Neth.: Hycamtin; ***Norw.:*** Hycamtin; ***Pol.:*** Hycamtin; ***Port.:*** Hycamtin; ***Rus.:*** Hycamtin (Гикамтин); ***S.Afr.:*** Hycamtin; ***Singapore:*** Hycamtin; ***Spain:*** Hycamtin; ***Swed.:*** Hycamtin; ***Switz.:*** Hycamtin; ***Thai.:*** Hycamtin; Topotel; ***Turk.:*** Hycamptin; ***UK:*** Hycamtin; ***USA:*** Hycamtin; ***Venez.:*** Hycamtin†.

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

Citrato de toremifeno; FC-1157a; Toremifen Sitrat; Torémifène, Citrate de; Toremifeni Citras. 2-{*p*-[(*Z*)-4-Chloro-1,2-diphenyl-1-butenyl]phenoxy}-*N*,*N*-dimethylethylamine citrate.

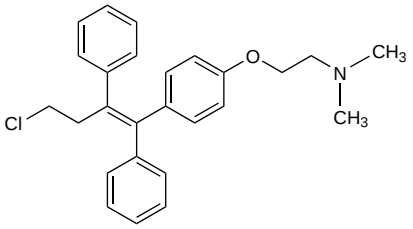
Торемифена Цитрат

$C_{26}H_{28}ClNO,C_6H_8O_7$ = 598.1.

CAS — 89778-26-7 (toremifene); 89778-27-8 (toremifene citrate).

ATC — L02BA02.

ATC Vet — QL02BA02.



(toremifene)

Adverse Effects and Precautions

As for Tamoxifen Citrate, p.772.

Use of toremifene is contra-indicated in patients with pre-existing endometrial hyperplasia, or in those with severe thromboembolic disease or severe hepatic impairment. Toremifene must be used with caution in patients with uncompensated heart failure or severe angina. Patients with bone metastases should be monitored for signs and symptoms of hypercalcaemia.

Interactions

Toremifene is metabolised by cytochrome P450 isoenzyme CYP3A4, and potent enzyme-inducing drugs such as phenytoin, phenobarbital and carbamazepine, might be expected to increase toremifene metabolism, thereby lowering the serum concentration. Conversely, azole antifungals and macrolide antibacterials may inhibit toremifene metabolism by inhibiting the isoenzyme.

Use with drugs that decrease renal calcium excretion, such as thiazide diuretics, may increase the incidence of hypercalcaemia. Use with coumarin anticoagulants should be avoided as there is a risk of increased bleeding time.

Antibacterials. *Rifampicin* was found to decrease plasma concentrations of toremifene in 9 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.

Pharmacokinetics

Toremifene citrate is well absorbed from the gastrointestinal tract, reaching peak plasma concentrations of toremifene within 3 hours. Plasma concentration declines biexponentially; the mean distribution half-life is about 4 hours and the elimination half-life is about 5 days. It is extensively bound to plasma proteins, mainly albumin. Toremifene is metabolised principally by the cytochrome P450 isoenzyme CYP3A4; the main metabolite is N-demethyltoremifene, which is reported to have anti-oestrogenic activity but with weak anti-tumour activity. It undergoes enterohepatic circulation and is eliminated mainly in the faeces as metabolites. About 10% is excreted in the urine.

◊ Reviews.

1. Taras TL, *et al.* Clinical pharmacokinetics of toremifene. *Clin Pharmacokinet* 2000; **39:** 327–34.

Uses and Administration

Toremifene is an anti-oestrogen with properties similar to those of tamoxifen (p.775). It is used in the treatment of metastatic breast cancer (p.661) in postmenopausal women with oestrogen-receptor positive tumours. It is also being investigated for the treatment of lung tumours and for the management of prostate cancer.

Toremifene is given orally as the citrate, but doses are calculated in terms of the base; 88.4 mg of toremifene citrate is equivalent to about 60 mg of toremifene. A dose of toremifene 60 mg once daily is used.

◊ References.

