric joint. *Am J Health-Syst Pharm* 1997; **54:** 1845–8.
6. Trissel LA. Fluorouracil precipitate. *Am J Health-Syst Pharm* 1998; **55:** 1314–15.
7. Allwood MC. Fluorouracil precipitate. *Am J Health-Syst Pharm* 1998; **55;** 1315–16.

Adverse Effects and Treatment

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

The main adverse effects of fluorouracil are on the bone marrow and the gastrointestinal tract, and may be dose-limiting. Toxicity is schedule dependent: reducing the rate of injection to a slow infusion is associated with less haematological toxicity but does not decrease gastrointestinal toxicity. With protracted continuous infusion in particular, the palmar-plantar erythrodysesthesia syndrome (erythema and painful desquamation of the hands and feet) may occur. Gastrointestinal toxicity may be exacerbated if fluorouracil is given with folinic acid.

Leucopenia, thrombocytopenia, stomatitis, gastrointestinal ulceration and bleeding, diarrhoea, or haemorrhage from any site, are signs that treatment should be stopped. The nadir of the white cell count may occur from 7 to 20 days after a dose, and counts usually return to normal after about 30 days. Thrombocytopenia is usually at a maximum 7 to 17 days after a dose. Anaemia may also occur. Nausea and vomiting, rashes, and alopecia are common. Ocular irritation, central neurotoxicity (notably cerebellar ataxia), and myocardial ischaemia have occurred.

Local inflammatory and photosensitivity reactions have occurred after topical use. Dermatitis and, rarely, erythema multiforme have been reported.

Effects on the eyes. Systemic fluorouracil therapy has been associated with various types of ocular toxicity including several cases of excessive lachrymation and watering of the eyes.[1] In one patient this was associated with symptoms suggesting fibrosis of the tear duct,[1] and possibly representing local irritation due to the presence of fluorouracil in tear fluid,[2] although symptoms have not always resolved on stopping the drug.[1] More seriously a case of bilateral total corneal epithelial erosion has been described.[3] Optic neuropathy, culminating in near blindness, has also occurred in a patient given fluorouracil as part of a combination regimen.[4] Severe ulceration and corneal abscess with hyopyon has followed local injection of fluorouracil into the eye in a diabetic patient with idiopathic band keratopathy.[5]

1. Haidak DJ, *et al.* Tear-duct fibrosis (dacryostenosis) due to 5-fluorouracil. *Ann Intern Med* 1978; **88:** 657.
2. Christophidis N, *et al.* Lacrimation and 5-fluorouracil. *Ann Intern Med* 1978; **89:** 574.
3. Hirsh A, *et al.* Bilateral total corneal epithelial erosion as a side effect of cytotoxic therapy. *Br J Ophthalmol* 1990; **74:** 638.
4. Adams JW, *et al.* Recurrent acute toxic optic neuropathy secondary to 5-FU. *Cancer Treat Rep* 1984; **68:** 565–6.
5. Hickey-Dwyer M, Wishart PK. Serious corneal complication of 5-fluorouracil. *Br J Ophthalmol* 1993; **77:** 250–1.

Effects on the heart. Life-threatening cardiotoxicity (arrhythmias, ventricular tachycardia, and cardiac arrest, secondary to transmural ischaemia) has been reported to occur in 0.55% of patients given fluorouracil,[1] although the incidence of angina and less severe cardiotoxicity associated with coronary artery spasm may be higher.[1-3] Possible risk factors include pre-existing heart disease or mediastinal radiotherapy, and prolonged infusion of the drug, but symptoms can also occur in patients without these risk factors.[2-4] Therefore, at present, it is not possible to reliably predict patients at risk.[5] Some suggest that the use of a trometamol buffer in the fluorouracil formulation may contribute to the formation of cardiotoxic degradation products.[6]

1. Keefe DL, *et al.* Clinical cardiotoxicity of 5-fluorouracil. *J Clin Pharmacol* 1993; **33:** 1060–70.
2. McLachlan SA, *et al.* The spectrum of 5-fluorouracil cardiotoxicity. *Med J Aust* 1994; **161:** 207–9.
3. Anand AJ. Fluorouracil cardiotoxicity. *Ann Pharmacother* 1994; **28:** 374–8.

4. Hannaford R. Sudden death associated with 5-fluorouracil. *Med J Aust* 1994; **161:** 225.
5. Becker K, *et al.* Cardiotoxicity of the antiproliferative compound fluorouracil. *Drugs* 1999; **57:** 475–84.
6. Lukaschek J, *et al.* Cardiotoxicity and neurotoxicity of high-dose continuous fluorouracil as a result of degradation compounds in the drug vials. *J Clin Oncol* 2004; **22:** 5022–5.

Effects on the nervous system. Central neurotoxicity, including cerebellar ataxia, confusion, disorientation, and emotional lability is reported to occur rarely in patients receiving fluorouracil, although the incidence may be increased with high-dose or intensive regimens. Patients with disorders of pyrimidine metabolism may be at increased risk of neurotoxicity.[1-3] It has also been suggested that fluorouracil may produce neurotoxicity by causing thiamine deficiency, and that thiamine may be used to treat it.[4]

1. Tuchman M, *et al.* Familial pyrimidinemia and pyrimidinuria associated with severe fluorouracil toxicity. *N Engl J Med* 1985; **313:** 245–9.
2. Stéphan F, *et al.* Depressed hepatic dihydropyrimidine dehydrogenase activity and fluorouracil-related toxicities. *Am J Med* 1995; **99:** 685–8.
3. Takimoto C, *et al.* Reversible 5-fluorouracil-associated encephalopathy in a dihydropyrimidine dehydrogenase (DPD) deficient patient. *Clin Pharmacol Ther* 1996; **59:** 161.
4. Pirzada NA, *et al.* Fluorouracil-induced neurotoxicity. *Ann Pharmacother* 2000; **34:** 35–8.

