Effects on the kidneys. For a report of haemolytic-uraemic syndrome after the use of bevacizumab and sunitinib, see Effects on the Kidneys, under Bevacizumab, p.685.

Effects on the nervous system. Coma has been reported with sunitinib; therapy was immediately stopped and the patient regained consciousness within 24 hours.[1]

1. Arnaud L, *et al.* Transient sunitinib-induced coma in a patient with fibromyxoid sarcoma. *J Clin Oncol* 2008; **26:** 1569–71.

Effects on the skin. A patient developed palmar-plantar syndrome and rashes resembling seborrhoeic dermatitis while taking sunitinib. Therapy was stopped and the rash was treated with a topical corticosteroid; blisters on the palms and soles resolved with desquamation.[1]

1. Tsai K-Y, *et al.* Hand-foot syndrome and seborrheic dermatitis-like rash induced by sunitinib in a patient with advanced renal cell carcinoma. *J Clin Oncol* 2006; **24:** 5786–8.

Effects on thyroid function. Hypothyroidism is common after sunitinib therapy. A cohort study found that 36% of patients developed hypothyroidism after an average of 50 weeks of therapy. The incidence of hypothyroidism increased with the duration of therapy, and the effect was not transient; patients needed replacement therapy with levothyroxine. Mild thyrotoxicosis may precede the onset of hypothyroidism. Although the mechanism is not clear, the drug may cause destructive thyroiditis. Patients should be screened for hypothyroidism and serum concentrations of thyroid-stimulating hormone (TSH) measured at suggested intervals of 2 to 3 months.[1]

1. Desai J, *et al.* Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. *Ann Intern Med* 2006; **145:** 660–4.

Tumour lysis syndrome. Tumour lysis syndrome has been reported after treatment with sunitinib; electrolytes and renal function should be closely monitored.[1,2]

1. Nicholaou T, *et al.* Tumour lysis syndrome in a patient with renal-cell carcinoma treated with sunitinib malate. *Lancet* 2007; **369:** 1923–4.
2. Saylor PJ, Reid TR. Tumor lysis syndrome after treatment of a gastrointestinal stromal tumor with the oral tyrosine kinase inhibitor sunitinib. *J Clin Oncol* 2007; **25:** 3544–6.

Interactions

Sunitinib is metabolised primarily by the cytochrome P450 isoenzyme CYP3A4 to produce an active metabolite, which is further metabolised by CYP3A4. Ketoconazole increased exposure to sunitinib, and use with other potent inhibitors of CYP3A4 (such as other azole antifungals, macrolide antibacterials, HIV-protease inhibitors, or grapefruit juice) may also increase sunitinib concentrations. Conversely, use with rifampicin decreased exposure to sunitinib, and inducers of CYP3A4 (such as dexamethasone, phenytoin, carbamazepine, phenobarbital, or St John's wort) may decrease plasma sunitinib concentrations. If the use of alternative drugs is not feasible, dose adjustments of sunitinib may be necessary (see Uses and Administration, below).

◊ The US manufacturer of *bevacizumab* has recommended that it should not be used with sunitinib after several patients receiving the combination had developed microangiopathic haemolytic anaemia.[1]

1. Genentech, USA. Important drug warning subject: microangiopathic hemolytic anemia (MAHA) in patients treated with Avastin (bevacizumab) and sunitinib malate (issued July 2008). Available at: http://www.fda.gov/medwatch/safety/2008/MAHA_DHCP.pdf (accessed 30/07/08)

Pharmacokinetics

Maximum plasma concentrations occur 6 to 12 hours after an oral dose of sunitinib. Bioavailability is unaffected by food. Sunitinib is metabolised mainly via the cytochrome P450 isoenzyme CYP3A4 to its primary active metabolite, which itself is then further metabolised via CYP3A4. Plasma protein binding of sunitinib and its metabolite is about 95% and 90%, respectively; plasma elimination half-lives are 40 to 60 hours, and 80 to 110 hours, respectively. Sunitinib is excreted mainly in faeces; about 16% is found in urine, as unchanged drug and metabolites.

Uses and Administration

Sunitinib malate is an inhibitor of several receptor tyrosine kinases. It is used for the treatment of gastrointestinal stromal tumours (see Soft-tissue Sarcoma, p.676) after disease progression during imatinib treatment, or in patients intolerant to imatinib. It is also used for the treatment of advanced and/or metastatic renal cell carcinoma (p.667).

Sunitinib is given orally as the malate, but doses are expressed in terms of the base; sunitinib malate 66.8 mg is equal to about 50 mg of sunitinib. The recommended dose is 50 mg once daily, for 4 weeks of a 6-week treatment cycle. Doses may be increased or decreased in steps of 12.5 mg, based on individual tolerability. UK licensed product information recommends that the daily dose should not normally exceed 75 mg nor be decreased below 25 mg.

Use of inhibitors or inducers of CYP3A4 may increase or decrease sunitinib plasma concentrations. If no alternative is available, a dose reduction of sunitinib to a minimum of 37.5 mg daily should be considered if it is given with a strong CYP3A4 inhibitor. Doses can be increased to a maximum of 87.5 mg daily if sunitinib is given with a CYP3A4 inducer; the patient should be closely monitored for toxicity.

◊ References.

1. Motzer RJ, *et al.* Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006; **24:** 16–24.
2. Faivre S, *et al.* Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J Clin Oncol* 2006; **24:** 25–35.
3. Motzer RJ, *et al.* Sunitinib malate for the treatment of solid tumours: a review of current clinical data. *Expert Opin Invest Drugs* 2006; **15:** 553–61.
4. Motzer RJ, *et al.* Sunitinib in patients with metastatic renal cell carcinoma. *JAMA* 2006; **295:** 2516–24.
5. Deeks ED, Keating GM. Sunitinib. *Drugs* 2006; **66:** 2255–66.
6. Demetri GD, *et al.* Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006; **368:** 1329–38.
7. Motzer RJ, *et al.* Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007; **356:** 115–24.
8. Goodman VL, *et al.* Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. *Clin Cancer Res* 2007; **13:** 1367–73.
9. O'Brien MF, *et al.* Sunitinib therapy in renal cell carcinoma. *BJU Int* 2008; **101:** 1339–42.
10. Socinski MA. The current status and evolving role of sunitinib in non-small cell lung cancer. *J Thorac Oncol* 2008; **3** (suppl 2): S119–S123.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Sutent; ***Austral.:*** Sutent; ***Braz.:*** Sutent; ***Cz.:*** Sutent; ***Fr.:*** Sutent; ***Gr.:*** Sutent; ***Hung.:*** Sutent; ***Malaysia:*** Sutent; ***NZ:*** Sutent; ***Port.:*** Sutent; ***UK:*** Sutent; ***USA:*** Sutent.

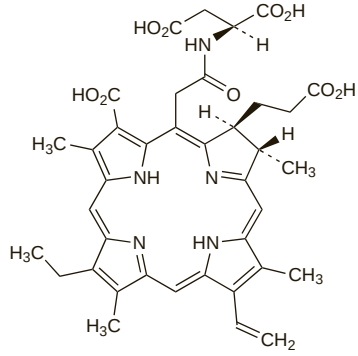
Talaporfin Sodium *(USAN, rINNM)*

LS-11; Monoaspartyl Chlorin e6 (talaporfin); Natrii Talaporfinum; NPe-6 (talaporfin); Talaporfina sódica; Talaporfine Sodique; Taporfin Sodium. Tetrasodium *N*-{[(7*S*,8*S*)-3-carboxy-7-(2-carboxyethyl)-13-ethenyl-18-ethyl-7,8-dihydro-2,8,12,17-tetramethyl-21*H*,23*H*-porphin-5-yl]acetyl}-L-aspartate.

Натрий Талапорфин

$C_{38}H_{41}N_5Na_4O_9$ = 803.7.

CAS — 110230-98-3 (talaporfin); 220201-34-3 (talaporfin sodium).



(talaporfin)

Profile

Talaporfin sodium is a photosensitiser that is used for the photodynamic therapy (see under Porfimer Sodium, p.764) of lung cancer. It is also under investigation for the treatment of other tumours.

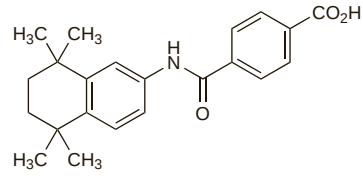
Tamibarotene *(rINN)*

AM-80; Tamibarotène; Tamibaroteno; Tamibarotenum. *N*-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)terephthalamic acid.

Тамибаротен

$C_{22}H_{25}NO_3$ = 351.4.

CAS — 94497-51-5.



Profile

Tamibarotene is a synthetic retinoid that is given orally for the treatment of relapsed or refractory acute promyelocytic leukaemia.

Malignant neoplasms. Tamibarotene has been used to induce remission in patients with acute promyelocytic leukaemia (see Acute Myeloid Leukaemias, p.652) who relapsed after successful remission induction with tretinoin.[1,2] Twenty-four patients received tamibarotene at a daily oral dose of 6 mg/m^2; 14 patients obtained complete remission after a median of 41 days.[1] Reported adverse effects include hypercholesterolaemia, hypertriglyceridaemia,[1,3] cheilitis, xerosis, gastrointestinal disturbances, bone pain, headache, dermatitis, liver damage, and leucocytosis; in one case, retinoic acid syndrome occurred.[1]

1. Tobita T, *et al.* Treatment with a new synthetic retinoid, Am80, of acute promyelocytic leukemia relapsed from complete remission induced by all-trans retinoic acid. *Blood* 1997; **90:** 967–73.
2. Shinjo K, *et al.* Good prognosis of patients with acute promyelocytic leukemia who achieved second complete remission (CR) with a new retinoid, Am80, after relapse from CR induced by all-trans-retinoic acid. *Int J Hematol* 2000; **72:** 470–3.
3. Takeuchi M, *et al.* Relapsed acute promyelocytic leukemia previously treated with all-trans retinoic acid: clinical experience with a new synthetic retinoid, Am-80. *Leuk Lymphoma* 1998; **31:** 441–51.

