

**Profile**

Tipifarnib is a farnesyl transferase inhibitor that is under investigation for the treatment of acute myeloid leukaemia.

## ♦ References.

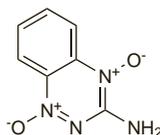
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- Siegel-Lakhai WS, et al. Clinical and pharmacologic study of the farnesyltransferase inhibitor tipifarnib in cancer patients with normal or mildly or moderately impaired hepatic function. *J Clin Oncol* 2006; **24**: 4558–64.
- Perez-Ruixo JJ, et al. Exposure-toxicity relationships for tipifarnib in cancer patients. *Br J Clin Pharmacol* 2007; **64**: 219–32.
- Martinelli G, et al. Farnesyltransferase inhibition in hematologic malignancies: the clinical experience with tipifarnib. *Clin Adv Hematol Oncol* 2008; **6**: 303–10.

**Tirapazamine** (USAN, *nINN*)

SR-4233; Tirapazamina; Tirapazaminum; Win-59075. 3-Amino-1,2,4-benzotriazine 1,4-dioxide.

Тирапазамин

$C_7H_6N_4O_2 = 178.1$   
CAS — 27314-97-2.

**Profile**

Tirapazamine is reported to be reduced in hypoxic cells to an active anion that causes DNA strand breaks. It sensitises hypoxic tumour cells to the cytotoxic activity of other drugs. It is under investigation for its cytotoxic actions, alone or with cisplatin or radiotherapy. Adverse effects reported with tirapazamine include nausea and vomiting, diarrhoea, skin rashes, muscle cramps and fatigue; myelosuppression is said to be rare.

## ♦ Reviews.

- Gandara DR, et al. Tirapazamine: prototype for a novel class of therapeutic agents targeting tumor hypoxia. *Semin Oncol* 2002; **29** (suppl 4): 102–9.

**Topotecan Hydrochloride**

(BANM, USAN, *pINN*)

Hydrochloruro de topotecán; SKF-104864A; SKFS-104864-A; Topotécane, Chlorhydrate de; Topotecani Hydrochloridum; Topotekanihydrokloridi; Topotekanihydroklorid. (S)-10-Dimethylaminomethyl-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7]indolizino[1,2b]quinoline-3,14(4H,12H)-dione hydrochloride.

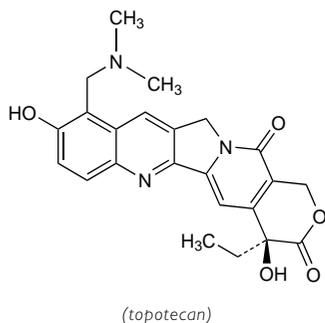
Топотекана Гидрохлорид

$C_{23}H_{23}N_3O_5 \cdot HCl = 457.9$ .

CAS — 123948-87-8 (topotecan); 119413-54-6 (topotecan hydrochloride).

ATC — L01XX17.

ATC Vet — QL01XX17.



(topotecan)

**Incompatibility.** Topotecan hydrochloride was found to degrade to 88.7% of its original concentration over 4 hours when mixed with ticarcillin sodium or potassium clavulanate. It was also found to be incompatible with dexamethasone sodium phosphate and fluorouracil.<sup>1</sup> When mixed with mitomycin solution an immediate colour change took place and concentrations of mitomycin fell by 15 to 20% over 4 hours. The pH of the mixtures remained constant at 3.3 to 3.5.

- Mayron D, Gennaro AR. Stability and compatibility of topotecan hydrochloride with selected drugs. *Am J Health-Syst Pharm* 1999; **56**: 875–81.

**Adverse Effects, Treatment, and Precautions**

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

Neutropenia is very common with topotecan and is usually dose-limiting. The nadir of white cell count usually occurs about 9 to 12 days after a dose. Febrile neutropenia, sepsis, and neutropenic colitis can occur; fatalities have been reported. Thrombocytopenia, anaemia, and leucopenia also occur commonly. Topotecan should not be given to those patients with pre-existing bone-marrow depression, and blood counts should be monitored regularly. Gastrointestinal disturbances and anorexia are also common with topotecan, and may be severe. Other adverse effects include fatigue and weakness, alopecia, malaise, pruritus, pyrexia, and hyperbilirubinaemia. Hypersensitivity reactions including rashes have been reported; anaphylaxis may occur rarely.

Licensed product information recommends that topotecan should not be given to patients with severe hepatic or renal impairment, due to a lack of data in these patients. Its use in breast feeding is contra-indicated for the same reason. Topotecan has been reported to produce fetal death and malformations in *animals*.

**Interactions**

For a report of topotecan reducing the clearance of docetaxel, see Antineoplastics, p.711.