Effects on the skin. In addition to reports of fluorouracil-associated dermatitis and photosensitivity a syndrome of erythema, pain, and desquamation of the skin of palms and soles has been reported[1-4] (the palmar-plantar erythrodysesthesia syndrome, p.639). Although particularly associated with continuous infusion[1,2] the syndrome can also occur after bolus doses.[3,4] Symptoms generally respond to stopping the drug, but addition of oral pyridoxine to chemotherapy regimens has been reported to prevent or resolve symptoms,[5] as has application of a nicotine patch in one patient.[6]

Rash and confusion developing in an elderly man with malabsorption and poor nutritional intake who received fluorouracil for a biliary-tract tumour were diagnosed as pellagra.[7] Symptoms responded to nicotinic acid therapy.

1. Lokich JJ, Moore C. Chemotherapy-associated palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med* 1984; **101:** 798–800.
2. Feldman LD, Ajani JA. Fluorouracil-associated dermatitis of the hands and feet. *JAMA* 1985; **254:** 3479.
3. Atkins JN. Fluorouracil and the palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med* 1985; **102:** 419.
4. Curran CF, Luce JK. Fluorouracil and palmar-plantar erythrodysesthesia. *Ann Intern Med* 1989; **111:** 858.
5. Vukelja SJ, *et al.* Pyridoxine for the palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med* 1989; **111:** 688–9.
6. Kingsley EC. 5-Fluorouracil dermatitis prophylaxis with a nicotine patch. *Ann Intern Med* 1994; **120:** 813.
7. Stevens HP, *et al.* Pellagra secondary to 5-fluorouracil. *Br J Dermatol* 1993; **128:** 578–80.

Hypersensitivity. Although local hypersensitivity reactions are included in licensed product information as potential adverse effects of topical fluorouracil, hypersensitivity reactions to systemic fluorouracil have been reported very rarely.[1-6] For a report of the successful use of fluorouracil in a patient allergic to capecitabine, suggesting that cross-sensitivity does not occur between the two, see p.692.

1. Reed WP, Morris DM. Maculopapular eruption resulting from systemic administration of 5-fluorouracil. *Cutis* 1984; **33:** 381–2.
2. Sridhar KS. Allergic reaction to 5-fluorouracil infusion. *Cancer* 1986; **58:** 862–4.
3. Milla Santos A, Sanchiz Medina F. Anaphylactic reaction following iv administration of 5-fluorouracil. *Cancer Treat Rep* 1986; **70:** 1346.
4. Duley JA, Nethersell AB. Delayed hypersensitivity to 5-fluorouracil associated with reduced dihydropyrimidine dehydrogenase (DPD) activity. *Adv Exp Med Biol* 1998; **431:** 147–50.
5. Eppinger T, Sperber K. Desensitization to 5-fluorouracil. *Allergy Asthma Proc* 1999; **20:** 189–91.
6. Biswal BM. Anaphylaxis following continuous 5-fluorouracil infusion chemotherapy. *Aust N Z J Med* 1999; **29:** 743–4.

Precautions

For general discussions see Antineoplastics, p.641. Fluorouracil should be given with care to weak or malnourished patients, to those with a history of heart disease, or to those with hepatic or renal insufficiency. Patients with a history of high-dose pelvic irradiation or treatment with alkylating agents, and those with widespread metastases to the bone marrow should also be treated with extreme caution. Blood cell counts should be determined frequently during therapy. Fluorouracil should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency as this can lead to increased toxicity.

Topical fluorouracil should not be used on mucous membranes. There is a possibility of increased absorption if used excessively or on ulcerated or inflamed skin. Occlusive dressings may increase inflammatory actions. Exposure to UV light during treatment should be avoided. Creams are preferably applied using a non-metal applicator or gloved hand; if bare fingertips are used the hands must be washed immediately afterwards.

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

Urine and faeces produced for up to 48 hours and 5 days respectively after an oral dose of fluorouracil should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Metabolic disorders. For reference to increased risk of neurotoxicity in patients with a defect of pyrimidine metabolism given fluorouracil, see under Effects on the Nervous System, above.

Interactions

For a general discussion of antineoplastic drug interactions, see p.642. The actions of fluorouracil may be modified by other drugs including allopurinol, cimetidine, folinic acid, methotrexate, and metronidazole (see also under Administration, below).

◊ References.

1. Jansman FGA, *et al.* Assessing the clinical significance of drug interactions with fluorouracil in patients with colorectal cancer. *Am J Health-Syst Pharm* 2005; **62:** 1788–93.

Antineoplastics. *Oxaliplatin*, which is given with fluorouracil and folinic acid in the treatment of colorectal cancer, reduced fluorouracil clearance in a study[1] of 29 patients with colorectal cancer. The effect was delayed and prolonged, lasting about 15 days, and an increase in toxicity correlated with raised fluorouracil concentrations. The mechanism of this interaction is unclear. In contrast, however, another study[2] found no effect of oxaliplatin on fluorouracil pharmacokinetics; the study was not designed to investigate a delayed effect and the dose of oxaliplatin was lower than that used in the first study.

Sorafenib has been reported to have variable effects on fluorouracil exposure.

For reference to the effect of fluorouracil on the action of *paclitaxel*, see Antineoplastics, p.759. For the increased risk of haemolytic-uraemic syndrome that may be seen if fluorouracil is used with *mitomycin*, see Effects on the Kidneys, p.752.

1. Boisdron-Celle M, *et al.* Influence of oxaliplatin on 5-fluorouracil plasma clearance and clinical consequences. *Cancer Chemother Pharmacol* 2002; **49:** 235–43.
2. Joel SP, *et al.* Lack of pharmacokinetic interaction between 5-fluorouracil and oxaliplatin. *Clin Pharmacol Ther* 2004; **76:** 45–54.

Antiprotozoals. *Metronidazole* increased the toxicity of fluorouracil in patients with colorectal cancer, apparently by reducing the clearance of the antineoplastic. No enhanced antineoplastic effect was seen with the combination *in vitro*.[1]

1. Bardakji Z, *et al.* 5-Fluorouracil–metronidazole combination therapy in metastatic colorectal cancer. *Cancer Chemother Pharmacol* 1986; **18:** 140–4.

