also given radiotherapy or corticosteroids, or during a longer dosing regimen of temozolomide. Other common adverse effects include gastrointestinal disturbances, anorexia, alopecia, fatigue, headache, rashes, convulsions, and insomnia or somnolence. Anxiety, depression, confusion, dizziness, hemiparesis, aphasia, dysphagia, peripheral neuropathy, paraesthesia, neurological and/or speech disorders, tremor, and concentration or memory impairment can occur, as can visual field defects, blurred vision, diplopia, hearing impairment, or tinnitus. Deafness has been reported. Vascular disorders such as haemorrhage, deep venous thrombosis, and peripheral oedema can occur; pulmonary embolism has been reported. Other commonly reported adverse effects include dyspnoea, coughing, dry skin, pruritus, arthralgia and/or myalgia, urinary incontinence, fever, pain, and dysgeusia. Liver enzyme values can increase, and hyperglycaemia may occur. Cushingoid disorders have occurred uncommonly. Hypersensitivity reactions, including rare cases of anaphylaxis, have been reported. Toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have been reported rarely. Temozolomide has carcinogenic, mutagenic, and teratogenic potential.

Pharmacokinetics

Temozolomide is rapidly and completely absorbed from the gastrointestinal tract, with peak plasma concentrations occurring 0.5 to 1.5 hours after a dose. Food reduces the rate and extent of absorption. It readily crosses the blood-brain barrier and can be detected in the CSF. The plasma elimination half-life is 1.8 hours. Temozolomide undergoes spontaneous hydrolysis to its active metabolite 5-(3-methyl-1-triazeno)imidazole-4-carboxamide (MTIC), which is then further hydrolysed to active and inactive compounds. It is largely eliminated by the kidneys, about 5 to 10% as unchanged drug.

Uses and Administration

Temozolomide is a prodrug that is converted to MTIC (see Pharmacokinetics, above), the active metabolite of dacarbazine (p.706). MTIC acts as an alkylating agent. Temozolomide is given orally and is licensed for the treatment of malignant gliomas such as glioblastoma multiforme and anaplastic astrocytoma, and malignant melanoma (below).

In adult patients with *newly diagnosed* **glioblastoma multiforme**, temozolomide is given initially with focal radiotherapy (the *concomitant phase*) in an oral dose of 75 mg/m^2 daily for 42 days. Treatment may be interrupted or stopped depending on toxicity. Complete blood counts should be monitored weekly. Four weeks after completing the concomitant phase, temozolomide *monotherapy* is begun at an oral dose of 150 mg/m^2 once daily for 5 days of a 28-day cycle. In cycle 2, the dose is increased to 200 mg/m^2 for 5 days, if toxicity allows. If the dose cannot be increased in cycle 2, it should not be increased in subsequent cycles. The dose used at cycle 2 is then given every 28 days, toxicity allowing. Up to 6 cycles of temozolomide monotherapy may be given.

The usual oral dose for *recurrent or progressive* malignant gliomas in adults and children over 3 years of age (and previously untreated with chemotherapy) is 200 mg/m^2 daily for 5 days, repeated every 28 days. In patients who have received previous courses of chemotherapy the dose should be reduced to 150 mg/m^2 for the first cycle of therapy, but may be increased to 200 mg/m^2 for subsequent courses if there is no haematological toxicity.

A dose of 200 mg/m^2 daily for 5 days every 28 days is also used for metastatic **malignant melanoma**.

Malignant neoplasms. Temozolomide has been studied[1-9] particularly in the management of malignant neoplasms of the brain (p.660). In the UK, guidance has been issued[10] on its use in patients with recurrent progressive malignant glioma who have failed first-line chemotherapy treatment with other agents (either because of lack of efficacy or because of adverse effects).

1. Dinnes J, *et al.* A rapid and systematic review of the effectiveness of temozolomide for the treatment of recurrent malignant glioma. *Br J Cancer* 2002; **86:** 501–5.
2. Wick W, *et al.* One week on/one week off: a novel active regimen of temozolomide for recurrent glioblastoma. *Neurology* 2004; **62:** 2113–15.
3. Levin N, *et al.* Chemotherapy as initial treatment in gliomatosis cerebri: results with temozolomide. *Neurology* 2004; **63:** 354–6.
4. Agarwala SS, *et al.* Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. *J Clin Oncol* 2004; **22:** 2101–7.
5. Stupp R, *et al.* Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005; **352:** 987–96.
6. Athanassiou H, *et al.* Randomized phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme. *J Clin Oncol* 2005; **23:** 2372–7.
7. Tosoni A, *et al.* Is protracted low-dose temozolomide feasible in glioma patients? *Neurology* 2006; **66:** 427–9.
8. Wick A, *et al.* Efficacy and tolerability of temozolomide in an alternating weekly regimen in patients with recurrent glioma. *J Clin Oncol* 2007; **25:** 3357–61.
9. Sher DJ, *et al.* The added value of concurrently administered temozolomide versus adjuvant temozolomide alone in newly diagnosed glioblastoma. *J Neurooncol* 2008; **88:** 43–50.
10. NICE. Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer) (issued April 2001). Available at: http://www.nice.org.uk/nicemedia/pdf/temozolomideguidance.pdf (accessed 30/07/08)