Greater myelosuppression is seen when topotecan is used with other cytotoxic drugs, which may require dosage reductions of either drug. However, with platinum drugs, there is a sequence-dependent interaction; giving a platinum drug on the first day of topotecan dosage requires lower doses of each, compared with giving it on the fifth day.

Granulocyte colony-stimulating factor can prolong the duration of neutropenia if given with topotecan, so if used, it should not be started until, 24 hours after topotecan dosage is complete.

Ciclosporin has been reported to increase exposure to topotecan.

**Pharmacokinetics**

Topotecan is rapidly absorbed after oral doses; peak plasma concentrations occur after about 1 to 2 hours. The oral bioavailability is about 40%. Food does not appreciably affect topotecan pharmacokinetics. Topotecan is widely distributed after intravenous doses. Plasma protein binding is about 35%. The drug undergoes reversible hydrolysis of the lactone ring to the inactive hydroxy acid form; only small amounts are demethylated in the liver. A significant proportion of a dose is excreted in urine. The terminal half-life has been reported to be 2 to 3 hours for the intravenous formulation, and 3 to 6 hours for the oral formulation.

## ♦ References.

- Herben VMM, et al. Clinical pharmacokinetics of topotecan. *Clin Pharmacokinet* 1996; **31**: 85–102.

**Uses and Administration**

Like irinotecan (p.738), topotecan is a semisynthetic derivative of the alkaloid camptothecin that exerts its antineoplastic activity by inhibition of topoisomerase I. It is used in the treatment of metastatic carcinoma of the ovary refractory to other therapy (see p.670) and in relapsed small cell lung cancer (p.668) after standard therapy. Topotecan is given with cisplatin in the treatment of metastatic, recurrent, or persistent carcinoma of the cervix (p.663) which is not amenable to curative treatment with surgery and/or radiation therapy. Topotecan is also under investigation in the management of myelodysplastic syndromes.

Topotecan is given as the hydrochloride but doses are calculated in terms of the base. Topotecan hydrochloride 1.09 mg is equivalent to about 1 mg of topotecan.

In **ovarian and small cell lung cancer**, topotecan hydrochloride may be given *intravenously* in an initial

dose equivalent to topotecan 1.5 mg/m<sup>2</sup>, infused over 30 minutes, on days 1 to 5 of a 21-day course. A minimum of 4 courses should be given, in the absence of tumour progression, and provided that blood counts and haemoglobin have recovered adequately (see also Bone-marrow Depression, p.639). If severe neutropenia occurs in any course the dose in the subsequent courses may be reduced by 250 micrograms/m<sup>2</sup>, or a granulocyte colony-stimulating factor may be given from day 6 of the course, 24 hours after topotecan dosage is complete. If severe toxicity recurs once the dose has been reduced to 1 mg/m<sup>2</sup> withdrawal of topotecan may be required. Dosage should also be reduced after severe thrombocytopenia and in patients with renal impairment (see below).

Topotecan may also be given *orally* for small cell lung cancer. The recommended dose is 2.3 mg/m<sup>2</sup> once daily for 5 consecutive days, repeated every 21 days. If neutropenia occurs, or if the platelet count falls below 25 000 cells/mm<sup>3</sup>, or for patients with severe diarrhoea, the daily dose should be reduced by 400 micrograms/m<sup>2</sup> for subsequent courses.

In **cervical cancer**, topotecan is given in an intravenous dose of 750 micrograms/m<sup>2</sup>, infused over 30 minutes, on days 1, 2, and 3 of a 21-day course; cisplatin 50 mg/m<sup>2</sup> is given by intravenous infusion after topotecan on day 1. Dosage adjustments for subsequent courses are specific for each drug; for cisplatin, see p.700. If severe febrile neutropenia occurs, or if the platelet count falls below 10 000 cells/mm<sup>3</sup>, the topotecan dose should be reduced to 600 micrograms/m<sup>2</sup>. Alternatively, in the event of severe febrile neutropenia, granulocyte colony-stimulating factor may be given from day 4 of the course, 24 hours after completion of the topotecan infusion; if febrile neutropenia recurs despite this, topotecan dosage should be further reduced to 450 micrograms/m<sup>2</sup> for subsequent courses.

