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.

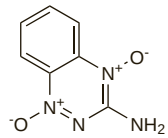
Tirapazamine *(USAN, rINN)*

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.

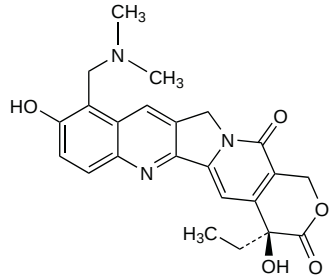
Топотекана Гидрохлорид

$C_{23}H_{23}N_3O_5$,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;