Uses and Administration

Temsirolimus is an ester analogue of sirolimus (p.1841) that is given intravenously for the treatment of advanced renal cell carcinoma in a dose of 25 mg once weekly. Treatment may continue until disease progression or toxicity occurs. Temsirolimus is given in 250 mL sodium chloride 0.9% and infused over 30 to 60 minutes, preferably via an infusion pump.

Treatment should be interrupted if the absolute neutrophil count falls below 1000 cells/mm^3, or the platelet count falls below 75 000 cells/mm^3, or if grade 3 toxicity occurs. Once these have resolved to grade 2 or less, temsirolimus may be restarted with the dose reduced by 5 mg weekly, to a dose no lower than 15 mg weekly.

Use of strong inhibitors or inducers of CYP3A4 may increase or decrease exposure to sirolimus, the active metabolite of temsirolimus. If no alternative is available, a dose reduction of temsirolimus to 12.5 mg weekly should be considered if it is given with a strong CYP3A4 inhibitor. Once the inhibitor is stopped, a washout period of about 1 week should be allowed before the dose of temsirolimus is increased back to the original dose. A dose increase of temsirolimus to 50 mg weekly should be considered if it is given with a strong CYP3A4 inducer; once the inducer is stopped, the dose of temsirolimus should be decreased to the original dose.

Temsirolimus is also under investigation for the treatment of mantle cell lymphoma.

◊ References.

1. Anonymous. Temsirolimus: CCI 779, CCI-779, cell cycle inhibitor-779. *Drugs R D* 2004; **5:** 363–7.
2. Mounier N, *et al.* Activitié clinique du CCI779 (temsirolimus), inhibiteur de mTOR. *Bull Cancer* 2006; **93:** 1139–43.
3. Hudes G, *et al.* Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007; **356:** 2271–81.
4. Simpson D, Curran MP. Temsirolimus: in advanced renal cell carcinoma. *Drugs* 2008; **68:** 631–8.

Preparations

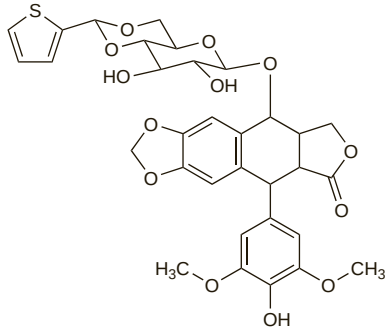
Proprietary Preparations (details are given in Part 3)
Cz.: Torisel; ***Fr.:*** Torisel; ***Port.:*** Torisel; ***USA:*** Torisel.

Teniposide *(BAN, USAN, rINN)*

ETP; NSC-122819; Teniposid; Téniposide; Teniposidi; Tenipósido; Teniposidum; VM-26. (5*S*,5a*R*,8a*S*,9*R*)-5,8,8a,9-Tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-9-(4,6-*O*-thenylidene-β-D-glucopyranosyloxy)isobenzofuro[5,6-*f*][1,3]benzodioxol-6(5a*H*)-one.

Тенипозид

$C_{32}H_{32}O_{13}S$ = 656.7.
CAS — 29767-20-2.
ATC — L01CB02.
ATC Vet — QL01CB02.



Stability. Precipitation occurred repeatedly in preparations for infusion containing teniposide 200 micrograms/mL in either glucose 5% or sodium chloride 0.9% injection, although previously such preparations had been used uneventfully.[1] Dilution of teniposide solutions to 100 micrograms/mL or less reduced the frequency of the problem, which could not be attributed to a change in formulation and remained unexplained.

1. Strong DK, Morris LA. Precipitation of teniposide during infusion. *Am J Hosp Pharm* 1990; **47:** 512,518.

Adverse Effects, Treatment, and Precautions

As for Etoposide, p.718. There is some evidence that teniposide may be a more potent mutagen and carcinogen than etoposide.

Hypersensitivity. Haemolytic anaemia and acute renal failure with tubular necrosis has been reported in a patient who developed an antibody to teniposide.[1] As with etoposide (p.718) hypersensitivity or infusion reactions occur, sometimes with the first dose, and may be severe;[2,3] the frequency may be as high as 13% in neuroblastoma patients.[2] Although it has been suggested that hypersensitivity reactions might be due to the polyoxyl castor oil in the injection vehicle,[2] studies *in vitro* suggest that it is the drug rather than the vehicle that is responsible.[3]

1. Habibi B, *et al.* Immune hemolytic anemia and renal failure due to teniposide. *N Engl J Med* 1982; **306:** 1091–3.
2. Siddall SJ, *et al.* Anaphylactic reactions to teniposide. *Lancet* 1989; **i:** 394.
3. Carstensen H, *et al.* Teniposide-induced hypersensitivity reactions in children. *Lancet* 1989; **ii:** 55.