Antivirals. Giving *interferon alfa-2b* with fluorouracil has produced a marked increase in the initial plasma concentration of fluorouracil and a decrease in fluorouracil clearance.[1]

Severe leucopenia, fatal in some cases, has been reported in patients given fluorouracil or fluorouracil prodrugs (such as tegafur) with *sorivudine*.[2,3] A metabolite of sorivudine appears to inhibit dihydropyrimidine dehydrogenase, the primary enzyme responsible for the inactivation of fluorouracil.[3]

1. Czejka MJ, *et al.* Clinical pharmacokinetics of 5-fluorouracil: influence of the biomodulating agents interferon, dipyridamole and folic acid alone and in combination. *Arzneimittelforschung* 1993; **43:** 387–90.
2. Yawata M. Deaths due to drug interaction. *Lancet* 1993; **342:** 1166.
3. Diasio RB. Sorivudine and 5-fluorouracil; a clinically significant drug-drug interaction due to inhibition of dihydropyrimidine dehydrogenase. *Br J Clin Pharmacol* 1998; **46:** 1–4.

Gastrointestinal drugs. Pretreatment with *cimetidine* for 4 weeks increased plasma concentrations of fluorouracil after intravenous and oral doses in 6 patients.[1] The effect was probably due to a combination of hepatic enzyme inhibition and reduced hepatic blood flow. No such effect was seen after single doses of cimetidine in 5 patients or pretreatment for just 1 week in 6. Care is required in patients given both drugs together.

1. Harvey VJ, *et al.* The influence of cimetidine on the pharmacokinetics of 5-fluorouracil. *Br J Clin Pharmacol* 1984; **18:** 421–30.

Pharmacokinetics

Absorption of fluorouracil from the gastrointestinal tract is unpredictable and fluorouracil is usually given intravenously. Little is absorbed when fluorouracil is applied to healthy skin.

After intravenous injection fluorouracil is cleared rapidly from plasma with a mean half-life of about 16 minutes. It is distributed throughout body tissues and fluids (including crossing the blood-brain barrier to appear in the CSF), and disappears from the plasma within about 3 hours. Within the target cell fluorouracil is converted to 5-fluorouridine monophosphate and floxuridine monophosphate (5-fluorodeoxyuridine monophosphate), the former undergoing conversion to the triphosphate which can be incorporated into RNA while the latter inhibits thymidylate synthetase. About 15% of an intravenous dose is excreted unchanged in the urine within 6 hours. The remainder is inactivated primarily in the liver and is catabolised via dihydropyrimidine dehydrogenase (DPD) similarly to endogenous uracil. A large amount is excreted as respiratory carbon dioxide; urea and other metabolites are also produced.

◊ References.

1. Ploylearmsaeng S-A, *et al.* How may anticancer chemotherapy with fluorouracil be individualised? *Clin Pharmacokinet* 2006; **45:** 567–92.

Chronopharmacology. Plasma concentrations of fluorouracil during continuous intravenous infusion are reported to undergo circadian variations of as much as 50% of the mean, peak concentrations occurring in the middle of the night.[1] The variation may be due to a circadian variation in the activity of the enzyme dihydropyrimidine dehydrogenase in blood,[2] but striking interpatient variations in peak concentrations of fluorouracil and peak enzyme activity suggest that any adjustment of infusion times would need to be individualised.[2] It has been suggested that pharmacokinetic monitoring should be investigated as a means of individualising fluorouracil doses with the aim of improving efficacy and reducing toxicity.[3]

1. Petit E, *et al.* Circadian rhythm-varying plasma concentration of 5-fluorouracil during a five-day continuous venous infusion at a constant rate in cancer patients. *Cancer Res* 1988; **48:** 1676–9.
2. Harris BE, *et al.* Relationship between dihydropyrimidine dehydrogenase activity and plasma 5-fluorouracil levels with evidence for circadian variation of enzyme activity and plasma drug levels in cancer patients receiving 5-fluorouracil by protracted continuous infusion. *Cancer Res* 1990; **50:** 197–201.
3. Young AM, *et al.* Can pharmacokinetic monitoring improve clinical use of fluorouracil. *Clin Pharmacokinet* 1999; **36:** 391–8.

Uses and Administration

Fluorouracil, an analogue of the pyrimidine uracil, is an antineoplastic that acts as an antimetabolite. After intracellular conversion to the active deoxynucleotide it interferes with the synthesis of DNA by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase. It can also interfere with RNA synthesis.

Fluorouracil is used alone or in combination in the adjuvant and palliative treatment of gastrointestinal cancer. In this setting it may be combined with folinic acid (see Administration, below). Fluorouracil is often given with cyclophosphamide and methotrexate or doxorubicin in the adjuvant treatment of breast cancer. It may also be used in the palliation of other malignant neoplasms such as those of the head and neck, liver, and pancreas. In addition, it may be used topically for treating malignant or premalignant lesions of the skin. Its use in these malignancies is further discussed under Choice of Antineoplastic as indicated by the cross-references given below.

Many dosage regimens have been used. Although it is most often given in combination regimens for the treatment of malignancy, many of the licensed dosage regimens relate to single-agent use. Such licensed regimens include:

- by *intravenous injection*, usual doses of 12 mg/kg daily (to a maximum of 0.8 to 1 g daily) for 3 or 4 days. If there is no evidence of toxicity, this may be followed after 1 day by 6 mg/kg on alternate days for 3 or 4 further doses. An alternative schedule is to give 15 mg/kg intravenously once a week throughout the course. The course may be repeated after 4 to 6 weeks or maintenance doses of 5 to 15 mg/kg to a maximum of 1 g may be given weekly.
- by *intravenous infusion*, usual doses of 15 mg/kg daily (to a maximum of 1 g daily) being infused in 500 mL of sodium chloride 0.9% or glucose 5% over 4 hours and repeated on successive days until toxicity occurs or a total of 12 to 15 g has been given. *Continuous infusion* may also be used. The course may be repeated after 4 to 6 weeks.
- by continuous *intra-arterial infusion*, in doses of 5 to 7.5 mg/kg daily (regional perfusion).
- by *mouth*, although the parenteral route is generally preferred, a dose of 15 mg/kg, to a maximum of 1 g in one day, has been given once weekly for maintenance.