MELANOMA. Temozolomide has been studied[1-3] as a treatment for advanced metastatic melanoma (p.673). A phase III trial compared the overall survival-time in 305 patients treated with either oral temozolomide or intravenous dacarbazine in standard doses for up to 12 cycles of therapy. Temozolomide was found to be at least equivalent to dacarbazine in these patients, and there were no major differences in adverse effects.[2] However, median survival-times were short in both groups (7.7 months and 6.4 months respectively). Another phase III study comparing temozolomide alone or with interferon alfa in 282 patients also found modest median survival-times of 8.4 and 9.7 months respectively.[4] Temozolomide has also been investigated in *animals* for regional therapy of melanoma of the extremities by isolated limb infusion in combination with hyperthermia.[5]

1. Bleehen NM, *et al.* Cancer research campaign phase II trial of temozolomide in metastatic melanoma. *J Clin Oncol* 1995; **13:** 910–13.
2. Middleton MR, *et al.* Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol* 2000; **18:** 158–66.
3. Quirt I, *et al.* Temozolomide for the treatment of metastatic melanoma: a systematic review. *Oncologist* 2007; **12:** 1114–23.
4. Kaufmann R, *et al.* Temozolomide in combination with interferon-alfa versus temozolomide alone in patients with advanced metastatic melanoma: a randomized, phase III, multicenter study from the Dermatologic Cooperative Oncology Group. *J Clin Oncol* 2005; **23:** 9001–7.
5. Ko SH, *et al.* Optimizing a novel regional chemotherapeutic agent against melanoma: hyperthermia-induced enhancement of temozolomide cytotoxicity. *Clin Cancer Res* 2006; **12:** 289–97.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Dralitem; Temodal†; ***Austral.:*** Temodal; ***Austria:*** Temodal; ***Belg.:*** Temodal; ***Braz.:*** Temodal; ***Canad.:*** Temodal; ***Chile:*** Temodal; ***Cz.:*** Temodal; ***Denm.:*** Temodal; ***Fin.:*** Temodal; ***Fr.:*** Temodal; ***Ger.:*** Temodal; ***Gr.:*** Temodal; ***Hong Kong:*** Temodal; ***Hung.:*** Temodal; ***Indon.:*** Temodal; ***Irl.:*** Temodal; ***Israel:*** Temodal; ***Ital.:*** Temodal; ***Malaysia:*** Temodal; ***Mex.:*** Temodal; ***Neth.:*** Temodal; ***Norw.:*** Temodal; ***NZ:*** Temodal; ***Philipp.:*** Temodal; ***Pol.:*** Temodal; ***Port.:*** Temodal; ***Rus.:*** Temodal (Темодал); ***S.Afr.:*** Temodal; Temoxol†; ***Singapore:*** Temodal; ***Spain:*** Temodal; ***Swed.:*** Temodal; ***Switz.:*** Temodal; ***Thai.:*** Temodal; ***Turk.:*** Temodal; ***UK:*** Temodal; ***USA:*** Temodar; ***Venez.:*** Temodal.

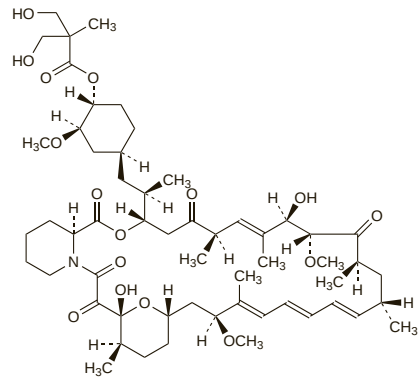
Temsirolimus *(BAN, USAN, rINN)*

CCI-779; Temsirolimusum. (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-{(1*R*)-2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl}-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4*H*,6*H*,31*H*)-pentone 4′[2,2-bis(hydroxymethyl)propionate].

Темсиролимус

$C_{56}H_{87}NO_{16}$ = 1030.3.

CAS — 162635-04-3.



Incompatibility. The formulation of temsirolimus injection contains polysorbate 80, which increases the rate of extraction of the plasticiser di-2-ethylhexylphthalate (DEHP) from PVC. In order to minimise exposure to DEHP, the infusion should be given in glass, polyolefin, or polyethylene containers, through non-DEHP giving sets with an in-line polyethersulfone filter of not greater than 5 microns.

