otepa eye drops. As with other alkylating agents, thiotepa is potentially mutagenic, teratogenic, and carcinogenic.

Thiotepa should be given with extreme care, if at all, to patients with pre-existing impairment of hepatic, renal, or bone-marrow function.

Pharmacokinetics

The absorption of thiotepa from the gastrointestinal tract is incomplete and unreliable; variable absorption also occurs from intramuscular injection sites. Absorption through serous membranes such as the bladder and pleura occurs to some extent. After intravenous doses it is rapidly cleared from plasma, with an elimination half-life of about 2.4 hours. It is extensively metabolised: triethylenephosphoramide (TEPA), the primary metabolite, and some of the other metabolites have cytotoxic activity and are eliminated more slowly than the parent compound. It is excreted in the urine: less than 2% of a dose is reported to be present as unchanged drug or its primary metabolite.

Uses and Administration

Thiotepa is an ethyleneimine compound whose antineoplastic effect is related to its alkylating action. It has generally been replaced by cyclophosphamide (p.703) or other drugs. It is not a vesicant and may be given by all parenteral routes, as well as directly into tumour masses.

Instillations of thiotepa may be used in the adjuvant treatment of superficial tumours of the bladder (p.659) and in the control of malignant effusions (p.659). It has been given parenterally in the palliative treatment of various solid tumours, including those of breast and ovary (p.661 and p.670). It has also been given intrathecally to patients with malignant meningeal disease, and has been used, in the form of eye drops, as an adjunct to the surgical removal of pterygium, to prevent recurrence (see p.753).

Thiotepa is given in a variety of dosage schedules. In general, initial doses to suit the individual patient are followed by maintenance doses given at intervals of 1 to 4 weeks. Blood counts are recommended before and during therapy and should continue for at least 3 weeks after stopping. Thiotepa should not be given if the white cell or platelet counts fall below acceptable levels (see also Bone-marrow Depression, p.639) and treatment should be stopped if the white cell count falls rapidly. Dosage should be reduced in patients with lesser degrees of leucopenia.

In the treatment of bladder cancer thiotepa in doses up to 60 mg may be instilled in 30 to 60 mL of sterile water or sodium chloride 0.9% into the bladder of a patient previously dehydrated for 8 to 12 hours, and retained if possible for 2 hours. The instillation may be repeated weekly for up to 4 weeks. Similar instillations have been given at intervals of 1 to 2 weeks, for up to 8 instillations in the prophylaxis of recurrence after surgical removal of bladder cancer. Single doses of 90 mg in 100 mL of sterile water have also been used prophylactically. For malignant effusions, doses of up to 60 mg of thiotepa in 20 to 60 mL of sterile water may be instilled after aspiration; in the USA the licensed dose is 600 to 800 micrograms/kg, a dose similar to that suggested for injection directly into tumours. Thiotepa for local use may be mixed with solutions of procaine and adrenaline.

Intramuscular and intravenous dosage regimens vary considerably; several regimens have used courses of 15 mg daily for 4 days. In the USA a licensed dose is 300 to 400 micrograms/kg given at 1- to 4-week intervals. A solution containing 1 mg/mL in sterile water has been tried intrathecally in doses of up to 10 mg given on alternate days, for up to 4 doses.

Thiotepa 0.05% in sterile Ringer's solution has been instilled as eye drops every 3 hours for up to 6 weeks after surgical removal of pterygium in order to reduce the likelihood of recurrence.

A dose of 60 mg weekly has been instilled into the urethra for the treatment of condylomata acuminata (genital warts). Topical application of thiotepa has also been used for condylomata.

Thiotepa is under investigation for use as conditioning therapy before haematopoietic stem cell transplantation.

Preparations

BP 2008: Thiotepa Injection;
USP 31: Thiotepa for Injection.

Proprietary Preparations (details are given in Part 3)
Gr.: Ledertepa†; ***Ital.:*** Thioplex; ***Neth.:*** Ledertepa; ***Spain:*** Onco Tiotepa†; ***USA:*** Thioplex.

Tioguanine *(BAN, rINN)*

NSC-752; 6-TG; Thioguanine *(USAN)*; 6-Thioguanine; Tioguaniini; Tioguanin; Tioguanina; Tioguaninum; WR-1141. 2-Aminopurine-6(1*H*)-thione; 2-Amino-6-mercaptopurine; 2-Aminopurine-6-thiol.

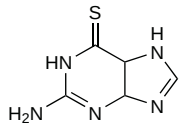
Тиогуанин

$C_5H_5N_5S$ = 167.2.

CAS — 154-42-7 (anhydrous tioguanine); 5580-03-0 (tioguanine hemihydrate).

ATC — L01BB03.

ATC Vet — QL01BB03.



Pharmacopoeias. In *Br.*, *Chin.*, and *US.*
BP 2008 (Tioguanine). A pale yellow, crystalline powder. Practically insoluble in water, in alcohol, and in chloroform; dissolves in dilute solutions of alkali hydroxides.
USP 31 (Thioguanine). It is anhydrous or contains one-half molecule of water of hydration. A pale yellow, odourless or practically odourless, crystalline powder. Insoluble in water and in chloroform; soluble 1 in 7700 of alcohol; freely soluble in dilute solutions of alkali hydroxides. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Mercaptopurine, p.744.