Interactions

For a general outline of antineoplastic drug interactions, see p.642.

Antiepileptics. Clearance of teniposide was markedly increased by *phenytoin* or *phenobarbital*; the resultant decrease in systemic exposure to the antineoplastic might reduce its efficacy, and increased dosage would be needed in patients receiving these drugs to guarantee equivalent exposure.[1]

1. Baker DK, *et al.* Increased teniposide clearance with concomitant anticonvulsant therapy. *J Clin Oncol* 1992; **10:** 311–15.

Ciclosporin. Use of ciclosporin with teniposide has been reported[1] to produce a decrease in the clearance of the latter, with increased terminal half-life, peak plasma concentrations, and toxicity.

1. Toffoli G, *et al.* Cyclosporin A as a multidrug-resistant modulator in patients with renal cell carcinoma treated with teniposide. *Br J Cancer* 1997; **75:** 715–21.

Uses and Administration

Teniposide is an antineoplastic agent with general properties similar to those of etoposide (p.718). It has been given alone or with other antineoplastic agents in the treatment of refractory acute lymphoblastic leukaemia (p.651). Teniposide has been tried in solid tumours including neuroblastoma (p.674), and retinoblastoma (p.675).

Teniposide is given by slow intravenous infusion over at least 30 to 60 minutes, as a solution of up to 1 mg/mL in sodium chloride 0.9% injection or glucose 5% injection. Dosage regimens have ranged from 30 mg/m^2 every 5 days, to 180 mg/m^2 weekly, as a single agent. Doses of 165 mg/m^2 twice weekly for 8 or 9 doses with cytarabine, or up to 250 mg/m^2 weekly for 4 to 8 weeks with vincristine and prednisone have been given in the treatment of refractory acute lymphoblastic leukaemia.

Preparations

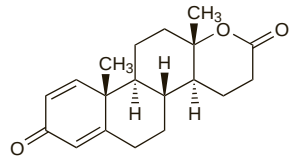
Proprietary Preparations (details are given in Part 3)
Arg.: Vumon; ***Austral.:*** Vumon; ***Austria:*** Vumon; ***Belg.:*** Vumon; ***Braz.:*** Vumon; ***Canad.:*** Vumon; ***Chile:*** Vumon; ***Cz.:*** Vumon†; ***Ger.:*** VM 26; ***Gr.:*** Vumon; ***Hong Kong:*** Vumon; ***Israel:*** Vumon†; ***Ital.:*** Vumon; ***Malaysia:*** Vumon†; ***Mex.:*** Vumon; ***Neth.:*** Vumon; ***NZ:*** Vumon; ***Pol.:*** Vumon; ***Port.:*** Vumon; ***S.Afr.:*** Vumon; ***Singapore:*** Vumon†; ***Spain:*** Vumon; ***USA:*** Vumon.

Testolactone *(USAN, rINN)* ⊗

1-Dehydrotestololactone; NSC-23759; SQ-9538; Testolactona; Testolactonum; Testolakton; Testolaktoni. D-Homo-17a-oxaandrosta-1,4-diene-3,17-dione.

Тестолактон

$C_{19}H_{24}O_3$ = 300.4.
CAS — 968-93-4.



Pharmacopoeias. In *US.*
USP 31 (Testolactone). A white to off-white, practically odourless, crystalline powder. Soluble 1 in 4050 of water; soluble in alcohol and in chloroform; slightly soluble in benzyl alcohol; insoluble in ether and in petroleum spirit. Store in airtight containers.

Profile

Testolactone is a derivative of testosterone (see p.2129). It is reported to be an aromatase inhibitor that reduces peripheral oestrogen synthesis but has no significant androgenic activity. It has been used in the palliative treatment of advanced breast cancer in postmenopausal women (p.661).

The usual oral dose is 250 mg four times daily.

It should not be given to men with breast cancer.

Peripheral neuropathies have occurred in patients given testolactone; gastrointestinal disturbances, pain or oedema of the extremities, hypertension, malaise, maculopapular erythema, and glossitis have also been reported.