Adverse Effects, Treatment, and Precautions

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

The most frequent adverse effects of temsirolimus include rash, asthenia, mucositis, gastrointestinal disturbances, anaemia, leucopenia, thrombocytopenia, hyperglycaemia, hyperlipidaemia, hypertriglyceridaemia, lymphopenia, and hypophosphataemia. Raised liver transaminase concentrations are common. Hypersensitivity reactions, including anaphylaxis, dyspnoea, flushing, and chest pain have occurred. Antihistamines should be given about 30 minutes before the start of the infusion. If the patient develops a hypersensitivity reaction, the infusion should be stopped and the patient observed for 30 to 60 minutes, after which treatment may be resumed if appropriate, at a slower infusion rate; a further dose of an H_1- or H_2-receptor antagonist may be given. Infections, including urinary-tract infection, pharyngitis, rhinitis, and pneumonia can occur. Acute, and sometimes fatal, renal failure has been reported. Interstitial lung disease has been reported, including some fatalities, although other cases were asymptomatic. Manifestations included dyspnoea, cough, hypoxia, or fever. Cases of fatal bowel perforation have occurred; patients presented with fever, abdominal pain, metabolic acidosis, bloody stools, diarrhoea, and/or acute abdomen. Abnormal wound healing has also been reported. Patients with CNS tumours given anticoagulants may be at increased risk of developing intracranial bleeding, which may be fatal.

Effects on the lungs. Eight out of 22 patients given temsirolimus developed pulmonary abnormalities compatible with drug-induced pneumonitis. Dyspnoea and dry cough were the most common symptoms, although 4 patients were asymptomatic. The risk of developing pulmonary toxicity is increased in those with abnormal pre-treatment pulmonary function, or a history of lung disease.[1]

1. Duran I, *et al.* Characterisation of the lung toxicity of the cell cycle inhibitor temsirolimus. *Eur J Cancer* 2006; **42:** 1875–80.

Interactions

Temsirolimus is metabolised primarily by the cytochrome P450 isoenzyme CYP3A4 to produce sirolimus. Ketoconazole had no effect on exposure to temsirolimus, but increased exposure to the metabolite. Use with other strong inhibitors of CYP3A4 (such as other azole antifungals, macrolide antibacterials, HIV-protease inhibitors, or grapefruit juice) may also increase sirolimus concentrations. Rifampicin had no effect on exposure to temsirolimus, but decreased exposure to sirolimus. Strong inducers of CYP3A4 (such as dexamethasone, phenytoin, carbamazepine, or phenobarbital) may also decrease exposure to sirolimus; St John's wort may decrease temsirolimus plasma concentrations unpredictably. If the use of alternative drugs is not feasible, dose adjustments of temsirolimus may be necessary (see Uses and Administration, below).

◊ References.

1. Boni J, *et al.* Pharmacokinetic profile of temsirolimus with concomitant administration of cytochrome P450-inducing medications. *J Clin Pharmacol* 2007; **47:** 1430–9.

Pharmacokinetics

Temsirolimus is mainly metabolised by cytochrome P450 isoenzyme CYP3A4 to 5 metabolites; sirolimus is the main active metabolite. The mean half-lives of temsirolimus and sirolimus are about 17 hours and 55 hours, respectively. Exposure to sirolimus may be much greater than that of temsirolimus, due principally to the longer half-life of sirolimus. Elimination is mainly in faeces; about 5% is recovered in the urine.

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

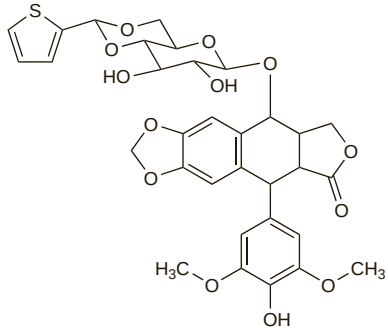
Proprietary Preparations (details are given in Part 3)
Cz.: Torisel; ***Fr.:*** Torisel; ***Port.:*** Torisel; ***USA:*** Torisel.

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

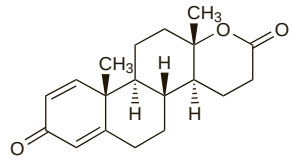
Proprietary Preparations (details are given in Part 3)
Arg.: Vumon; ***Austral.:*** Vumon; ***Austria:*** Vumon; ***Belg.:*** Vumon; ***Braz.:*** Vumon; ***Canad.:*** Vumon; ***Chile:*** Vumon; ***Cz.:*** Vumon†; ***Ger.:*** VM 26; ***Gr.:*** Vumon; ***Hong Kong:*** Vumon; ***Israel:*** Vumon†; ***Ital.:*** 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.

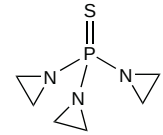
Proprietary Preparations (details are given in Part 3)
Chile: Teslac†; ***Ger.:*** Fludestrin†; ***USA:*** Teslac†.

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-