1. Wiseman LR, Goa KL. Toremifene: a review of its pharmacological properties and clinical efficacy in the management of advanced breast cancer. *Drugs* 1997; **54:** 141–60.
2. Anonymous. Toremifene and letrozole for advanced breast cancer. *Med Lett Drugs Ther* 1998; **40:** 43–5.
3. Holli K. Adjuvant trials of toremifene vs tamoxifen: the European experience. *Oncology (Huntingt)* 1998; **12** (suppl 5): 23–7.
4. Holli K, *et al.* Safety and efficacy results of a randomized trial comparing adjuvant toremifene and tamoxifen in postmenopausal patients with node-positive breast cancer. *J Clin Oncol* 2000; **18:** 3487–94.
5. Taneja SS, *et al.* Toremifene—a promising therapy for the prevention of prostate cancer and complications of androgen deprivation therapy. *Expert Opin Invest Drugs* 2006; **15:** 293–305.
6. Smith MR, *et al.* Toremifene increases bone mineral density in men receiving androgen deprivation therapy for prostate cancer: interim analysis of a multicenter phase 3 clinical study. *J Urol (Baltimore)* 2008; **179:** 152–5.
7. Smith MR, *et al.* Toremifene improves lipid profiles in men receiving androgen-deprivation therapy for prostate cancer: interim analysis of a multicenter phase III study. *J Clin Oncol* 2008; **26:** 1824–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Fareston†; ***Austral.:*** Fareston; ***Austria:*** Fareston; ***Belg.:*** Fareston; ***Cz.:*** Fareston; ***Fin.:*** Fareston; ***Fr.:*** Fareston; ***Ger.:*** Fareston; ***Gr.:*** Fareston; ***Hung.:*** Fareston; ***Irl.:*** Fareston; ***Ital.:*** Fareston; ***Mex.:*** Fareston; ***Neth.:*** Fareston; ***NZ:*** Fareston; ***Port.:*** Fareston; ***Rus.:*** Fareston (Фарестон); ***S.Afr.:*** Fareston; ***Spain:*** Fareston; ***Swed.:*** Fareston; ***Switz.:*** Fareston; ***Thai.:*** Fareston; ***Turk.:*** Fareston; ***UK:*** Fareston; ***USA:*** Fareston.

Tositumomab *(rINN)*

B-1; Tositumomabum. Immunoglobulin G2a anti-(human antigen CD 20) (mouse monoclonal clone B1R1 γ2a-chain), disulfide with mouse monoclonal clone B1R1 λ_x-chain, dimer.

Тоситумомаб

CAS — 192391-48-3.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Infusion reactions suggestive of a cytokine release syndrome, and other hypersensitivity reactions including anaphylaxis, have been reported with tositumomab. Prolonged and severe neutropenia, thrombocytopenia, and anaemia occur commonly; full blood counts should be monitored weekly for up to 12 weeks. Other adverse effects include gastrointestinal disturbances, dehydration, abdominal pain, pleural effusion, and increased susceptibility to infection. Delayed adverse effects such as the development of secondary malignancies, leukaemia, or myelodysplastic syndrome may occur. Patients receiving the radiolabelled regimen may be susceptible to hypothyroidism and pretreatment with thyroid blocking drugs is recommended (see Uses and Administration, below); levels of thyroid-stimulating hormone should be measured before treatment and annually thereafter.

Uses and Administration

Tositumomab is an anti-B1 monoclonal antibody that is directed against the CD20 antigen found on the surface of B lymphocytes. It is radiolabelled with iodine-131 (p.2054) for the treatment of patients with CD20 antigen-expressing, relapsed or refractory, low-grade, follicular, or transformed non-Hodgkin's lymphoma (p.656), and including those patients who have disease refractory to rituximab.

The regimen consists of a dosimetric step, followed 7 to 14 days later by a therapeutic step. The dosimetric step consists of 450 mg of tositumomab given intravenously in 50 mL sodium chloride 0.9% over 60 minutes. Tositumomab 35 mg radiolabelled with iodine-131 is then given intravenously in 30 mL sodium chloride 0.9% over 20 minutes. This is followed by whole body imaging to determine whether biodistribution is acceptable, and to allow calculation of the therapeutic dose of radiolabelled tositumomab. In the therapeutic step, tositumomab 450 mg is given again, and followed by the calculated dose of radiolabelled tositumomab.

The rate of infusion may be halved for mild to moderate infusional toxicity, and stopped if this is severe; the infusions may be restarted at half the rate once toxicity resolves. Patients are pretreated with thyroid protective agents at least 24 hours before the first radiolabelled dose of tositumomab; treatment is continued until 2 weeks after the radiolabelled therapeutic dose. Analgesics and antihistamines are also given by mouth 30 minutes before doses of tositumomab.

◊ References.