Suggested regimens with folinic acid include:

- 200 mg/m^2 of folinic acid (as calcium folinate) by slow intravenous injection followed immediately by an intravenous bolus of fluorouracil 370 mg/m^2; the treatment is given daily for 5 consecutive days, and may be repeated every 4 to 5 weeks
- lower doses of folinic acid (20 mg/m^2) followed by fluorouracil 425 mg/m^2 for 5 consecutive days, repeated every 4 to 5 weeks (the Mayo regimen)
- an initial dose of 200 mg/m^2 of folinic acid, followed by fluorouracil 400 mg/m^2 as an initial intravenous bolus injection and then 600 mg/m^2 by continuous intravenous infusion. This dosage is given for 2 consecutive days every 2 weeks (the de Gramont regimen)

The white cell count should be determined frequently during treatment with fluorouracil and therapy stopped immediately if the count falls rapidly or if the white cell or platelet count falls below acceptable levels (see also Bone-marrow Depression, p.639) or if severe adverse effects occur. Doses should be reduced by up to half in patients with poor nutritional status, impaired bone-marrow, hepatic, or renal function, and within 30 days of major surgery.

Fluorouracil is used topically in the treatment of solar (actinic) keratoses and other superficial tumours and premalignant conditions of the skin including Bowen's disease and superficial basal cell carcinomas. For actinic keratosis it is usually applied as a 0.5 to 5% cream or as a 1 to 5% solution in propylene glycol once or twice daily for 2 to 4 weeks; the higher strength may be applied for at least 3 to 6 weeks for superficial basal cell carcinomas.

Administration. Modulation of fluorouracil by other drugs has been tried in an effort to enhance its effects, particularly in the treatment of colorectal cancer (p.665).

Folinic acid has been extensively used to modulate the effects of fluorouracil, and has become the agent of choice. Various regimens have been used, modifying the fluorouracil schedule (continuous infusion versus bolus), folinic acid dose (low-dose versus high-dose) and the regimen frequency (monthly, bimonthly, or weekly). Despite numerous studies, the optimum regimen in terms of efficacy and tolerability has yet to be determined.

In the adjuvant setting, a large-scale randomised trial[1] found no difference in efficacy between low-dose and high-dose folinic acid when added to fluorouracil given either once weekly for 30 doses, or for 5 consecutive days per month over 6 months. Fluorouracil and low-dose folinic acid may therefore become the preferred regimen in the adjuvant setting.

In the palliation of advanced disease, meta-analyses have revealed the value of the addition of folinic acid to fluorouracil,[2] and the use of infusions rather than bolus fluorouracil,[3] in terms of response rates. An updated meta-analysis confirmed the benefit of addition of folinic acid to fluorouracil in terms of response rate, and found a small but statistically significant advantage in terms of overall survival. Survival benefit was restricted to trials using the same dose of fluorouracil in the treatment arms (fluorouracil alone versus fluorouracil and folinic acid), suggesting that the benefit of modulation with folinic acid could be compensated by an increase of fluorouracil dose in the fluorouracil alone arm. However, increased toxicity from high-dose fluorouracil might occur.[4] The data for low-dose folinic acid versus high-dose are less clear.[5] In 1 randomised trial,[6] a bimonthly infusion regimen of fluorouracil plus high-dose folinic acid (the de Gramont regimen[7]) was more effective than a monthly bolus regimen of fluorouracil plus low-dose folinic acid. Further studies comparing the effect of high- and low-dose folinic acid added to the same schedule of continuous infusion fluorouracil are required.

Interferon alfa also appears to modify[8] the actions of fluorouracil (see also under Interactions, above), and has been investigated in combination with fluorouracil and folinic acid. Although some early results were promising, later randomised controlled trials failed to show any benefit for the addition of interferon alfa to fluorouracil or fluorouracil plus folinic acid.[8] It is not clear whether interferon beta will prove of any greater benefit.

Based on the results of early adjuvant studies, *levamisole* was used as standard therapy to modulate fluorouracil, particularly in the USA. However, more recent trials indicate that levamisole is no more effective than placebo when added to fluorouracil,[1] or to fluorouracil plus folinic acid.[9]

Methotrexate has also been used to modulate fluorouracil. Meta-analysis of several studies of fluorouracil preceded by methotrexate found that the combination doubled the response rate to fluorouracil in metastatic colorectal cancer and produced some survival benefits.[10] (Combination in the reverse order, i.e. methotrexate preceded by fluorouracil, may reduce methotrexate toxicity—see under Treatment of Adverse Effects, p.747.)

1. QUASAR Collaborative Group. Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. *Lancet* 2000; **355:** 1588–96.
2. Advanced Colorectal Cancer Meta-analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol* 1992; **10:** 896–903.
3. Meta-analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol* 1998; **16:** 301–8.
4. The Meta-Analysis Group in Cancer. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: an updated meta-analysis. *J Clin Oncol* 2004; **22:** 3766–75. Correction. *ibid.* 2005; **23:** 1337–8.
5. Rustum YM, *et al.* Rationale for treatment design: biochemical modulation of 5-fluorouracil by leucovorin. *Cancer J Sci Am* 1998; **4:** 12–18.
6. de Gramont A, *et al.* Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French Intergroup study. *J Clin Oncol* 1997; **15:** 808–15.
7. de Gramont A, *et al.* A review of GERCOD trials of bimonthly leucovorin plus 5-fluorouracil 48-h continuous infusion in advanced colorectal cancer: evolution of a regimen. *Eur J Cancer* 1998; **34:** 619–26.
8. Makower D, Wadler S. Interferons as biomodulators of fluoropyrimidines in the treatment of colorectal cancer. *Semin Oncol* 1999; **26:** 663–71.
9. Wolmark N, *et al.* Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project C-04. *J Clin Oncol* 1999; **17:** 3553–9.
10. Advanced Colorectal Cancer Meta-analysis Project. Meta-analysis of randomized trials testing the biochemical modulation of fluorouracil by methotrexate in metastatic colorectal cancer. *J Clin Oncol* 1994; **12:** 960–9.

Darier's disease. Two patients with resistant Darier's disease (p.1578) receiving long-term oral retinoid therapy responded to treatment with topical fluorouracil applied as a 1% cream once daily.[1] There was complete clearance of skin lesions after 3 weeks of treatment.

1. Knulst AC, *et al.* Topical 5-fluorouracil in the treatment of Darier's disease. *Br J Dermatol* 1995; **133:** 463–6.