Preparations

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

Tamoxifen Citrate *(BANM, USAN, rINNM)* ⊗

Citrato de tamoxifeno; ICI-46474; Tamoksifeenisitraatti; Tamoksifen Sitrat; Tamoksifeno citratas; Tamoxifen citrát; Tamoxifencitrat; Tamoxifén-citrát; Tamoxifène, citrate de; Tamoxifeni citras. (*Z*)-2-[4-(1,2-Diphenylbut-1-enyl)phenoxy]ethyldimethylamine citrate.

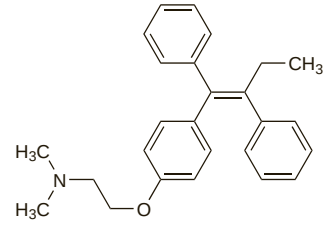
Тамоксифена Цитрат

$C_{26}H_{29}NO,C_6H_8O_7$ = 563.6.

CAS — 10540-29-1 (tamoxifen); 54965-24-1 (tamoxifen citrate).

ATC — L02BA01.

ATC Vet — QL02BA01.



(tamoxifen)

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

Ph. Eur. 6.2 (Tamoxifen Citrate). A white or almost white, polymorphic, crystalline powder. Slightly soluble in water and in acetone; soluble in methyl alcohol.

USP 31 (Tamoxifen Citrate). A white, fine, crystalline powder. Very slightly soluble in water, in alcohol, in acetone, and in chloroform; soluble in methyl alcohol. Protect from light.

Adverse Effects

The most frequent adverse effects of tamoxifen are hot flushes. Other adverse effects include fluid retention, nausea, gastrointestinal intolerance, vaginal bleeding or discharge, pruritus vulvae, rashes, dry skin, and alopecia. There have also been reports of dizziness, head-

ache, depression, confusion, fatigue, and muscle cramps. There may be an increased tendency to thromboembolism, and pulmonary embolism has occurred. Tumour pain and flare may be a sign of response, but hypercalcaemia, sometimes severe, has developed in patients with bony metastases. Transient thrombocytopenia and leucopenia have been reported. Blurred vision and loss of visual acuity, corneal opacities, retinopathies, and cataracts have occurred rarely. Tamoxifen has been associated with increased liver enzymes, and rarely with cholestasis and hepatitis. Hypertriglyceridaemia has occurred. Uterine fibroids and endometrial changes including hyperplasia and polyps may occur, and an increased incidence of endometrial carcinoma, and rarely uterine sarcoma, has been reported. Suppression of menstruation may occur in premenopausal women and cystic ovarian swellings have occasionally occurred. Very rare cases of interstitial pneumonitis have been reported.

Carcinogenicity. Tamoxifen has a stimulant effect on the endometrium (probably by acting as a partial oestrogen agonist) and its use has been associated with the development of endometrial polyps[1,2] and endometriosis,[3] and an increased risk of endometrial cancer.[4-6] The risk, which increases with duration of therapy, is generally agreed to be modest, and the clinical benefit in women with breast cancer outweighs any increased risk of endometrial neoplasm.[7-10] Women taking tamoxifen to prevent breast cancer have been estimated to have a 2.53-fold greater risk of developing endometrial carcinoma than untreated women.[11] The risk may increase with more prolonged use and a case-control study has reported that long-term (over 2 years) users may have a worse prognosis if endometrial cancer develops, due to less favourable history and stage.[12] Another case-control study showed that the relative risk of endometrial cancer increased with duration of tamoxifen treatment, up to at least 10 years. Risk was not associated with the daily dose of tamoxifen, and was comparable in pre- and postmenopausal women.[13]

It has been recommended that women with breast cancer taking tamoxifen should have annual gynaecological examinations, and any unusual symptoms, including abnormal bleeding or spotting should be investigated promptly.[14] Women taking tamoxifen for prophylaxis of breast cancer should be monitored carefully for endometrial hyperplasia. If atypical hyperplasia develops, tamoxifen should be stopped while the condition is treated and a hysterectomy should be considered before tamoxifen is re-started.[14] However, up to 39% of postmenopausal women taking tamoxifen show endometrial changes and as these seldom progress to cancer, the value of routine endometrial biopsies has been questioned.[8,9,14,15] Transvaginal ultrasonography has been used as a noninvasive method of endometrial screening, but has a high rate of false-positive results.[16] It has been suggested that colour doppler ultrasonography, which distinguishes vascularised lesions such as polyps and carcinomas from avascular atrophic lesions, may be a useful alternative.[17] There is some evidence that a levonorgestrel-releasing intra-uterine device can protect against the uterine changes induced by tamoxifen.[18]

Although rare, there is an increase in the risk of uterine sarcoma in women receiving tamoxifen. Between 1978, when tamoxifen was first marketed in the USA, and April 2001, the FDA was aware of 43 cases in women who had been receiving tamoxifen; there had also been reports in 116 women in other countries.[19] Although less than the expected rate in this population, this was considered to be due to underreporting. An evaluation of data from 39 451 breast cancer patients initially treated with tamoxifen found that the overall risk of uterine corpus cancer was more than doubled with the use of tamoxifen; the risk of rare but aggressive forms of uterine tumours, notably malignant mixed mullerian tumours, was increased more than fourfold.[20]

Tamoxifen has been shown to form DNA adducts in *rat* livers, and there has been speculation that it may cause liver cancer in humans. However, there is considerable interspecies variation in the metabolism of tamoxifen and several large-scale clinical trials did not find an increase in liver carcinogenicity in humans.[10] There is also little evidence of an increased relative risk of other secondary malignancies such as gastrointestinal or ovarian cancers.[10]

1. Corley D, *et al.* Postmenopausal bleeding from unusual endometrial polyps in women on chronic tamoxifen therapy. *Obstet Gynecol* 1992; **79:** 111–16.
2. Buijs C, *et al.* Tamoxifen and uterine abnormalities. *J Clin Oncol* 2004; **22:** 2505–7.
3. Cano A, *et al.* Tamoxifen and the uterus and endometrium. *Lancet* 1989, **i:** 376.
4. Fornander T, *et al.* Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. *Lancet* 1989; **i:** 117–20.
5. Gusberg SB. Tamoxifen for breast cancer: associated endometrial cancer. *Cancer* 1990; **65:** 1463–4.
6. van Leeuwen FE, *et al.* Risk of endometrial cancer after tamoxifen treatment of breast cancer. *Lancet* 1994; **343:** 448–52.
7. Baum M, *et al.* Endometrial cancer during tamoxifen treatment. *Lancet* 1994; **343:** 1291.
8. Bissett D, *et al.* Gynaecological monitoring during tamoxifen therapy. *Lancet* 1994; **344:** 1244.
9. Neven P, Vergote I. Should tamoxifen users be screened for endometrial lesions? *Lancet* 1998; **351:** 155–7.
10. Stearns V, Gelmann EP. Does tamoxifen cause cancer in humans? *J Clin Oncol* 1998; **16:** 779–92.
11. Fisher B, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998; **90:** 1371–88.
12. Bergman L, *et al.* Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. *Lancet* 2000; **356:** 881–7.
13. Swerdlow AJ, Jones ME. Tamoxifen treatment for breast cancer and risk of endometrial cancer: a case-control study. *J Natl Cancer Inst* 2005; **97:** 375–84.
14. American College of Obstetrics and Gynaecologists. ACOG Committee Opinion: tamoxifen and endometrial cancer. *Int J Gynaecol Obstet* 1996; **53:** 197–9.
15. Barakat RR, *et al.* Effect of adjuvant tamoxifen on the endometrium in women with breast cancer: a prospective study using office endometrial biopsy. *J Clin Oncol* 2000; **18:** 3459–63.
16. Gerber B, *et al.* Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound. *J Clin Oncol* 2000; **18:** 3464–70.
17. Aleem FA, Predanic M. Endometrial changes in patients on tamoxifen. *Lancet* 1995; **346:** 1292–3.
18. Gardner FJE, *et al.* Endometrial protection from tamoxifen-stimulated changes by a levonorgestrel-releasing intrauterine system: a randomised controlled trial. *Lancet* 2000; **356:** 1711–17.
19. Wysowski DK, *et al.* Uterine sarcoma associated with tamoxifen use. *N Engl J Med* 2002; **346:** 1832–3.
20. Curtis RE, *et al.* Risk of malignant mixed mullerian tumors after tamoxifen therapy for breast cancer. *J Natl Cancer Inst* 2004; **96:** 70–4.

Effects on the blood. Pancytopenia developed shortly after beginning tamoxifen therapy in an elderly woman, and persisted for some years;[1] the patient eventually developed very severe leucopenia and died of infection. Thrombocytopenia has also been reported.[2]

1. Miké V, *et al.* Fatal neutropenia associated with long-term tamoxifen therapy. *Lancet* 1994; **344:** 541–2.
2. Nasiroğlu N, *et al.* Tamoxifen induced-thrombocytopenia: it does occur. *Med Oncol* 2007; **24:** 453–4.