In some patients, gastrointestinal reactions are reported to be less frequent than with mercaptopurine.

Effects on the blood. For the view that it may be possible to predict those individuals likely to have severe bone-marrow depression with tioguanine based on measurement of the activity of thiopurine methyltransferase or the concentration of tioguanine nucleotide, see under Azathioprine, p.1819.

Effects on the liver. The use of tioguanine has been limited by reports of hepatic veno-occlusive disease attributed to the drug.[1-4] The manufacturer (*GlaxoSmithKline*) has stated that, in most cases, liver toxicity is reversible upon withdrawal of chemotherapy. A comparison with mercaptopurine in the maintenance treatment of children with acute lymphoblastic leukaemia found that of 95 patients who developed veno-occlusive disease, 82 were receiving tioguanine, representing about 11% of all patients assigned to the drug.[5] In addition, although tioguanine was associated with fewer CNS relapses, patients in the tioguanine arm were more likely to develop fatal infections.

Centrilobular hepatic necrosis has also been reported; reports are confounded by the use of high doses of tioguanine, other antineoplastics, oral contraceptives, and chronic alcohol abuse.

1. Gill RA, *et al.* Hepatic veno-occlusive disease caused by 6-thioguanine. *Ann Intern Med* 1982; **96:** 58–60.
2. Krivoy N, *et al.* Reversible hepatic veno-occlusive disease and 6-thioguanine. *Ann Intern Med* 1982; **96:** 788.
3. Kao NL, Rosenblate HJ. 6-Thioguanine therapy for psoriasis causing toxic hepatic venoocclusive disease. *J Am Acad Dermatol* 1993; **28:** 1017–18.
4. Romagosa R, *et al.* Treatment of psoriasis with 6-thioguanine and hepatic venoocclusive disease. *J Am Acad Dermatol* 2002; **47:** 970–2.
5. Vora A, *et al.* Medical Research Council/National Cancer Research Network Childhood Leukaemia Working Party. Toxicity and efficacy of 6-thioguanine versus 6-mercaptopurine in childhood lymphoblastic leukaemia: a randomised trial. *Lancet* 2006; **368:** 1339–48.

Handling and disposal. For reference to a method for the destruction of tioguanine in wastes, see Mercaptopurine, p.744.

Interactions

Unlike mercaptopurine (p.744), normal doses of tioguanine may be used with allopurinol.

A number of cases of portal hypertension with hepatic nodular regenerative hyperplasia have been reported in patients who received tioguanine with busulfan (see p.691).

It has been suggested that daunorubicin might enhance the hepatotoxicity of tioguanine (see p.709).

Pharmacokinetics

Tioguanine is incompletely and variably absorbed from the gastrointestinal tract; on average about 30% of a dose is absorbed after oral doses. It is rapidly activated in the body by intracellular conversion to its nucleotide, thioguanylic acid and its thioguanosine phosphate derivatives. With repeated doses increasing amounts of the nucleotide are incorporated into DNA. Very little unchanged tioguanine has been detected circulating in the blood but the half-life of the nucleotide in the tissues is prolonged. Tioguanine is inactivated primarily by methylation to aminomethylthiopurine; small amounts are deaminated to thioxanthine, and may go on to be oxidised by xanthine oxidase to thiouric acid, but inactivation is essentially independent of xanthine oxidase and is not affected by inhibition of the enzyme.

It is excreted in the urine almost entirely as metabolites; only negligible amounts of tioguanine have been detected. Tioguanine does not appear to cross the blood-brain barrier to a significant extent; very little is found in CSF after normal clinical doses. It crosses the placenta.

Uses and Administration

Tioguanine is an analogue of the naturally occurring purine, guanine, and is an antineoplastic with actions and uses similar to those of mercaptopurine (p.744). It appears to cause fewer gastrointestinal reactions but cross-resistance exists so that patients who do not respond to one are unlikely to respond to the other.

Tioguanine may be given orally, usually with other antineoplastics, in the induction of remissions in acute myeloid leukaemia (p.652). It has also been used in other malignancies including acute lymphoblastic leukaemia (p.651) and chronic myeloid leukaemia (p.653).

Doses of between 100 and 200 mg/m^2 daily have been given at various stages of treatment for short term cycles; similar doses have been used in children. A dose of 2 mg/kg daily increased after 4 weeks, if there is no response or toxicity allows, to 3 mg/kg daily may be given to adults and children in those rare cases when single agent therapy is considered appropriate.

Blood counts should be made frequently, particularly during induction and when tioguanine is given with other antineoplastics. Therapy should be withdrawn at the first sign of severe bone-marrow depression. Tioguanine is not recommended for long-term continuous therapy because of the high risk of hepatotoxicity (see Effects on the Liver, above).

Tioguanine has been given intravenously as the sodium salt.