Eye disorders. Aside from its use in glaucoma surgery (below), fluorouracil has been used adjunctively in other ocular surgery. It has also shown promising results in the treatment of ocular surface malignancies.[1]

1. Abraham LM, *et al.* The clinical applications of fluorouracil in ophthalmic practice. *Drugs* 2007; **67:** 237–55.

Glaucoma. A regimen of subconjunctival injections of fluorouracil is effective in improving the outcome of glaucoma filtering surgery[1-3] in selected patients when used as an adjunct to prevent the formation of scar tissue (see p.1873). However, in view of the increased risk of late-onset conjunctival wound leaks caution has been suggested in its use in eyes with a good prognosis.[3] Although one study[4] found that fluorouracil improved the success rate of combined glaucoma filtering surgery and cataract surgery earlier studies had failed to demonstrate any advantage.[5,6] A systematic review[7] of these and 2 other studies concluded that fluorouracil reduced the risk of surgical failure of trabeculectomy in eyes at high risk of failure, and in those undergoing surgery for the first time, but noted that the methodological quality of the studies was not high, and that this practice has largely been superseded by the use of intra-operative mitomycin. However, a later survey[8] in the UK found that the use of antimetabolites in glaucoma surgery was much less common than in the USA or Japan, and that fluorouracil was strongly preferred to mitomycin.

Intra-operative topical application of fluorouracil has been tried as an alternative to subconjunctival injection with conflicting results.[9-11]

1. Ophir A, Ticho U. A randomized study of trabeculectomy and subconjunctival administration of fluorouracil in primary glaucomas. *Arch Ophthalmol* 1992; **110:** 1072–5.
2. Goldenfeld M, *et al.* 5-Fluorouracil in initial trabeculectomy: a prospective, randomized, multicenter study. *Ophthalmology* 1994; **101:** 1024–9.
3. The Fluorouracil Filtering Surgery Study Group. Five-year follow-up of the Fluorouracil Filtering Surgery Study. *Am J Ophthalmol* 1996; **121:** 349–66.
4. Gandolfi SA, Vecchi M. 5-Fluorouracil in combined trabeculectomy and clear-cornea phacoemulsification with posterior chamber intraocular lens implantation: a one-year randomized, controlled clinical trial. *Ophthalmology* 1997; **104:** 181–6.
5. Wong PC, *et al.* 5-Fluorouracil after primary combined filtration surgery. *Am J Ophthalmol* 1994; **117:** 149–54.
6. O'Grady JM, *et al.* Trabeculectomy, phacoemulsification, and posterior chamber lens implantation with and without 5-fluorouracil. *Am J Ophthalmol* 1993; **116:** 594–9.
7. Wormald R, *et al.* Post-operative 5-fluorouracil for glaucoma surgery. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 12/05/05).
8. Siriwardena D, *et al.* National survey of antimetabolite use in glaucoma surgery in the United Kingdom. *Br J Ophthalmol* 2004; **88:** 873–6.
9. Egbert PR, *et al.* A prospective trial of intraoperative fluorouracil during trabeculectomy in a black population. *Am J Ophthalmol* 1993; **116:** 612–16.
10. Lachkar Y, *et al.* Trabeculectomy with intraoperative sponge 5-fluorouracil in Afro-Caribbeans. *Br J Ophthalmol* 1997; **81:** 555–8.
11. Yorston D, Khaw PT. A randomised trial of the effect of intraoperative 5-FU on the outcome of trabeculectomy in east Africa. *Br J Ophthalmol* 2001; **85:** 1028–30.

Malignant neoplasms. Fluorouracil plays an important role in the adjuvant treatment of gastrointestinal cancer, as discussed on p.664, and has been widely used in adjuvant regimens for early breast cancer (p.661). It may also be employed in the management of a wide variety of other malignancies including pancreatic endocrine tumours (p.643), cancers of the cervix (p.663) and head and neck (p.666), liver metastases (p.667), and tumours of the exocrine pancreas (p.671). It is reported to have only modest activity in neoplasms of the kidney (p.667). In addition, it is sometimes applied topically as part of the management of malignant or pre-malignant lesions of the skin (see Basal Cell and Squamous Cell Carcinoma, p.673), or surface neoplasia of the eye (p.664).

The role of fluorouracil in chemoradiotherapy of various malignancies has been reviewed.[1]

1. Rich TA, *et al.* Four decades of continuing innovation with fluorouracil: current and future approaches to fluorouracil chemoradiation therapy. *J Clin Oncol* 2004; **22:** 2214–32.

Toxoplasmosis. For mention of the use of fluorouracil with clindamycin to treat cerebral toxoplasmosis, see p.253.

Warts. Fluorouracil has been used, as a 1% or, more usually, a 5% cream or solution in the treatment of genital warts (condylomata acuminata).[1-3] It has been tried as an adjuvant to laser therapy in severe papillomavirus-associated vulvar disease,[4] with variable results, and in men with subclinical or clinically apparent penile lesions.[5] A preparation of fluorouracil 3% in a collagen gel basis, together with adrenaline as a local vasoconstrictor, has been tried by injection into genital warts.[6] A combination of fluorouracil 0.5% and salicylic acid 10% has also been stated to be effective in the topical treatment of common and plantar warts.[7] For a discussion of the various agents, including cytotoxics such as fluorouracil, employed to produce destruction of warts, see p.1584.

1. Kling AR. Genital warts—therapy. *Semin Dermatol* 1992; **11:** 247–55.
2. Stone KM. Human papillomavirus infection and genital warts: update on epidemiology and treatment. *Clin Infect Dis* 1995; **20** (suppl 1): S91–7.
3. Beutner KR, Ferenczy A. Therapeutic approaches to genital warts. *Am J Med* 1997; **102:** 28–37.
4. Reid R, *et al.* Superficial laser vulvectomy IV: extended laser vaporization and adjunctive 5-fluorouracil therapy of human papillomavirus-associated vulvar disease. *Obstet Gynecol* 1990; **76:** 439–48.
5. Bergman A, Nalick R. Genital human papillomavirus infection in men: diagnosis and treatment with a laser and 5-fluorouracil. *J Reprod Med* 1991; **36:** 363–6.
6. Swinehart JM, *et al.* Intralesional fluorouracil/epinephrine injectable gel for treatment of condylomata acuminata: a phase 3 clinical study. *Arch Dermatol* 1997; **133:** 67–73.
7. Zschocke I, *et al.* Wirksamkeit und Nutzen eines 5-FU-/Salicylsäure-haltigen Präparates in der Therapie vulgärer und plantarer Warzen—systematische Literaturübersicht und Metaanalyse. *J Dtsch Dermatol Ges* 2004; **2:** 187–93.