Effects on blood lipids. Tamoxifen has been reported to have a generally favourable effect on serum lipid profiles.[1] Patients with breast cancer and subsequent chemotherapy-induced ovarian failure developed marked increases in total cholesterol and low-density lipoprotein levels; adjuvant tamoxifen was found to decrease these serum lipid concentrations to below baseline concentrations. No significant changes in high-density lipoprotein or serum triglyceride concentrations were observed.[2] However, some cases of increased serum triglycerides in women with pre-existing hypertriglyceridaemia have been reported. Pancreatitis has also resulted. It has been suggested that tamoxifen should be used with caution in patients with hypertriglyceridaemia.[3,4]

1. Love RR, *et al.* Effects of tamoxifen on cardiovascular risk factors in postmenopausal women. *Ann Intern Med* 1991; **115:** 860–4.
2. Vehmanen L, *et al.* Tamoxifen treatment reverses the adverse effects of chemotherapy-induced ovarian failure on serum lipids. *Br J Cancer* 2004; **91:** 476–81.
3. Kanel KT, *et al.* Delayed severe hypertriglyceridaemia from tamoxifen. *N Engl J Med* 1997; **337:** 281.
4. Colls BM, George PM. Severe hypertriglyceridaemia and hypercholesterolaemia associated with tamoxifen use. *Clin Oncol* 1998; **10:** 270–1.

Effects on the cardiovascular system. ***ISCHAEMIC HEART DISEASE.*** For discussion of whether the effects of tamoxifen on lipid profiles can alter the incidence of ischaemic heart disease, see Cardiovascular Disorders under Uses and Administration, below.

STROKE. An excess risk of stroke was seen in tamoxifen compared with placebo recipients (5 cases versus 1) in a study of adjuvant tamoxifen.[1] A statistically non-significant increase in stroke was also seen in a study on the use of tamoxifen for breast cancer prevention (0.5 excess cases per 1000 women per year).[2] A meta-analysis[3] of 9 trials for prevention or treatment of breast cancer, involved data from 39 601 women, of whom 19 954 received tamoxifen. It concluded that use of tamoxifen increased the risk of ischaemic stroke by 82%, and the risk of any stroke by 29%; however, the absolute increase in risk was small.

In contrast, a case-control study of 11 045 women with breast cancer, found that tamoxifen use was not associated with an increased risk of first stroke.[4]

1. Dignam JJ, Fisher B. Occurrence of stroke with tamoxifen in NSABP B-24. *Lancet* 2000; **355:** 848–9.
2. Fisher B, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998; **90:** 1371–88.
3. Bushnell CD, Goldstein LB. Risk of ischemic stroke with tamoxifen treatment for breast cancer: a meta-analysis. *Neurology* 2004; **63:** 1230–3.
4. Geiger AM, *et al.* Stroke risk and tamoxifen therapy for breast cancer. *J Natl Cancer Inst* 2004; **96:** 1528–36.

THROMBOEMBOLISM. A case control study,[1] involving 25 cases of deep-vein thrombosis or pulmonary embolism among more than 10 000 women with breast cancer, suggested that current use of tamoxifen was associated with an estimated relative risk of developing idiopathic venous thromboembolism of 7.1 (95% confidence interval 1.5 to 33). Past use of tamoxifen was not associated with a materially increased risk. In a randomised placebo-controlled study, there was an increase in pulmonary emboli in women receiving tamoxifen for cancer prevention (excess of 0.46 cases per 1000 women per year).[2] The fatality rate from pulmonary emboli in tamoxifen recipients was about 17%. In this study, there was also a trend towards more deep-vein thrombosis in tamoxifen recipients. In another controlled study[3] of breast cancer prevention, tamoxifen approximately doubled the risk of developing a major thromboembolic event such as pulmonary embolism, deep-vein thrombosis, or retinal thrombosis. Cerebral sinus thrombosis has also been reported.[4] An analysis[5] of 4 tamoxifen prevention studies also found that venous thromboembolic events were increased in all studies, with a relative risk of 1.9 for those taking tamoxifen compared with placebo. However, another randomised study[6] found only a borderline significantly higher risk of developing venous thromboembolic events in those women allocated to tamoxifen; most of these events were superficial thrombophlebitis. Furthermore, women already at risk for atherosclerosis had a higher risk of venous thromboembolism. While the authors could not exclude a selection bias for healthier subjects in the study, they commented that the prothrombotic effect of tamoxifen may depend on the patient's existing endocrine status, and may be attenuated in those women taking HRT, especially when it is used transdermally.

1. Meier CR, Jick H. Tamoxifen and risk of idiopathic venous thromboembolism. *Br J Clin Pharmacol* 1998; **45:** 608–12.
2. Fisher B, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998; **90:** 1371–88.
3. Duggan C, *et al.* Inherited and acquired risk factors for venous thromboembolic disease among women taking tamoxifen to prevent breast cancer. *J Clin Oncol* 2003; **21:** 3588–93.
4. Masjuan J, *et al.* Tamoxifen: a new risk factor for cerebral sinus thrombosis. *Neurology* 2004; **62:** 334–5.
5. Cuzick J, *et al.* Overview of the main outcomes in breast-cancer prevention trials. *Lancet* 2003; **361:** 296–300.
6. Decensi A, *et al.* Effect of tamoxifen on venous thromboembolic events in a breast cancer prevention trial. *Circulation* 2005; **111:** 650–6.

Effects on the eyes. Tamoxifen has been reported to be associated with decreased visual acuity, corneal opacities and cataract, and retinopathy. The latter is sometimes progressive although in most cases it has shown improvement once the drug was stopped.[1] A prospective study in 63 patients taking tamoxifen 20 mg daily found evidence of decreased visual acuity, macular oedema, and retinal opacities in 4, occurring after 10 to 35 months of therapy.[2] A small excess risk of developing cataracts (3.1 extra per year per 1000 women) and of requiring cataract surgery (1.7 per year per 1000 women) was found in women taking tamoxifen for up to 5 years to reduce the risk of breast cancer.[3] Studies *in vitro* have suggested that cataract formation may be due to inhibition of chloride channels in the lens by tamoxifen or its hydroxy metabolite.[4] Retinopathy after high-dose tamoxifen treatment may be associated with crystalline deposition of the drug in the retina.[5]

1. Mihm LM, Barton TL. Tamoxifen-induced ocular toxicity. *Ann Pharmacother* 1994; **28:** 740–2.
2. Pavlidis NA, *et al.* Clear evidence that long-term, low-dose tamoxifen treatment can induce ocular toxicity. *Cancer* 1992; **69:** 2961–4.
3. Fisher B, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998; **90:** 1371–88.
4. Zhang JJ, *et al.* Tamoxifen blocks chloride channels: a possible mechanism for cataract formation. *J Clin Invest* 1994; **94:** 1690–7.
5. Bourla DH, *et al.* Peripheral retinopathy and maculopathy in high-dose tamoxifen therapy. *Am J Ophthalmol* 2007; **144:** 126–8.

Effects on the genito-urinary system. Persistent nocturnal priapism was reported in a man receiving tamoxifen 20 mg daily.[1] Symptoms abated within 24 hours of withdrawing the drug. Impotence has been reported in men receiving tamoxifen, and has been attributed to a paradoxical oestrogenic effect.[2]

1. Fernando IN, Tobias JS. Priapism in patient on tamoxifen. *Lancet* 1989; **i:** 436.
2. Collinson MP, *et al.* Two case reports of tamoxifen as a cause of impotence in male subjects with carcinoma of the breast. *Breast* 1993; **2:** 48–9.

Effects on the liver. Cholestasis and increased liver enzyme values have been reported on use of tamoxifen in a 75-year-old patient.[1] Enzyme activity rose again on rechallenge with tamoxifen. Fatal hepatocellular necrosis and agranulocytosis, possibly exacerbated by continuing to take the drug once jaundice developed, has also been reported;[2] the authors noted that 4 cases of hepatic failure (3 fatal) and 5 cases of hepatitis (1 fatal) had been reported to the UK CSM. Patients taking tamoxifen may also develop steatohepatitis,[3-7] which must be distinguished from alcohol-induced liver disease. Steatohepatitis is reversible on withdrawal of tamoxifen.[3,5,6] A study in healthy women who had had hysterectomies found the risk of steatohepatitis to be particularly high among obese women, moderately high among overweight women, and similar to that with placebo in women of normal weight.[8] Bezafibrate has been tried to prevent progression of steatohepatitis and permit continued use of tamoxifen.[9]

For a report of peliosis hepatis and liver haemorrhage in a patient receiving tamoxifen and warfarin, see under Interactions, below.

For reference to studies in *animals* suggesting that tamoxifen has the potential to cause liver cancer, see Carcinogenicity, above.