1. Kaminski MS, *et al.* Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. *J Clin Oncol* 2001; **19:** 3918–28.
2. Wahl RL. The clinical importance of dosimetry in radioimmunotherapy with tositumomab and iodine I 131 tositumomab. *Semin Oncol* 2003; **30** (suppl): 31–8.
3. Anonymous. Iodine-131 tositumomab (Bexxar) for treatment of lymphoma. *Med Lett Drugs Ther* 2003; **45:** 86–7.
4. Friedberg JW, Fisher RI. Iodine-131 tositumomab (Bexxar): radioimmunoconjugate therapy for indolent and transformed B-cell non-Hodgkin's lymphoma. *Expert Rev Anticancer Ther* 2004; **4:** 18–26.
5. Davies AJ, *et al.* Tositumomab and iodine I 131 tositumomab for recurrent indolent and transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol* 2004; **22:** 1469–79.
6. Vose JM. Bexxar : novel radioimmunotherapy for the treatment of low-grade and transformed low-grade non-Hodgkin's lymphoma. *Oncologist* 2004; **9:** 160–72.
7. Horning SJ, *et al.* Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab. *J Clin Oncol* 2005; **23:** 712–19.
8. Kaminski MS, *et al.* I-Tositumomab therapy as initial treatment for follicular lymphoma. *N Engl J Med* 2005; **352:** 441–9.
9. Fisher RI, *et al.* Tositumomab and iodine-131 tositumomab produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin's lymphomas. *J Clin Oncol* 2005; **23:** 7565–73.
10. Dosik AD, *et al.* Subsequent therapy can be administered after tositumomab and iodine I-131 tositumomab for non-Hodgkin lymphoma. *Cancer* 2005; **106:** 616–22.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Bexxar.

Trabectedin *(USAN, rINN)*

Ecteinascidin-743; ET-743; NSC-648766; Trabectedina; Trabectédine; Trabectedinum. (1′*R*,6*R*,6a*R*,7*R*,13*S*,14*S*,16*R*)-6′,8,-14-Trihydroxy-7′,9-dimethoxy-4,10,23-trimethyl-19-oxo-3′,4′,6,-7,12,13,14,16-octahydrospiro[6,16-(epithiopropanooxymethano)-7,13-imino-6a*H*-1,3-dioxolo[7,8]isoquino[3,2-*b*][3]benzazocine-20,1′(2′*H*)-isoquinolin]-5-yl acetate.

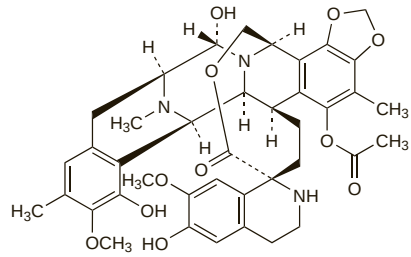
Трабектедин

$C_{39}H_{43}N_3O_{11}S$ = 761.8.

CAS — 114899-77-3.

ATC — L01CX01.

ATC Vet — QL01CX01.



Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p.635, p.639, and p.641. Neutropenia, thrombocytopenia, anaemia, and leucopenia are very common with trabectedin; febrile neutropenia often occurs. Full blood counts should be performed at baseline, weekly for the first 2 cycles, and then once between cycles thereafter. Dose reductions may be needed in those with haematological toxicity. Hepatobiliary disorders are also very common, and include hyperbilirubinaemia and alterations in liver function tests, which are mostly transient. Patients with liver disease should be closely monitored, and trabectedin should not be given to those with hyperbilirubinaemia.

Other very common adverse effects include gastrointestinal disturbances, anorexia, headache, and fatigue. Antiemetic prophylaxis with dexamethasone should be given to all patients. Peripheral sensory neuropathy, paraesthesia, dysgeusia, dizziness, pyrexia, and oedema are common, as are dyspnoea, cough, alopecia, myalgia, arthralgia, dehydration, hypokalaemia, hypotension, and flushing. Injection site reactions can occur, and the use of a central line is recommended.

Deaths associated with trabectedin treatment often involved a combination of adverse events including pancytopenia, febrile neutropenia, and in some cases sepsis, hepatic involvement, renal failure, and rhabdomyolysis.

Trabectedin may cause serious birth defects if given during pregnancy, although data are limited. Women and men of fertile age are advised to use effective contraception during treatment, and for 3 and 5 months, respectively, after stopping treatment. Breast