Preparations

BP 2008: Fluorouracil Cream; Fluorouracil Injection;
USP 31: Fluorouracil Cream; Fluorouracil Injection; Fluorouracil Topical Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Cinco-Fu†; Efudix; Ifocid†; Oncofu†; Triosules; ***Austral.:*** Efudix; ***Belg.:*** Efudix; Fluracedyl; Fluroblastine; ***Braz.:*** Killit†; Utoral†; ***Canad.:*** Adrucil†; Efudex; ***Chile:*** Efudix; Fluoracilo; ***Cz.:*** La-Fu; ***Denm.:*** Flurablastin; ***Fin.:*** Flurablastin; ***Fr.:*** Efudix; ***Ger.:*** Efudix; Neofluor; O-fluor†; Onkofluor; Ribofluor; ***Gr.:*** Uracifor; ***Hong Kong:*** Efudix†; ***Hung.:*** Efudix; ***India:*** Fivefluro; Florac; Fluracil; ***Indon.:*** Curacil; Fluracedyl; ***Irl.:*** Efudix; ***Israel:*** Efudix; ***Ital.:*** Efudix; ***Malaysia:*** Fluracedyl; ***Mex.:*** Efudix; Flurox; Ifacil†; Tecflu; ***Neth.:*** Efudix; Fluracedyl; ***Norw.:*** Flurablastin; ***NZ:*** Efudix; ***Philipp.:*** Fivoflu; Fluoxan; Fluracedyl; Fluroblastin; Uflahex; Utoral; ***Pol.:*** Efudix; ***Port.:*** Cinkef-U; ***Rus.:*** Flurox (Флуроκс)†; ***S.Afr.:*** Efudix; Fluroblastin; ***Singapore:*** Efudix; ***Spain:*** Efudix†; ***Swed.:*** Flurablastin; Fluracedyl†; ***Switz.:*** Efudix; ***Thai.:*** Fivoflu; Fluracedyl†; Flurox; ***UK:*** Efudix; ***USA:*** Adrucil; Carac; Efudex; Fluoroplex; ***Venez.:*** Fivoflu; Fluroblastin.

Multi-ingredient: ***Austria:*** Verrumal; ***Braz.:*** Efurix; ***Cz.:*** Verrumal; ***Ger.:*** Verrumal; ***Gr.:*** Verruca Hermal; ***Hong Kong:*** Verrumal; ***Hung.:*** Verrumal; ***Israel:*** Verrumal; Verucid†; ***Malaysia:*** Verrumal; ***Pol.:*** Verrumal; ***Port.:*** Verrucare; Verrumal; ***Singapore:*** Verrumal; ***Switz.:*** Verrumal; ***Thai.:*** Verrumal; ***Turk.:*** Verrutol.

Flutamide *(BAN, USAN, rINN)*

Flutamid; Flutamida; Flutamidas; Flutamidi; Flutamidum; Sch-13521. α′,α′,α′-Trifluoro-4′-nitroisobutyro-*m*-toluidide; α,α,α-Trifluoro-2-methyl-4′-nitro-*m*-propionotoluidide.

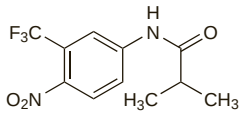
Флутамид

$C_{11}H_{11}F_3N_2O_3$ = 276.2.

CAS — 13311-84-7.

ATC — L02BB01.

ATC Vet — QL02BB01.



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

Ph. Eur. 6.2 (Flutamide). A pale yellow, crystalline powder. Practically insoluble in water; freely soluble in alcohol and in acetone. Protect from light.

USP 31 (Flutamide). A pale yellow, crystalline powder. Practically insoluble in water, in liquid paraffin, and in petroleum spirit; freely soluble in acetone, in ethyl acetate, and in methyl alcohol; soluble in chloroform and in ether. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

The most frequently reported adverse effects with flutamide are hot flushes and reversible gynaecomastia or breast tenderness, sometimes accompanied by galactorrhoea. Nausea, vomiting, diarrhoea, increased appetite, anorexia, and sleep disturbances may occur. There have been reports of skin reactions, including epidermal necrolysis, and of liver damage, sometimes fatal. Other adverse effects reported in patients receiving flutamide include anaemias, haemolysis, headache, dizziness, malaise, blurred vision, anxiety, depression, decreased libido, impotence, and hypertension. Abdominal pain, chest pain, dyspnoea, and cough have been reported rarely. Discoloration of the urine to amber or yellow-green can be caused by the presence of flutamide and/or its metabolites.

Flutamide should be used with care in patients with cardiovascular disease because of the possibility of fluid retention. It should also be used with caution in patients with hepatic impairment and is contra-indicated in those with severe impairment. Regular liver function testing is recommended in all patients: therapy should be stopped or dosage reduced if there is evidence of hepatotoxicity.

Effects on the blood. A report[1] of methaemoglobinaemia in an elderly man was attributed to flutamide. A study[2] of 45 patients given flutamide found no cases of methaemoglobinaemia, but the authors noted a further 3 published case reports.

1. Schott AM, *et al.* Flutamide-induced methemoglobinemia. *DICP Ann Pharmacother* 1991; **25:** 600–1.
2. Schulz M, *et al.* Lack of methemoglobinemia with flutamide. *Ann Pharmacother* 2001; **35:** 21–5.