1. Blackburn AM, *et al.* Tamoxifen and liver damage. *BMJ* 1984; **289:** 288.
2. Ching CK, *et al.* Tamoxifen-associated hepatocellular damage and agranulocytosis. *Lancet* 1992; **339:** 940.
3. Pratt DS, *et al.* Tamoxifen-induced steatohepatitis. *Ann Intern Med* 1995; **123:** 236.
4. Van Hoof M, *et al.* Tamoxifen-induced steatohepatitis. *Ann Intern Med* 1996; **124:** 855–6.
5. Ogawa Y, *et al.* Tamoxifen-induced fatty liver in patients with breast cancer. *Lancet* 1998; **351:** 725.
6. Oien KA, *et al.* Cirrhosis with steatohepatitis after adjuvant tamoxifen. *Lancet* 1999; **353:** 36–7.
7. Osman KA, *et al.* Tamoxifen-induced non-alcoholic steatohepatitis: where are we now and where are we going? *Expert Opin Drug Saf* 2007; **6:** 1–4.
8. Bruno S, *et al.* Incidence and risk factors for non-alcoholic steatohepatitis: prospective study of 5408 women enrolled in Italian tamoxifen chemoprevention trial. *BMJ* 2005; **330:** 932–5.
9. Saibara T, *et al.* Bezafibrate for tamoxifen-induced non-alcoholic steatohepatitis. *Lancet* 1999; **353:** 1802.

Effects on the ovaries. Ovarian cysts are relatively common as an adverse effect in women receiving adjuvant tamoxifen: a study[1] in 95 such women reported the development of ovarian cysts in 6 of 16 (37.5%) who were premenopausal and in 5 of 79 postmenopausal women (6.3%). In 2 of the premenopausal women the cysts were complex. Two women underwent laparotomy for persistent cysts that were found to be benign, and 1 for leiomyoma; the cysts in the other 8 women resolved after withdrawal of tamoxifen. A study of 142 breast cancer patients receiving tamoxifen found ovarian cysts in 24 patients after treatment. Cyst development was more common in pre-menopausal women, patients with high oestrogen levels, and patients who did not receive high-dose chemotherapy.[2] There is little evidence that tamoxifen increases the risk of ovarian cancer (see Carcinogenicity, above).

1. Shushan A, *et al.* Ovarian cysts in premenopausal and postmenopausal tamoxifen-treated women with breast cancer. *Am J Obstet Gynecol* 1996; **174:** 141–4.
2. Mourits MJE, *et al.* Ovarian cysts in women receiving tamoxifen for breast cancer. *Br J Cancer* 1999; **79:** 1761–64.

Effects on the skin and hair. Vasculitis has been reported in patients given tamoxifen.[1,2] Withdrawal of the drug resulted in complete clearance of the lesions;[1,2] in one case, on re-introduction, purpura developed again within a few days.[1] The results suggest that tamoxifen can produce immune-mediated vascular damage.

In another report a patient with white hair developed darkening and repigmentation of the hair after about 2½ years of tamoxifen therapy.[3] Alopecia has also been reported in women given tamoxifen,[4,5] and in older patients the follicle may not recover.[4]

1. Drago F, *et al.* Tamoxifen and purpuric vasculitis. *Ann Intern Med* 1990; **112:** 965–6.
2. Baptista MZ, *et al.* Tamoxifen-related vasculitis. *J Clin Oncol* 2006; **24:** 3504–5.
3. Hampson JP, *et al.* Tamoxifen-induced hair colour change. *Br J Dermatol* 1995; **132:** 483–4.
4. Gateley CA, Bundred NJ. Alopecia and breast disease. *BMJ* 1997; **314:** 481.
5. Ayoub J-PM, *et al.* Tamoxifen-induced female androgenetic alopecia in a patient with breast cancer. *Ann Intern Med* 1997; **126:** 745–6.

Precautions

All patients being considered for treatment with tamoxifen should be assessed for any increased risk of thromboembolism. Tamoxifen should not be used for treatment of infertility or the prophylaxis of breast cancer in women with a history of thromboembolic events. When used to treat breast cancer in such women, the risks and benefits should be considered; in some patients, especially those given cytotoxic drugs, prophylactic anticoagulation may be justified. Care is also needed during or immediately after major surgery or prolonged immobility; all patients should be given prophylaxis against thrombosis. In patients being treated for infertility, tamoxifen should be stopped at least 6 weeks before surgery or long-term immobility and only restarted when the patient is fully mobile. Patients should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness or any pain in the calf of one leg. Tamoxifen should be withdrawn immediately in any patient developing thromboembolism and appropriate treatment given. Treatment should not usually be restarted for infertility therapy but resumption of tamoxifen with prophylactic anticoagulation may be justified in selected patients with breast cancer.

Women treated with tamoxifen should have routine gynaecological monitoring, and any abnormal symptoms such as menstrual irregularities, abnormal vaginal bleeding or discharge, or pelvic pain should be investigated (see also under Carcinogenicity, above). Periodic complete blood counts and liver function tests have been suggested.

Abuse. Although the supervised use of tamoxifen for the treatment of gynaecomastia resulting from the abuse of anabolic steroids has been reported[1] it also appears to be widely used without medical supervision. Tamoxifen can be used to treat idiopathic gynaecomastia and gynaecomastia resulting as an adverse effect of nonsteroidal anti-androgens used to treat prostate cancer (see under Breast Disorders, Non-malignant, below).

1. de Luis DA, *et al.* Anabolizantes esteroideos y ginecomastia: revisión de la literatura. *An Med Interna* 2001; **18:** 489–91.

Breast feeding. Tamoxifen was shown to inhibit lactation in 60 puerperal women.[1] Licensed product information recommends that it should not be given to lactating women.

1. Masala A, *et al.* Inhibition of lactation and inhibition of prolactin release after mechanical breast stimulation in puerperal women given tamoxifen or placebo. *Br J Obstet Gynaecol* 1978; **85:** 134–7.

Porphyria. Tamoxifen has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Tamoxifen is contra-indicated in pregnancy. Ambiguous genitalia have been reported in an infant exposed to tamoxifen *in utero*, although no causal link was demonstrated.[1] Another infant was born with Goldenhar's syndrome (oculoauriculovertebral dysplasia) after exposure to tamoxifen throughout a 26-week pregnancy.[2] The mother had also taken cocaine and marijuana during the first 6 weeks of pregnancy, and a bone scan using technetium Tc99m medronate had been performed. The US manufacturer of tamoxifen (*Zeneca, USA*) was aware of 50 pregnancies in patients taking tamoxifen, resulting in 19 normal births, 8 terminations, 13 unknown outcomes and 10 infants with fetal or neonatal abnormalities.[2]

Tamoxifen has also been used to stimulate ovulation in women with luteal phase dysfunction. In one study tamoxifen was given to 40 women, resulting in 14 pregnancies. Although 9 infants were born with no congenital abnormalities, there were 5 spontaneous abortions, which the authors felt was unacceptably high.[3] Another study, using lower doses of tamoxifen (in some cases sequentially with clomifene), reported 32 pregnancies and only 3 spontaneous abortions in 65 treated patients.[4]

1. Tewari K, *et al.* Ambiguous genitalia in infant exposed to tamoxifen in utero. *Lancet* 1997; **350:** 183.
2. Cullins SL, *et al.* Goldenhar's syndrome associated with tamoxifen given to the mother during gestation. *JAMA* 1994; **271:** 1905–6.
3. Ruiz-Velasco V, *et al.* Chemical inducers of ovulation: comparative results. *Int J Fertil* 1979; **24:** 61–64.
4. Wu CH. Less miscarriage in pregnancy following tamoxifen treatment of infertile patients with luteal phase dysfunction as compared to clomiphene treatment. *Early Pregnancy* 1997; **3:** 301–5.

Radiotherapy. There are reports of radiation recall, with erythema at the site of previous radiotherapy, in patients receiving tamoxifen.[1,2]

1. Parry BR. Radiation recall induced by tamoxifen. *Lancet* 1992; **340:** 49.
2. Extermann M, *et al.* Radiation recall in a patient with breast cancer treated for tuberculosis. *Eur J Clin Pharmacol* 1995; **48:** 77–8.

Interactions

There is a risk of increased anticoagulant effect if tamoxifen is given with coumarin anticoagulants. Conversely, use with cytotoxic drugs may increase the risk of thromboembolic events; prophylactic anticoagulation should be considered. Tamoxifen increases the dopaminergic effect of bromocriptine. Use with inhibitors of cytochrome P450 isoenzyme CYP2D6 has been shown to reduce plasma concentrations of endoxifen, a tamoxifen metabolite (see Pharmacokinetics, below); the clinical relevance is unclear.

Allopurinol. For reference to exacerbation of hepatotoxicity when tamoxifen was given with allopurinol, see p.553.

Antibacterials. *Rifampicin* was found to decrease plasma concentrations of tamoxifen in 10 healthy subjects. This was thought to be due to induction of cytochrome P450 isoenzyme CYP3A4 by rifampicin.[1]

1. Kivistö KT, *et al.* Tamoxifen and toremifene concentrations in plasma are greatly decreased by rifampin. *Clin Pharmacol Ther* 1998; **64:** 648–54.

Anticoagulants. Cases of a potentially life-threatening interaction between tamoxifen and *warfarin*, with marked prolongation of prothrombin times, haematuria, and haematoma, have been reported.[1-3] It has been suggested that in addition to enhancement of the effects of warfarin, competition for the same metabolic enzyme systems might reduce the activity of tamoxifen against tumours,[2] but this remains speculative.