## ♦ References.

- Rocha Lima CM, Chiappori A. Treatment of relapsed small-cell lung cancer—a focus on the evolving role of topotecan. *Lung Cancer* 2003; **40**: 229–36.
- Armstrong DK. Topotecan dosing guidelines in ovarian cancer: reduction and management of hematologic toxicity. *Oncologist* 2004; **9**: 33–42.
- Ahmad T, Gore M. Review of the use of topotecan in ovarian carcinoma. *Expert Opin Pharmacother* 2004; **5**: 2333–40.
- Long HJ, et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group study. *J Clin Oncol* 2005; **23**: 4626–33.
- Randall-Whitis LM, Monk BJ. Topotecan in the management of cervical cancer. *Expert Opin Pharmacother* 2007; **8**: 227–36.
- Eckardt JR, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol* 2007; **25**: 2086–92. Correction. *ibid.*; 3387.
- Nicum SJ, O'Brien ME. Topotecan for the treatment of small-cell lung cancer. *Expert Rev Anticancer Ther* 2007; **7**: 795–801.
- O'Brien M, et al. Recent advances with topotecan in the treatment of lung cancer. *Oncologist* 2007; **12**: 1194–204.
- Ackermann S, et al. Topotecan in cervical cancer. *Int J Gynecol Cancer* 2007; **17**: 1215–23.
- Peng LH, et al. Topotecan for ovarian cancer. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 08/05/08).

**Administration in renal impairment.** Licensed product information for *intravenous* topotecan recommends the following for patients with **ovarian or small cell lung cancer** according to creatinine clearance (CC):

- mild renal impairment (CC 40 to 60 mL/minute): no dosage adjustment
- moderate renal impairment (CC 20 to 39 mL/minute): 0.75 mg/m<sup>2</sup> daily for 5 consecutive days

For patients with small cell lung cancer given *oral* topotecan, the following is suggested:

- mild renal impairment (CC 50 to 80 mL/minute): no dosage adjustment
- moderate renal impairment (CC 30 to 49 mL/minute): 1.8 mg/m<sup>2</sup> once daily for 5 consecutive days

Data are insufficient to make dose recommendations in patients with severe renal impairment.

In patients with **cervical cancer**, treatment with topotecan and cisplatin should only be started in those with a serum creatinine of 1.5 mg or less per 100 mL.

**Preparations**

**Proprietary Preparations** (details are given in Part 3)

**Arg.:** Asotecan; Hycamtin; Potekam; Tisogen; Topestin<sup>®</sup>; Topokebir; Topotag<sup>®</sup>; TPT<sup>®</sup>; **Austral.:** Hycamtin; **Austria:** Hycamtin; **Belg.:** Hycamtin; **Braz.:** Hycamtin; **Canad.:** Hycamtin; **Chile:** Hycamtin; **Cz.:** Hycamtin; **Denm.:** Hycamtin; **Fin.:** Hycamtin; **Fr.:** Hycamtin; **Ger.:** Hycamtin; **Gr.:** Hycamtin; **Hong Kong:** Hycamtin; **Hung.:** Hycamtin; **Viatopin.:** India: Topotel; **Irl.:** Hycamtin; **Israel:** Hycamtin; **Ital.:** Hycamtin; **Mex.:** Toranex;

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

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

Citrato de toremifeno; FC-1157a; Toremifene Citrat; Torémiféne, Citrate de; Toremifeni Citras. 2-[p-[(Z)-4-Chloro-1,2-diphenyl-1-butenyl]phenoxy]-N,N-dimethylethylamine citrate.

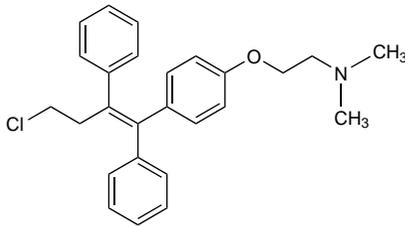
Торемифена Цитрат

C<sub>26</sub>H<sub>28</sub>ClNO<sub>7</sub> = 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.<sup>1</sup>

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 Pharmacokinetics* 2000; **39**: 327–34.

The symbol † denotes a preparation no longer actively marketed

**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; **Il.:** Fareston; **Ital.:** Fareston; **Mex.:** Fareston; **Neth.:** Fareston; **NZ:** Fareston; **Port.:** Fareston; **Rus.:** Fareston (Дапекрол); **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<sub>c</sub>-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 infusion 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): radioimmunotherapy 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,6R,6aR,7R,13S,14S,16R)-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-6aH-1,3-dioxolo[7,8]isouquinol[3,2-b]3]benzazocine-20,1'(2'H)-isouquinolin]-5-yl acetate.

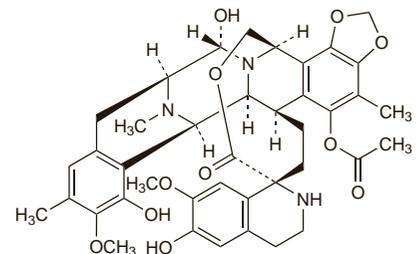
Трабектедин

C<sub>39</sub>H<sub>43</sub>N<sub>3</sub>O<sub>11</sub>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

The symbol ⊗ denotes a substance whose use may be restricted in certain sports (see p.vii)