Psoriasis. A report of the use of tioguanine, in doses ranging from 20 mg twice weekly to 120 mg daily, in the management of patients with refractory psoriasis.[1] Dramatic improvement occurred in 14 of 18 patients, but a further 2 were unable to tolerate the drug. Myelosuppression was the principal toxic effect and it was suggested that thiopurine methyltransferase activity could be measured as a basis to determine initial dosage and the risk of toxicity. For the conventional management of psoriasis see p.1583.

1. Mason C, Krueger GG. Thioguanine for refractory psoriasis. *J Am Acad Dermatol* 2001; **44:** 67–72.

Preparations

BP 2008: Tioguanine Tablets;
USP 31: Thioguanine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Lanvis; ***Austral.:*** Lanvis; ***Belg.:*** Lanvis; ***Braz.:*** Lanvis; ***Canad.:*** Lanvis; ***Chile:*** Lanvis; ***Cz.:*** Lanvis; ***Fr.:*** Lanvis; ***Gr.:*** Lanvis; ***Hong Kong:*** Lanvis; ***Irl.:*** Lanvis; ***Israel:*** Lanvis; ***Malaysia:*** Lanvis; ***Neth.:*** Lanvis; ***NZ:*** Lanvis; ***Pol.:*** Lanvis; ***S.Afr.:*** Lanvis; ***Singapore:*** Lanvis†; ***Swed.:*** Lanvis; ***Switz.:*** Lanvis; ***Thai.:*** Lanvis; ***UK:*** Lanvis; ***USA:*** Tabloid.

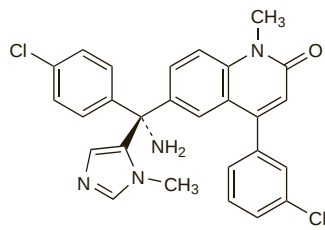
Tipifarnib *(USAN, rINN)*

R-115777; Tipifarnibum. (+)-6-[(*R*)-Amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone.

Типифарниб

$C_{27}H_{22}Cl_2N_4O$ = 489.4.

CAS — 192185-72-1.



Profile

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

◊ References.

1. Zhang S, *et al.* Pharmacokinetics of tipifarnib after oral and intravenous administration in subjects with advanced cancer. *J Clin Pharmacol* 2006; **46:** 1116–27.
2. 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.
3. Perez-Ruixo JJ, *et al.* Exposure-toxicity relationships for tipifarnib in cancer patients. *Br J Clin Pharmacol* 2007; **64:** 219–32.
4. Martinelli G, *et al.* Farnesyltransferase inhibition in hematologic malignancies: the clinical experience with tipifarnib. *Clin Adv Hematol Oncol* 2008; **6:** 303–10.

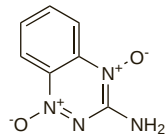
Tirapazamine *(USAN, rINN)*

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.

1. 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, pINNM)

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

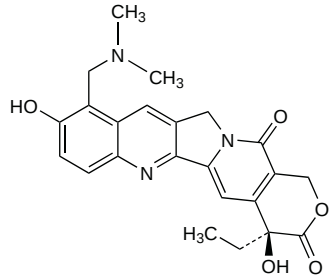
Топотекана Гидрохлорид

$C_{23}H_{23}N_3O_5$,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.[1] 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.

1. 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.

1. 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^2, 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^2, 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^2 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^2 once daily for 5 consecutive days, repeated every 21 days. If neutropenia occurs, or if the platelet count falls below 25 000 cells/mm^3, or for patients with severe diarrhoea, the daily dose should be reduced by 400 micrograms/m^2 for subsequent courses.

In **cervical cancer**, topotecan is given in an intravenous dose of 750 micrograms/m^2, infused over 30 minutes, on days 1, 2, and 3 of a 21-day course; cisplatin 50 mg/m^2 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^3, the topotecan dose should be reduced to 600 micrograms/m^2. 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^2 for subsequent courses.

◊ References.

1. 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.
2. Armstrong DK. Topotecan dosing guidelines in ovarian cancer: reduction and management of hematologic toxicity. *Oncologist* 2004; **9:** 33–42.
3. Ahmad T, Gore M. Review of the use of topotecan in ovarian carcinoma. *Expert Opin Pharmacother* 2004; **5:** 2333–40.
4. 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.
5. Randall-Whitis LM, Monk BJ. Topotecan in the management of cervical cancer. *Expert Opin Pharmacother* 2007; **8:** 227–36.
6. 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.
7. Nicum SJ, O'Brien ME. Topotecan for the treatment of small-cell lung cancer. *Expert Rev Anticancer Ther* 2007; **7:** 795–801.
8. O'Brien M, *et al.* Recent advances with topotecan in the treatment of lung cancer. *Oncologist* 2007; **12:** 1194–204.
9. Ackermann S, *et al.* Topotecan in cervical cancer. *Int J Gynecol Cancer* 2007; **17:** 1215–23.
10. 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^2 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^2 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†; Topokebir; Topotag†; TPT†; ***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;