Peliosis hepatis and fatal liver haemorrhage have been reported in a patient who was receiving tamoxifen with warfarin and a liothyronine-levothyroxine preparation.[4]

1. Lodwick R, *et al.* Life threatening interaction between tamoxifen and warfarin. *BMJ* 1987; **295:** 1141.
2. Tenni P, *et al.* Life threatening interaction between tamoxifen and warfarin. *BMJ* 1989; **298:** 93.
3. Ritchie LD, Grant SMT. Tamoxifen-warfarin interaction: the Aberdeen hospitals drug file. *BMJ* 1989; **298:** 1253.
4. Loomus GN, *et al.* A case of peliosis hepatis in association with tamoxifen therapy. *Am J Clin Pathol* 1983; **80:** 881–3.

Antidepressants. The metabolism of tamoxifen to an active metabolite, 4-hydroxy-*N*-desmethyltamoxifen (endoxifen), may be inhibited by paroxetine, a potent inhibitor of the cytochrome P450 isoenzyme CYP2D6.[1] However, the clinical consequences of this are, as yet, unclear.[1] In addition, a case-control study[2] found that patients taking tamoxifen with known inhibitors of CYP isoenzymes, including CYP2D6, were no more likely to relapse than those not receiving a CYP inhibitor.

1. Stearns V, *et al.* Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. *J Natl Cancer Inst* 2003; **95:** 1758–64.
2. Lehmann D, *et al.* Lack of attenuation in the antitumor effect of tamoxifen by chronic CYP isoform inhibition. *J Clin Pharmacol* 2004; **44:** 861–5.

Antineoplastics. *Aminoglutethimide* reduces serum tamoxifen concentrations, possibly by increasing its metabolism.[1] For mention of an increased risk of haemolytic-uraemic syndrome in patients who received therapy with tamoxifen and *mitomycin* see Effects on the Kidneys, under Mitomycin, p.752. Tamoxifen is reported to reduce plasma concentrations of *letrozole*, see p.740.

1. Lien EA, *et al.* Decreased serum concentrations of tamoxifen and its metabolites induced by aminoglutethimide. *Cancer Res* 1990; **50:** 5851–7.

Immunosuppressants. For the results of a study *in vitro* suggesting that tamoxifen might inhibit the metabolism of *tacrolimus* by inhibiting the cytochrome P450 isoenzyme system, see under Interactions of Tacrolimus, p.1845.

Neuromuscular blockers. For reference to prolonged neuromuscular blockade in a patient given *atracurium* while receiving tamoxifen, see p.1904.

Pharmacokinetics

Peak plasma concentrations of tamoxifen occur 4 to 7 hours after an oral dose. It is extensively protein bound. Plasma clearance is reported to be biphasic and the terminal half-life may be up to 7 days. It is extensively metabolised by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2D6. The major serum metabolite, *N*-desmethyltamoxifen, has a half-life at steady state of about 14 days. 4-Hydroxytamoxifen is a minor metabolite. *In-vitro* studies suggest that both these metabolites are further metabolised to 4-hydroxy-*N*-desmethyltamoxifen (endoxifen). Several of the metabolites are stated to have similar pharmacological activity to the parent compound. Tamoxifen is excreted slowly in the faeces, mainly as conjugates. Small amounts are excreted in urine. Tamoxifen appears to undergo enterohepatic circulation.

Genetic factors. Tamoxifen is metabolised by the cytochrome P450 isoenzymes, and its metabolites may play a role in its antineoplastic effect. Studies have suggested that patients with low or absent CYP2D6 activity or who are being treated with CYP2D6 inhibitors have lower concentrations of endoxifen. Patients with CYP2D6*3, *4, *5, and *6 alleles are designated as poor metabolisers, those with *9, *10, *17, *29, and *41 as intermediate metabolisers, and those with *1, *2, and *35 as extensive metabolisers.[1,2] Genetic polymorphism in the enzymes responsible for tamoxifen biotransformation has the potential to affect clinical outcomes. While a small study[3] showed a decreased risk of breast cancer recurrence in patients with the CYP2D6*4 allele when treated with tamoxifen, another[4] found that this allele was an independent predictor of a higher risk of disease relapse and a lower incidence of hot flashes in postmenopausal women with breast cancer. A further study[5] found that carriers of CYP2D6 alleles *4 or *5 showed a greater risk for breast cancer relapse. Furthermore, carriers of the CYP2C19*17 genotype had a more favourable clinical outcome. These results prompted the Clinical Pharmacology Subcommittee of the US FDA Advisory Committee for Pharmaceutical Science to advise that availability of genotypic testing be included in licensed product information for tamoxifen.[6,7] Some have commented[7] that it would seem reasonable to confine CYP2D6 testing to situations where it might guide the choice between tamoxifen and an alternative.

1. Borges S, *et al.* Quantitative effect of CYP2D6 genotype and inhibitors on tamoxifen metabolism: implication for optimization of breast cancer treatment. *Clin Pharmacol Ther* 2006; **80:** 61–74.
2. Goetz MP, *et al.* Tamoxifen pharmacogenomics: the role of CYP2D6 as a predictor of drug response. *Clin Pharmacol Ther* 2008; **83:** 160–6.

3. Wegman P, *et al.* Genotype of metabolic enzymes and the benefit of tamoxifen in postmenopausal breast cancer patients. *Breast Cancer Res* 2005; **7:** R284–R290.
4. Goetz MP, *et al.* Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. *J Clin Oncol* 2005; **23:** 9312–18.
5. Schroth W, *et al.* Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes. *J Clin Oncol* 2007; **25:** 5187–93.
6. Young D. Genetics examined in tamoxifen's effectiveness: recurrence warning urged for labeling. *Am J Health-Syst Pharm* 2006; **63:** 2286, 2296.
7. Desta Z, Flockhart DA. Germline pharmacogenetics of tamoxifen response: have we learned enough? *J Clin Oncol* 2007; **25:** 5147–9.

Metabolism. Tamoxifen is extensively metabolised by cytochrome P450 isoenzymes, to active metabolites that include *N*-desmethyltamoxifen, 4-hydroxytamoxifen, and 4-hydroxy-*N*-desmethyltamoxifen (endoxifen).[1] *In-vitro* studies suggest that both *N*-desmethyltamoxifen and 4-hydroxytamoxifen are further metabolised to endoxifen.[2] However, the biotransformation of tamoxifen has not been fully elucidated, and there is growing interest in how genetic polymorphism might influence the efficacy and toxicity of tamoxifen and its metabolites (see Genetic Factors, above).

1. Rochat B. Role of cytochrome P450 activity in the fate of anticancer agents and in drug resistance: focus on tamoxifen, paclitaxel and imatinib metabolism. *Clin Pharmacokinet* 2005; **44:** 349–66.
2. Desta Z, *et al.* Comprehensive evaluation of tamoxifen sequential biotransformation by the human cytochrome P450 system in vitro: prominent roles for CYP3A and CYP2D6. *J Pharmacol Exp Ther* 2004; **310:** 1062–75.

Uses and Administration

Tamoxifen is an oestrogen antagonist with actions similar to those of clomifene citrate (see p.2086). It may also inhibit the production or release of cellular growth factors and induce apoptosis. It is used in the adjuvant endocrine therapy of node-positive breast cancer, in the treatment of metastatic disease, and for prophylaxis in women at increased risk including those with ductal carcinoma in situ. It has been tried in some other malignancies including tumours of the ovary and in malignant melanoma. Tamoxifen is also used to stimulate ovulation in women with anovulatory infertility. See also the cross-references below.

Tamoxifen is given orally as the citrate but doses are calculated in terms of the base; tamoxifen citrate 15.2 mg is equivalent to about 10 mg of tamoxifen. In the treatment of breast cancer, usual doses are tamoxifen 20 mg daily, in 2 divided doses or as a single daily dose. Doses of up to 40 mg daily may be given but no additional benefit has been demonstrated. Adjuvant therapy is normally continued for up to 5 years, although the optimum duration is still uncertain (p.661). To reduce breast cancer incidence in women at high risk of the disease, the licensed dose of tamoxifen is 20 mg daily for 5 years.

In the treatment of anovulatory infertility the usual dose is tamoxifen 20 mg daily on days 2 to 5 of the menstrual cycle, increased if necessary in subsequent cycles up to 80 mg daily. In women with irregular menstruation the initial course may be begun on any day, and a second course begun at a higher dose after 45 days if there has been no response. If the patient responds with menstruation, subsequent courses may begin on day 2 of the cycle.

A topical formulation of 4-hydroxytamoxifen, a metabolite of tamoxifen, is under investigation for the treatment of cyclic mastalgia.

◊ Reviews.

1. Kramer R, Brown P. Should tamoxifen be used in breast cancer prevention? *Drug Safety* 2004; **27:** 979–89.
2. Singh Ranger G. Current concepts in the endocrine therapy of breast cancer: tamoxifen and aromatase inhibitors. *J Clin Pharm Ther* 2005; **30:** 313–17.
3. Morales L, *et al.* Choosing between an aromatase inhibitor and tamoxifen in the adjuvant setting. *Curr Opin Oncol* 2005; **17:** 559–65.
4. Poole R, Paridaens R. The use of third-generation aromatase inhibitors and tamoxifen in the adjuvant treatment of postmenopausal patients with hormone-dependent breast cancer: evidence based review. *Curr Opin Oncol* 2007; **19:** 564–72.
5. Munshi A, Singh P. Tamoxifen in breast cancer: not so easy to write off. *Breast* 2008; **17:** 121–4.