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

Precocious puberty. Encouraging results have been reported using testolactone in the treatment of 5 girls with precocious puberty (p.2081) due to the McCune-Albright syndrome.[1] Testolactone is an aromatase inhibitor and blocks the synthesis of oestrogens from androgens. Long-term therapy (for up to 5 years) was associated with continued benefit in many patients; however, signs of puberty were not always completely suppressed, in some cases perhaps because of difficulties in maintaining the dosage regimen.[2] Encouraging results were also obtained using testolactone with spironolactone in the treatment of familial precocious puberty in boys, although neither agent was successful when used alone.[3] Again, signs of a reduced response to longer-term therapy have occurred; in this case control was restored by addition of a gonadorelin analogue.[4] Another study[5] in 10 boys who were treated for at least 6 years with spironolactone and testolactone, with deslorelin added at the onset of secondary central precocious puberty, found normalisation in growth rate and bone maturation, and improvements in predicted adult height.

1. Feuillan PP, *et al.* Treatment of precocious puberty in the McCune-Albright syndrome with the aromatase inhibitor testolactone. *N Engl J Med* 1986; **315:** 1115–19.
2. Feuillan PP, *et al.* Long term testolactone therapy for precocious puberty in girls with the McCune-Albright syndrome. *J Clin Endocrinol Metab* 1993; **77:** 647–51.
3. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone and testolactone. *N Engl J Med* 1989; **320:** 496–502.
4. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone, testolactone, and deslorelin. *J Clin Endocrinol Metab* 1993; **76:** 151–5.
5. Leschek EW, *et al.* Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. *J Clin Endocrinol Metab* 1999; **84:** 175–8.

Preparations

USP 31: Testolactone Tablets.

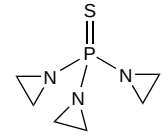
Proprietary Preparations (details are given in Part 3)
Chile: Teslac†; ***Ger.:*** Fludestrin†; ***USA:*** Teslac†.

Thiotepa *(BAN, rINN)*

NSC-6396; TESPA; Thiophosphamide; Thiotépa; Thiotepum; Tiotepa; Triethylenethiophosphoramide; TSPA; WR-45312. Phosphorothioic tri(ethyleneamide); Tris(aziridin-1-yl)phosphine sulphide.

Тиотепа

$C_6H_{12}N_3PS$ = 189.2.
CAS — 52-24-4.
ATC — L01AC01.
ATC Vet — QL01AC01.



Pharmacopoeias. In *Br.*, *Chin.*, *Fr.*, *Jpn*, and *US.*
BP 2008 (Thiotepa). Fine white, crystalline flakes. M.p. 52° to 57°. Freely soluble in water, in alcohol, and in chloroform. Store at 2° to 8°. At higher temperatures it polymerises and becomes inactive.
USP 31 (Thiotepa). Fine white, crystalline flakes, having a faint odour. M.p. 52° to 57°. Soluble 1 in 13 of water, 1 in about 8 of alcohol, 1 in about 2 of chloroform, and 1 in about 4 of ether. Store at 2° to 8° in airtight containers. Protect from light.

Incompatibility. Lyophilised thiotepa 1 mg/mL in glucose 5% was incompatible when mixed with solutions of cisplatin or minocycline hydrochloride.[1]

1. Trissel LA, Martinez JF. Compatibility of thiotepa (lyophilized) with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1041–5.

Stability. A solution of a lyophilised thiotepa preparation 0.5 mg/mL in glucose 5% was considered to be stable (less than 10% loss of thiotepa) for 8 hours at both 4° and 23°.[1] After 24 hours losses ranged between about 10 and 17%. A higher thiotepa concentration (5 mg/mL) was stable for 3 days at 23° and 14 days at 4°. Another study found that solutions containing 1 or 3 mg/mL of thiotepa in sodium chloride 0.9% were stable for 24 hours at 25° and 48 hours at 8°, but solutions containing 0.5% thiotepa needed to be used immediately.[2]

1. Xu QA, *et al.* Stability of thiotepa (lyophilized) in 5% dextrose injection at 4 and 23°C. *Am J Health-Syst Pharm* 1996; **53:** 2728–30.
2. Murray KM, *et al.* Stability of thiotepa (lyophilized) in 0.9% sodium chloride injection. *Am J Health-Syst Pharm* 1997; **54:** 2588–91.

Adverse Effects, Treatment, and Precautions

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

Bone-marrow depression may be delayed; the nadir of white cell and platelet counts may occur up to 30 days after therapy has been stopped. Bone-marrow depression has been reported after intravesical as well as parenteral use, and has occasionally been prolonged or fatal.

Gastrointestinal disturbances, fatigue, weakness, headache and dizziness, hypersensitivity reactions, blurred vision and conjunctivitis may occur. Amenorrhoea and impaired fertility have also been reported. Local irritation, and rarely frank chemical or haemorrhagic cystitis may follow intravesical instillation. Depigmentation of periorbital skin has occurred after the use of thi-