Effects on the liver. Hepatitis occurred in a 79-year-old man taking flutamide 750 mg daily as sole therapy after a prostatectomy,[1] but a subsequent study[2] in 1091 patients given flutamide 250 mg three times daily as part of a regimen for prostate cancer found marked signs of liver damage only in 4, of whom only 2 had clinical evidence of hepatotoxicity. In the USA, the FDA had 46 reports of patients with hepatotoxicity associated with flutamide up to December 1994. Of these patients, 20 died from progressive liver disease.[3] Further cases have continued to be reported.[4-6] Early tapering of the dose, stopping therapy, or switching to another anti-androgen may resolve hepatotoxic effects.[7] Patients with chronic viral hepatitis may be at higher risk of developing hepatotoxicity with anti-androgen therapy.[8]

1. Hart W, Stricker BHC. Flutamide and hepatitis. *Ann Intern Med* 1989; **110:** 943–4.
2. Gomez J-L, *et al.* Incidence of liver toxicity associated with the use of flutamide in prostate cancer patients. *Am J Med* 1992; **92:** 465–70.
3. Wysowski DK, Fourcroy JL. Flutamide hepatotoxicity. *J Urol (Baltimore)* 1996; **155:** 209–12. Correction *ibid:* 396.
4. Garcia Cortes M, *et al.* Flutamide-induced hepatotoxicity: report of a case series. *Rev Esp Enferm Dig* 2001; **93:** 423–32. Correction. *ibid.*; 634.
5. Lubbert C, *et al.* Ikterus und schwere Leberfunktionsstorung bei der hormonablativen Behandlung des Prostatakarzinoms. *Internist (Berl)* 2004; **45:** 333–40.
6. Osculati A, Castiglioni C. Fatal liver complications with flutamide. *Lancet* 2006; **367:** 1140–1.
7. Lin ADY, *et al.* Antiandrogen-associated hepatotoxicity in the management of advanced prostate cancer. *J Chin Med Assoc* 2003; **66:** 735–40.
8. Pu Y-S, *et al.* Antiandrogen hepatotoxicity in patients with chronic viral hepatitis. *Eur Urol* 1999; **36:** 293–7.

Effects on the lungs. In a review[1] of 78 cases of pneumonitis reported to the FDA between 1998 and 2000 that were associated with bicalutamide, flutamide, or nilutamide, it was found that 14 patients had died of respiratory failure. It was estimated that the incidence of pneumonitis was highest for nilutamide (0.77%), but lower for flutamide (0.04%) and bicalutamide (0.01%).

1. Bennett CL, *et al.* Pneumonitis associated with nonsteroidal antiandrogens: presumptive evidence of a class effect. *Ann Intern Med* 2002; **137:** 625.

Effects on the skin. Photosensitivity reactions have been reported in patients receiving flutamide.[1,2] Some consider it to be an early manifestation of SLE.[2]

1. Fujimoto M, *et al.* Photosensitive dermatitis induced by flutamide. *Br J Dermatol* 1996; **135:** 496–7.
2. Kaur C, Thami GP. Flutamide-induced photosensitivity: is it a forme fruste of lupus? *Br J Dermatol* 2003; **148:** 603–4.

Gynaecomastia. Gynaecomastia (p.2092) and breast pain are frequent adverse effects of nonsteroidal anti-androgens used to treat prostate cancer. Nearly 90% of patients treated with bicalutamide in the Early Prostate Cancer programme experienced breast pain, gynaecomastia, or both.[1] Some patients who develop gynaecomastia will accept it as a tolerable adverse effect of therapy but others will require specific treatment, and a number of different measures have been tried for both prevention and treatment. The risk of breast changes can be reduced by the use of prophylactic low-dose irradiation of the breast area before nonsteroidal anti-androgen therapy is started. However, skin irritation can occur, and the long-term risk for development of breast cancer is unknown. Irradiation is unlikely to be effective once breast enlargement has occurred but it can help to reduce pain. Empirical use of oral analgesics or topical local anaesthetics may be considered for breast pain. Specific surgical treatment to reduce breast tissue includes liposuction and breast tissue excision.[2,3]

Hormonal therapy using tamoxifen or anastrozole has been suggested, largely based on reports of benefit in various patient groups with gynaecomastia.[1,2] Two randomised controlled studies[4,5] of men who were treated with bicalutamide for prostate cancer found that prophylactic tamoxifen was effective for the prevention of gynaecomastia and breast pain, but that anastrozole was no better than placebo. One of these studies[5] also assessed the use of these drugs as treatment and found that gynaecomastia and breast pain resolved in at least 65% of patients treated with tamoxifen, but only in about 18% of those treated with anastrozole. Tamoxifen is considered to be more effective than radiotherapy for prevention of gynaecomastia.[3]

1. Sieber PR. Treatment of bicalutamide-induced breast events. *Expert Rev Anticancer Ther* 2007; **7:** 1773–9.
2. Leibovitch I, *et al.* Management options for gynaecomastia and breast pain associated with nonsteroidal antiandrogen therapy: case studies in context. *Clin Drug Invest* 2003; **23:** 205–15.
3. Di Lorenzo G, *et al.* Management of gynaecomastia in patients with prostate cancer: a systematic review. *Lancet Oncol* 2005; **6:** 972–9.
4. Boccardo F, *et al.* Evaluation of tamoxifen and anastrozole in the prevention of gynecomastia and breast pain induced by bicalutamide monotherapy of prostate cancer. *J Clin Oncol* 2005; **23:** 808–15.
5. Saltzstein D, *et al.* Prevention and management of bicalutamide-induced gynecomastia and breast pain: randomized endocrinologic and clinical studies with tamoxifen and anastrozole. *Prostate Cancer Prostatic Dis* 2005; **8:** 75–83.

Interactions

Flutamide may increase the effect of warfarin, see Antineoplastics, p.1429.

Pharmacokinetics

Flutamide is reported to be rapidly and completely absorbed from the gastrointestinal tract with peak plasma concentrations occurring 1 hour after a dose. It is rapidly and extensively metabolised; the major metabolite (2-hydroxyflutamide) possesses anti-androgenic properties. The half-life of the metabolite is about 6 hours. Both flutamide and 2-hydroxyflutamide are more than 90% bound to plasma proteins. Excretion is mainly in the urine with only minor amounts appearing in the faeces.

◊ References.

1. Radwanski E, *et al.* Single and multiple dose pharmacokinetic evaluation of flutamide in normal geriatric volunteers. *J Clin Pharmacol* 1989; **29:** 554–8.

Uses and Administration

Flutamide is a nonsteroidal compound with anti-androgenic properties which appears to act by inhibiting the uptake and/or binding of androgens in target tissues. It is used, usually with gonadorelin analogues, in the palliative treatment of prostatic carcinoma (p.671). The usual oral dose is 250 mg three times daily. When used in combination therapy UK licensed product information recommends that flutamide treatment should be started at least 3 days before the gonadorelin analogue to suppress any 'flare' reaction; however, in some other countries it is recommended that treatment with both agents be begun simultaneously for optimum effect.