Breast disorders, non-malignant. ***GYNAECOMASTIA.*** Tamoxifen, usually in doses of 10 mg twice daily, has been reported to be effective[1-7] in reducing pain, swelling, and breast size in men or pubertal boys with gynaecomastia (p.2092). Tamoxifen has been recommended as a drug of choice in patients requiring drug therapy, given for 3 months to see if a response occurs.[7] It has also been reported to be effective for the prevention and treatment of gynaecomastia and breast pain caused by the nonsteroidal anti-androgen bicalutamide,[8-11] which is used in the treatment of prostate cancer (see Gynaecomastia under Adverse Effects and Precautions of Flutamide, p.725).

1. Jefferys DB. Painful gynaecomastia treated with tamoxifen. *BMJ* 1979; **1:** 1119–20.
2. Hooper PD. Puberty gynaecomastia. *J R Coll Gen Pract* 1985; **35:** 142.
3. McDermott MT, *et al.* Tamoxifen therapy for painful idiopathic gynecomastia. *South Med J* 1990; **83:** 1283–5.
4. Ting AC, *et al.* Comparison of tamoxifen with danazol in the management of idiopathic gynecomastia. *Am Surg* 2000; **66:** 38–40.
5. Lawrence SE, *et al.* Beneficial effects of raloxifene and tamoxifen in the treatment of pubertal gynecomastia. *J Pediatr* 2004; **145:** 71–6.
6. Hanavadi S, *et al.* The role of tamoxifen in the management of gynaecomastia. *Breast* 2006; **15:** 276–80.
7. Braunstein GD. Gynecomastia. *N Engl J Med* 2007; **357:** 1229–37.
8. 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.
9. Perdonà S, *et al.* Efficacy of tamoxifen and radiotherapy for prevention and treatment of gynaecomastia and breast pain caused by bicalutamide in prostate cancer: a randomised controlled trial. *Lancet Oncol* 2005; **6:** 295–300.
10. Di Lorenzo G, *et al.* Gynecomastia and breast pain induced by adjuvant therapy with bicalutamide after radical prostatectomy in patients with prostate cancer: the role of tamoxifen and radiotherapy. *J Urol (Baltimore)* 2005; **174:** 2197–2203.
11. Fradet Y, *et al.* Tamoxifen as prophylaxis for prevention of gynaecomastia and breast pain associated with bicalutamide 150 mg monotherapy in patients with prostate cancer: a randomised, placebo-controlled, dose-response study. *Eur Urol* 2007; **52:** 106–14.

MASTALGIA. Tamoxifen 20 mg daily has been shown to be effective in patients with both cyclic and non-cyclic mastalgia,[1] and improvement has also been reported at a lower dose of 10 mg daily.[2] However, there is concern about the use of tamoxifen in otherwise healthy premenopausal women,[3-5] particularly since many patients relapse on withdrawal,[2] and it has been recommended[6,7] that tamoxifen be reserved for patients who fail to respond to other drugs (see p.2092).

A topical formulation of 4-hydroxytamoxifen, a metabolite of tamoxifen, is under investigation in the treatment of cyclic mastalgia.

1. Fentiman IS, *et al.* Double-blind controlled trial of tamoxifen therapy for mastalgia. *Lancet* 1986; **i:** 287–8.
2. Fentiman IS, *et al.* Studies of tamoxifen in women with mastalgia. *Br J Clin Pract* 1989; **43** (suppl 68): 34–6.
3. Anonymous. Tamoxifen for benign breast disease. *Lancet* 1986; **i:** 305.
4. Smallwood JA, Taylor I. Tamoxifen for mastalgia. *Lancet* 1986; **i:** 680–1.
5. Fentiman IS, *et al.* Tamoxifen for mastalgia. *Lancet* 1986; **i:** 681.
6. Gateley CA, Mansel RE. Management of the painful and nodular breast. *Br Med Bull* 1991; **47:** 284–94.
7. Anonymous. Cyclical breast pain: what works and what doesn't. *Drug Ther Bull* 1992; **30:** 1–3.

Cardiovascular disorders. Tamoxifen has been reported to have a generally favourable effect on lipid profiles (see Effects on Blood Lipids, under Adverse Effects, above) suggesting it may have cardiovascular benefits.[1] A cohort study of adjuvant tamoxifen found that the drug reduced the incidence of myocardial infarction,[2] and a randomised study of the same therapy also showed a trend towards a decrease in mortality from coronary heart disease.[3] However, in a much larger breast cancer prevention trial, tamoxifen did not reduce the risk of, and mortality from, ischaemic heart disease, neither of which differed between placebo and tamoxifen recipients.[4,5] This lack of difference was independent of pre-existing cardiovascular disease.[5] A review[6] noted that while the available data suggested an overall benefit, most of them came from studies in women at low absolute risk of myocardial infarction; studies in men at high absolute risk would be needed to determine whether tamoxifen and related drugs were suitable as cardioprotectants.

1. Pritchard KI, Abramson BL. Cardiovascular health and aromatase inhibitors. *Drugs* 2006; **66:** 1727–40.
2. McDonald CC, *et al.* Scottish Cancer Trials Breast Group. Cardiac and vascular morbidity in women receiving adjuvant tamoxifen for breast cancer in a randomised trial. *BMJ* 1995; **311:** 977–80.
3. Costantino JP, *et al.* Coronary heart disease mortality and adjuvant tamoxifen therapy. *J Natl Cancer Inst* 1997; **89:** 776–82.
4. Fisher B, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998; **90:** 1371–88.
5. Reis SE, *et al.* Cardiovascular effects of tamoxifen in women with and without heart disease: breast cancer prevention trial. *J Natl Cancer Inst* 2001; **93:** 16–21.
6. Grainger DJ, Schofield PM. Tamoxifen for the prevention of myocardial infarction in humans: preclinical and early clinical evidence. *Circulation* 2005; **112:** 3018–24.

Disorders related to the menstrual cycle. Apart from cyclic mastalgia (see above) tamoxifen has been used in a number of cases in which disorders were linked to the hormonal changes of the menstrual cycle, including menorrhagia due to myometrial hypertrophy,[1] an auto-immune dermatitis due to post-ovulatory rises in serum progesterone[2,3] (see Effects on the Skin under Progesterone, p.2125), and premenstrual migraine.[4] However, tamoxifen was thought to be a cause of recurrent migraines in another patient, because of its action at oestrogen receptors.[5]

1. Fraser IS. Menorrhagia due to myometrial hypertrophy: treatment with tamoxifen. *Obstet Gynecol* 1987; **70:** 505–6.
2. Wojnarowska F, *et al.* Progesterone-induced erythema multiforme. *J R Soc Med* 1985; **78:** 407–8.
3. Stephens CJM, *et al.* Autoimmune progesterone dermatitis responding to tamoxifen. *Br J Dermatol* 1989; **121:** 135–7.
4. O'Dea JPK, Davis EH. Tamoxifen in the treatment of menstrual migraine. *Neurology* 1990; **40:** 1470–1.
5. Mathew P, Fung F. Recapitulation of menstrual migraine with tamoxifen. *Lancet* 1999; **353:** 467–8.

Infertility. Tamoxifen is reported to be as effective as clomifene in the treatment of anovulatory infertility (p.2080) in women,[1,2] and may be useful in women in whom abnormal cervical mucus acts as a barrier to spermatozoa.[3] In infertile men, however, results are reportedly contradictory, with some studies reporting increase in sperm density and improved pregnancy rates while others failed to demonstrate any effect.[4] The addition of testosterone may improve outcomes, however, and a later study of men with idiopathic oligozoospermia reported that tamoxifen with testosterone improved sperm variables and pregnancy rates compared with a placebo group (there was no comparison with tamoxifen alone).[5]

1. Messinis IE, Nillius SJ. Comparison between tamoxifen and clomiphene for induction of ovulation. *Acta Obstet Gynecol Scand* 1982; **61:** 377–9.
2. Boostanfar R, *et al.* A prospective randomized trial comparing clomiphene citrate with tamoxifen citrate for ovulation induction. *Fertil Steril* 2001; **75:** 1024–6.
3. Annapurna V, *et al.* Effect of two anti-estrogens, clomiphene citrate and tamoxifen, on cervical mucus and sperm-cervical mucus interaction. *Int J Fertil* 1997; **42:** 215–18.
4. Howards SS. Treatment of male infertility. *N Engl J Med* 1995; 312–17.
5. Adamopoulos DA, *et al.* Effectiveness of combined tamoxifen citrate and testosterone undecanoate treatment in men with idiopathic oligozoospermia. *Fertil Steril* 2003; **80:** 914–20.

Malignant neoplasms. For reference to the use of tamoxifen in malignant neoplasms of breast, ovary, and in cutaneous melanoma, see p.661, p.670, and p.673. The most common use of tamoxifen is for the endocrine therapy of oestrogen-receptor positive early or advanced breast cancer, where there seems to be a clear benefit. How long such therapy should be continued remains uncertain although continuing therapy beyond 5 years may not increase the overall benefit. However, extending therapy by following 5 years of tamoxifen therapy with several years of an aromatase inhibitor such as letrozole (see, p.740) does seem to provide additional benefit.

Extension of tamoxifen use to the attempted prophylaxis of breast cancer has proved controversial (see p.662). Nonetheless, evidence that tamoxifen can reduce short-term incidence of breast cancer in some women at increased risk has been seen, and tamoxifen has been approved for such use in the USA.

Despite some positive data, tamoxifen does not appear to be effective in the treatment of hepatocellular carcinoma (see p.667).

Osteoporosis. Tamoxifen has been reported to have favourable effects on bone mass,[1-3] but any general role in the prevention of osteoporosis (p.1084) seems unlikely given concerns about the carcinogenicity of tamoxifen. The effects are reported to be comparable in magnitude to those of calcium supplementation, and less than those of oestrogens (see also p.2077) or bisphosphonates. It has been suggested that such an effect on bone would provide an additional benefit in women receiving tamoxifen for the prophylaxis of breast cancer,[4] although others dispute the benefits.[5]

1. Love RR, *et al.* Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med* 1992; **326:** 852–6.
2. Love RR, *et al.* Effect of tamoxifen on lumbar spine bone mineral density in postmenopausal women after 5 years. *Arch Intern Med* 1994; **154:** 2585–8.
3. Grey AB, *et al.* The effect of the antiestrogen tamoxifen on bone mineral density in normal late postmenopausal women. *Am J Med* 1995; **99:** 636–41.
4. Powles TJ. The case for clinical trials of tamoxifen for prevention of breast cancer. *Lancet* 1992; **340:** 1145–7.
5. Fugh-Berman A, Epstein S. Tamoxifen: disease prevention or disease substitution? *Lancet* 1992; **340:** 1143–5.

Precocious puberty. Tamoxifen has been reported to be beneficial in the treatment of precocious puberty (p.2081).

Preparations

BP 2008: Tamoxifen Tablets;
USP 31: Tamoxifen Citrate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Crisafeno; Diemon; Farmifeno†; Ginarsan; Nolvadex; Rolap; Tamofen†; Tamoxis; Taxfeno; Trimetrox; ***Austral.:*** Genox; Nolvadex; Tamosin; Tamoxen; ***Austria:*** Ebefen; Kessar; Nolvadex; Tamax; Tamofen†; Tamoplex; ***Belg.:*** Doctamoxifene; Nolvadex; Tamizam; Tamoplex; ***Braz.:*** Bioxifeno; Estrocur†; Festone; Kessar; Nolvadex; Tamooex†; Tamoplex†; Tamox†; Tamoxin; Taxofen; Tecnotax; ***Canad.:*** Apo-Tamox; Nolvadex; Tamofen; ***Chile:*** Kessar; Nolvadex; Oncotamox; Tamolem†; Taxus; ***Cz.:*** Nolvadex; Tamifen†; Tamoplex; Zitazonium; ***Denm.:*** Tamofen†; ***Fin.:*** Nolvadex†; Tadex; Tamexin; Tamofen; ***Fr.:*** Kessar; Nolvadex; Oncotam†; Tamofene†; ***Ger.:*** Jenoxifen; Kessar†; Mandofen; Nolvadex; Nourytam; Tamokadin; Tamopham†; Tamox; Tamoxasta†; Tamoximerck; Tamoxistad; Zemide†; ***Gr.:*** Adifen; Defarol†; Kessar; Nolvadex; Puretam; Tamoplex; Zymoplex; ***Hong Kong:*** Apo-Tamox; Nolvadex; Novofen; Tamifen†; Zitazonium; ***Hung.:*** Zitazonium; ***India:*** Caditam; Cytotam; Mamofen; Nolvadex; Tamodex†; ***Indon.:*** Nolvadex; Tamofen; Tamoplex; Taxen; ***Irl.:*** Nolgen†; Nolvadex; Tamofen†; Tamox; ***Israel:*** Nolvadex; Tamofen; Tamoxen;

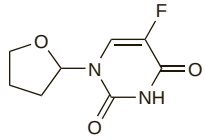
Tamoxi; ***Ital.:*** Kessar; Ledertam†; Nolvadex; Nomafen; Tamoxene; Virtamox†; ***Malaysia:*** Genox; Nolvadex; Novofen; Tamoplex; Zitazonium; ***Mex.:*** Bilem; Cryoxifeno; Fenobest; Kessar†; Nolvadex; Ralsifen-X; Tamoxan†; Taxus; Tecnofen; ***Neth.:*** Nolvadex; ***Norw.:*** Nolvadex; ***NZ:*** Genox; Nolvadex; Tamofen; ***Philipp.:*** Fenahex; Gynatam; Gyraxen; Kessar; Nolvadex; Tamoplex; Tamoxsta; Zitazonium; ***Pol.:*** Nolvadex; ***Port.:*** Mastofen; Nolvadex; Tamoxan; ***Rus.:*** Bilem (Билем)†; Tamifen (Тамифен); Zitazonium (Зитазониум); ***S.Afr.:*** Kessar; Neophedan; Nolvadex; Tamoplex; ***Singapore:*** Apo-Tamox; Nolvadex; Tamofen; ***Spain:*** Nolvadex; Sinmaren†; Yacesal; ***Swed.:*** Nolvadex; ***Switz.:*** Kessar†; Nolvadex; Tamec; ***Thai.:*** Bilem; Gynatam; Nolvadex; Novofen; Tamofen†; Tamoplex; Tuosomin; Zitazonium; ***Turk.:*** Nolvadex; Tadex; Tamofen; ***UAE:*** Tamophar; ***UK:*** Nolvadex; Soltamox; ***USA:*** Nolvadex†; Soltamox; ***Venez.:*** Gynatam; Nolvadex; Taxus.

Tegafur *(BAN, USAN, rINN)*

FT-207; Ftorafur; MJF-12264; NSC-148958; Tégafur; Tegafurum; Tegafuuri; WR-220066. 5-Fluoro-1-(tetrahydro-2-furyl)uracil; 5-Fluoro-1-(tetrahydro-2-furyl)pyrimidine-2,4(1*H*,3*H*)-dione.

Тегафур

$C_8H_9FN_2O_3$ = 200.2.
CAS — 17902-23-7.
ATC — L01BC03.
ATC Vet — QL01BC03.



Pharmacopoeias. In *Chin.* and *Jpn*.

Adverse Effects, Treatment, and Precautions

As for Fluorouracil, p.722.

Bone-marrow depression may be less severe with tegafur but gastrointestinal toxicity is often dose-limiting and central neurotoxicity is more common. Peripheral oedema and dyspnoea occur commonly. Increases in liver function test values are common and there are reports of fatal fulminant hepatitis. Liver function should be monitored in patients with hepatic impairment given tegafur; it should not be given in severe hepatic impairment.

Interactions

Tegafur should not be used with drugs that inhibit dihydropyrimidine dehydrogenase; fatalities have occurred in patients given tegafur and sorivudine (see Antivirals under Interactions of Fluorouracil, p.723). Increased plasma concentrations of phenytoin, and symptoms of toxicity during use with tegafur and uracil, have been reported.

Pharmacokinetics

Tegafur is well absorbed from the gastrointestinal tract after oral doses. After an intravenous dose it is reported to have a prolonged plasma half-life of 6 to 16 hours. Tegafur appears to be slowly metabolised in the liver to fluorouracil (p.723), and some intracellular conversion to fluorouracil may also occur. Tegafur crosses the blood-brain barrier and is found in the CSF.

◊ References.

1. Etienne-Grimaldi M-C, *et al.* A clinical pharmacokinetic analysis of tegafur-uracil (UFT) plus leucovorin given in a new twice-daily oral administration schedule. *Clin Pharmacokinet* 2007; **46:** 953–63.

Uses and Administration

Tegafur is considered to be an orally active prodrug of fluorouracil (p.723). It has been used in the management of malignant neoplasms including those of the breast, gallbladder, gastrointestinal tract, head and neck, liver, and pancreas. Tegafur has been given orally in doses up to 1 g/m^2 daily. It is often given with uracil (UFT; p.2407). Tegafur 300 mg/m^2 daily, with uracil 672 mg/m^2 daily, may be given in 3 divided oral doses, together with calcium folinate, in the management of metastatic colorectal cancer. Doses are given for a cycle of 28 days, followed by 7 days without treatment. The drugs should be taken 1 hour before or after meals, and doses modified according to toxicity. Doses of tegafur 1 to 3 g/m^2 daily for 5 days have been given intravenously.

Administration. Tegafur is an orally active prodrug of fluorouracil. Although it has been given as a single agent, it is more often used with drugs that modify its bioavailability and toxicity.[1] These include uracil (p.2407) and gimestat (5-chlorodihydropyrimidine, CDHP), which can increase fluorouracil concentrations by inhibition of dihydropyrimidine dehydrogenase, the enzyme responsible for its further catabolism,[1-3] and oxonic acid (otastat), which inhibits another enzyme, orotate pyrimidine phosphoribosyl transferase, thought to play a role in the gastrointestinal toxicity of fluorouracil and its prodrugs.[2]

UFT consists of tegafur and uracil in the optimal molar ratio 1:4.[1] It is available for the treatment of colorectal cancer (p.665)—for doses, see above. A preliminary analysis of a large study comparing oral UFT and calcium folinate therapy with intravenous fluorouracil and calcium folinate found both regimens to be well tolerated with similar levels of toxicity.[4] Adjuvant therapy with UFT appears to improve survival in patients with adenocarcinoma of the lung[5] and node-negative breast cancer.[6]

S-1 (TS-1, *Taiho Jpn*) is a combination of tegafur, gimestat and the potassium salt of oxonic acid in the molar ratio 10:4:10. It has been tried in gastric and colorectal cancers,[2,3,7,8] and initial results have suggested comparable activity to fluorouracil and calcium folinate in induction regimens, but the incidence of diarrhoea and stomatitis was reduced.