Congenital adrenal hyperplasia. For mention of the use of flutamide with testolactone to block androgenic effects in congenital adrenal hyperplasia, see p.1502.

Hirsutism. Anti-androgens (usually cyproterone or spironolactone) are widely used for the drug treatment of hirsutism (p.2089). Flutamide has no particular advantage in this context;[1,2] one study has found flutamide to be more effective than spironolactone in inhibiting hirsutism,[3] but others found them to be of similar efficacy,[4,5] and the risk of hepatotoxicity with flutamide is a problem.[2] Nonetheless, flutamide has continued to be investigated.[6-8]

1. Rittmaster RS. Hyperandrogenism—what is normal? *N Engl J Med* 1992; **327:** 194–6.
2. Rittmaster RS. Hirsutism. *Lancet* 1997; **349:** 191–5.
3. Cusan L, *et al.* Comparison of flutamide and spironolactone in the treatment of hirsutism: a randomized controlled trial. *Fertil Steril* 1994; **61:** 281–7.
4. Erenus M, *et al.* Comparison of the efficacy of spironolactone versus flutamide in the treatment of hirsutism. *Fertil Steril* 1994; **61:** 613–6.
5. Moghetti P, *et al.* Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2000; **85:** 89–94.
6. Muderris II, *et al.* Treatment of hirsutism with lowest-dose flutamide (62.5 mg/day). *Gynecol Endocrinol* 2000; **14:** 38–41.
7. Venturoli S, *et al.* Low-dose flutamide (125 mg/day) as maintenance therapy in the treatment of hirsutism. *Horm Res* 2001; **56:** 25–31.
8. Gambineri A, *et al.* Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 2004; **60:** 241–9.

Malignant neoplasms. Androgen blockade, which may include the use of flutamide, is used in the management of metastatic hormone-responsive prostate cancer (p.671); once the cancer begins to progress despite such therapy, stopping flutamide occasionally produces paradoxical disease regression. Promising preliminary results have also followed the use of flutamide in patients with adenocarcinoma of the pancreas (p.671).

Polycystic ovary syndrome. Flutamide has been used, usually with metformin, in the management of polycystic ovary syndrome (p.2080);[1-4] additive effects have been reported with this combination.

1. Ibáñez L, *et al.* Additive effects of insulin-sensitizing and antiandrogen treatment in young nonobese women with hyperinsulinism, hyperandrogenism, dyslipidemia, and anovulation. *J Clin Endocrinol Metab* 2002; **87:** 2870–4.
2. Ibáñez L, *et al.* Low-dose flutamide-metformin therapy reverses insulin resistance and reduces fat mass in nonobese adolescents with ovarian hyperandrogenism. *J Clin Endocrinol Metab* 2003; **88:** 2600–6.
3. Gambineri A, *et al.* Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 2004; **60:** 241–9.
4. Gambineri A, *et al.* Treatment with flutamide, metformin, and their combination added to a hypocaloric diet in overweight-obese women with polycystic ovary syndrome: a randomized, 12-month, placebo-controlled study. *J Clin Endocrinol Metab* 2006; **91:** 3970–80.

Preparations

USP 31: Flutamide Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: Asoflut; Dedile; Eulexin†; Flutaplex; Flutax†; Flutepan; Flutrax; FTDA†; Olter†; ***Austral.:*** Eulexin; Flutamin; Fugerel†; ***Austria:*** Afluta; Androbloc; Flutabene; Flutahexal; Flutastad; Fugerel; ***Belg.:*** Eulexin; Flutaplex; ***Braz.:*** Biomida†; Eulexin; Tecnoflut; Teflut; ***Canad.:*** Euflex; ***Chile:*** Androdor†; Drogenil; Etaconil; Flulem; ***Cz.:*** Andraxan; Flucinom; Flumed; Flutacan†; Flutaplex; Prostandril; Xadaren†; ***Denm.:*** Eulexin; Fluprosin; Flutacan†; Profamid; ***Fin.:*** Eulexin; Profamid; ***Fr.:*** Eulexine; Prostadirex; ***Ger.:*** Apimid†; Flumid; Fluta; Flutexin†; Fugerel; Prostica; Prostogenat†; Testotard†; ***Gr.:*** Adiprost; Andraxan; Elbat; Flucinom; Flutaplex; Palistop; Prostamide; Rikital; Tremexal; ***Hong Kong:*** Flutan†; Fugerel; ***Hung.:*** Cytamid†; Fluprost; Flutam; Flutasin; Fugerel; ***India:*** Cytomid; Prostamid; ***Indon.:*** Flutaplex; Fugerel; ***Irl.:*** Androstat; Drogenil; ***Israel:*** Eulexin; ***Ital.:*** Drogenil†; Eulexin; Fluprost; Virflutam†; ***Malaysia:*** Flutan†; Flutaplex; Fugerel†; ***Mex.:*** Eulexin; Flimutal; Fluken†; Flulem; Tafenil; ***Neth.:*** Drogenil; Eulexin; Flutaplex; Prostatil; ***Norw.:*** Eulexin; ***NZ:*** Eulexin; Flutamin; Flutol†; ***Philipp.:*** Fugerel; Prostanon; ***Pol.:*** Apo-Flutam; Fugerel; Prostandril; ***Port.:*** Drogenil; Eulexin; Prosneo; ***Rus.:*** Flutamid (Флутамид); Flutaplex (Флутаплекс); ***S.Afr.:*** Eulexin; Flutahexal; Flutaplex; ***Singapore:*** Flutan; Fugerel†; ***Spain:*** Eulexin; Flutandrona; Flutaplex†; Grisetin; Oncosal; Prostacur; ***Swed.:*** Eulexin; Flutacan†; ***Switz.:*** Flucinome; ***Thai.:*** Andraxan; Flulem; Flutan; Flutaplex; Fugerel; ***Turk.:*** Andraxan; Eulexin; ***UK:*** Chimax; Drogenil; ***USA:*** Eulexin†; ***Venez.:*** Etaconil; Eulexin.