1. Adjei AA. A review of the pharmacology and clinical activity of new chemotherapy agents for the treatment of colorectal cancer. *Br J Clin Pharmacol* 1999; **48:** 265–77.
2. Sakata Y, *et al.* Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) in advanced gastric cancer patients. *Eur J Cancer* 1998; **34:** 1715–20.
3. Sugimachi K, *et al.* An early phase II study of oral S-1, a newly developed 5-fluorouracil derivative for advanced and recurrent gastrointestinal cancers. *Oncology* 1999; **57:** 202–10.
4. Smith R, *et al.* UFT plus calcium folinate vs 5-FU plus calcium folinate in colon cancer. *Oncology (Huntingt)* 1999; **13** (suppl 3): 44–7.
5. Kato H, *et al.* A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *N Engl J Med* 2004; **350:** 1713–21.
6. Noguchi S, *et al.* Postoperative adjuvant therapy with tamoxifen, tegafur plus uracil, or both in women with node-negative breast cancer: a pooled analysis of six randomized controlled trials. *J Clin Oncol* 2005; **23:** 2172–84.
7. Osugi H, *et al.* Oral fluoropyrimidine anticancer drug TS-1 for gastric cancer patients with peritoneal dissemination. *Oncol Rep* 2002; **9:** 811–15.
8. Shibahara K, *et al.* Retrospective study of S-1 versus tegafur/uracil and oral leucovorin in patients with metastatic colorectal cancer. *Anticancer Res* 2008; **28:** 1779–83.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Ftorafur; UFT; ***Hong Kong:*** Futraful; ***Hung.:*** Ftorafur; ***Indon.:*** Futraful; ***Ital.:*** Citofur†; ***Jpn:*** Futraful; ***Rus.:*** Ftorafur (Фторафур); ***Spain:*** Utefos; ***Thai.:*** UFUR.

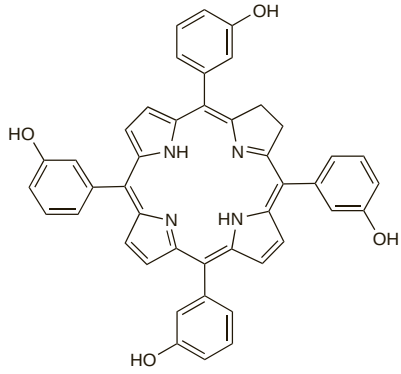
Multi-ingredient: ***Arg.:*** Asofurtal; UFT; ***Austria:*** UFT; ***Belg.:*** UFT; ***Braz.:*** UFT; ***Denm.:*** Uftoral; ***Fr.:*** UFT; ***Ger.:*** UFT; ***Gr.:*** UFT; ***Hong Kong:*** UFT; ***Hung.:*** UFT; ***Israel:*** UFT†; ***Ital.:*** UFT; ***Jpn:*** UFT; ***Malaysia:*** UFT; ***Mex.:*** UFT; ***Neth.:*** UFT; ***Norw.:*** UFT; ***NZ:*** Orzel†; ***Philipp.:*** Tefudex; UFT; ***Port.:*** UFT; ***Rus.:*** UFT (УФТ); ***S.Afr.:*** UFT; ***Singapore:*** UFT; ***Spain:*** UFT; ***Swed.:*** UFT; ***Thai.:*** UFT; ***Turk.:*** UFT; ***UK:*** Uftoral.

Temoporfin *(BAN, USAN, rINN)*

EF-9; mTHPC; Temoporfiini; Temoporfina; Témoporfine; Temoporfinum; *meso*-Tetrahydroxyphenylchlorin; *meta*-Tetrahydroxyphenylchlorin. 3,3′,3″,3‴-(7,8-Dihydroporphyrin-5,10,15,20-tetryl)tetraphenol; 7,8-Dihydro-5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrin.

Темопорфин

$C_{44}H_{32}N_4O_4$ = 680.7.
CAS — 122341-38-2.
ATC — L01XD05.
ATC Vet — QL01XD05.



Adverse Effects and Precautions

Adverse effects of temoporfin include photosensitivity, local inflammatory reactions, and gastrointestinal disturbances. Patients should be advised to avoid direct sunlight or bright indoor light for 15 days, and to protect the injection site from light for at least 3 months if extravasation has occurred.

Porphyria. The use of temoporfin is contra-indicated in patients with porphyria.

Interactions

Use of temoporfin with other drugs causing photosensitivity should be avoided as the reaction may be increased; this has been reported with topical fluorouracil.

Pharmacokinetics

Peak plasma concentrations of temoporfin are reached about 2 to 4 hours after intravenous infusion. Thereafter, elimination is bi-exponential, with a terminal plasma half-life of about 65 hours. Plasma protein binding is about 85%. *Animal* data indicate that temoporfin is metabolised in the liver and excreted in the faeces via the bile.

Uses and Administration

Temoporfin is a porphyrin derivative. It is used palliatively as a photosensitiser in the photodynamic therapy (see under Porfimer Sodium, p.764) of refractory squamous cell carcinoma of the head and neck (p.666), that cannot be treated with radiotherapy, surgery, or systemic chemotherapy. It is also under investigation in the treatment of various other malignant neoplasms. Temoporfin is given by slow intravenous injection over at least 6 minutes, at a dose of 150 micrograms/kg. This is followed 96 hours later by activation using a laser tuned to a wavelength of 652 nanometres for about 200 seconds, sufficient to supply a dose of 20 J/cm^2. Treatment may be repeated once after 4 weeks if necessary.

◊ References.

1. Kubler AC, *et al.* Photodynamic therapy of primary nonmelanomatous skin tumours of the head and neck. *Lasers Surg Med* 1999; **25:** 60–8.
2. Baas P, *et al.* Photodynamic therapy with *meta*-tetrahydroxyphenylchlorin for basal cell carcinoma: a phase I/II study. *Br J Dermatol* 2001; **145:** 75–8.
3. Kubler AC, *et al.* Treatment of squamous cell carcinoma of the lip using Foscan-mediated photodynamic therapy. *Int J Oral Maxillofac Surg* 2001; **30:** 504–9.
4. Javaid B, *et al.* Photodynamic therapy (PDT) for oesophageal dysplasia and early carcinoma with mTHPC (m-tetrahydroxyphenyl chlorin): a preliminary study. *Lasers Med Sci* 2002; **17:** 51–6.
5. Friedberg JS, *et al.* A phase I study of Foscan-mediated photodynamic therapy and surgery in patients with mesothelioma. *Ann Thorac Surg* 2003; **75:** 952–9.
6. Copper MP, *et al.* Meta-tetra(hydroxyphenyl)chlorin photodynamic therapy in early-stage squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg* 2003; **129:** 709–11.
7. D'Cruz AK, *et al.* mTHPC-mediated photodynamic therapy in patients with advanced, incurable head and neck cancer: a multicenter study of 128 patients. *Head Neck* 2004; **26:** 232–40.
8. Etienne J, *et al.* Photodynamic therapy with green light and mtetrahydroxyphenyl chlorin for intramucosal adenocarcinoma and high-grade dysplasia in Barrett's esophagus. *Gastrointest Endosc* 2004; **59:** 880–9. Correction. *ibid.*; **60:** 1042.
9. Hopper C, *et al.* mTHPC-mediated photodynamic therapy for early oral squamous cell carcinoma. *Int J Cancer* 2004; **111:** 138–46.
10. Lou PJ, *et al.* Interstitial photodynamic therapy as salvage treatment for recurrent head and neck cancer. *Br J Cancer* 2004; **91:** 441–6.
11. Campbell SM, *et al.* Photodynamic therapy using meta-tetrahydroxyphenylchlorin (Foscan) for the treatment of vulval intraepithelial neoplasia. *Br J Dermatol* 2004; **151:** 1076–80.
12. Naim R. Photodynamische Therapie mit m-THPC (Foscan): Behandlung von Plattenepithelkarzinomen im Kopf-Hals-Bereich. *HNO* 2008; **56:** 490–2.

Preparations

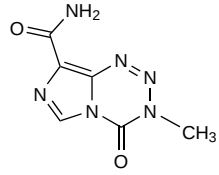
Proprietary Preparations (details are given in Part 3)
Belg.: Foscan; ***Cz.:*** Foscan; ***Denm.:*** Foscan; ***Ger.:*** Foscan; ***Gr.:*** Foscan; ***Israel:*** Foscan; ***Neth.:*** Foscan; ***Port.:*** Foscan; ***UK:*** Foscan.

Temozolomide *(BAN, USAN, rINN)*

CCRG-81045; M&B-39831; NSC-362856; Sch-52365; Temotsolomidi; Temozolomid; Temozolomida; Témozolomide; Temozolomidum. 3,4-Dihydro-3-methyl-4-oxoimidazo[5,1-*d*][1,2,-3,5]tetrazine-8-carboxamide.

Темозоломид

$C_6H_6N_6O_2$ = 194.2.
CAS — 85622-93-1.
ATC — L01AX03.
ATC Vet — QL01AX03.



Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641. Myelosuppression is common with temozolomide and is dose-limiting. The nadir of cell counts usually occurs 21 to 28 days after treatment, with recovery within the next 1 to 2 weeks. Patients over 70 years of age are thought to be more susceptible to severe myelosuppression. Prolonged pancytopenia may result in aplastic anaemia, and fatalities have been reported. Opportunistic infections can occur; *Pneumocystis jirovecii* pneumonia has been reported in patients