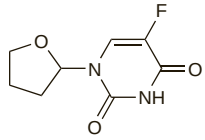
Tamoxi; ***Ital.:*** Kessar; Ledertam†; Nolvadex; Nomafen; Tamoxene; Virtamox†; ***Malaysia:*** Genox; Nolvadex; Novofen; Tamoplex; Zitazonium; ***Mex.:*** Bilem; Cryoxifeno; Fenobest; Kessar†; Nolvadex; Ralsifen-X; Tamoxan†; Taxus; Tecnofen; ***Neth.:*** Nolvadex; ***Norw.:*** Nolvadex; ***NZ:*** Genox; Nolvadex; Tamofen; ***Philipp.:*** Fenahex; Gynatam; Gyraxen; Kessar; Nolvadex; Tamoplex; Tamoxsta; Zitazonium; ***Pol.:*** Nolvadex; ***Port.:*** Mastofen; Nolvadex; Tamoxan; ***Rus.:*** Bilem (Билем)†; Tamifen (Тамифен); Zitazonium (Зитазониум); ***S.Afr.:*** Kessar; Neophedan; Nolvadex; Tamoplex; ***Singapore:*** Apo-Tamox; Nolvadex; Tamofen; ***Spain:*** Nolvadex; Sinmaren†; Yacesal; ***Swed.:*** Nolvadex; ***Switz.:*** Kessar†; Nolvadex; Tamec; ***Thai.:*** Bilem; Gynatam; Nolvadex; Novofen; Tamofen†; Tamoplex; Tuosomin; Zitazonium; ***Turk.:*** Nolvadex; Tadex; Tamofen; ***UAE:*** Tamophar; ***UK:*** Nolvadex; Soltamox; ***USA:*** Nolvadex†; Soltamox; ***Venez.:*** Gynatam; Nolvadex; Taxus.

Tegafur *(BAN, USAN, rINN)*

FT-207; Ftorafur; MJF-12264; NSC-148958; Tégafur; Tegafurum; Tegafuuri; WR-220066. 5-Fluoro-1-(tetrahydro-2-furyl)uracil; 5-Fluoro-1-(tetrahydro-2-furyl)pyrimidine-2,4(1*H*,3*H*)-dione.

Тегафур

$C_8H_9FN_2O_3$ = 200.2.
CAS — 17902-23-7.
ATC — L01BC03.
ATC Vet — QL01BC03.



Pharmacopoeias. In *Chin.* and *Jpn*.

Adverse Effects, Treatment, and Precautions

As for Fluorouracil, p.722.

Bone-marrow depression may be less severe with tegafur but gastrointestinal toxicity is often dose-limiting and central neurotoxicity is more common. Peripheral oedema and dyspnoea occur commonly. Increases in liver function test values are common and there are reports of fatal fulminant hepatitis. Liver function should be monitored in patients with hepatic impairment given tegafur; it should not be given in severe hepatic impairment.

Interactions

Tegafur should not be used with drugs that inhibit dihydropyrimidine dehydrogenase; fatalities have occurred in patients given tegafur and sorivudine (see Antivirals under Interactions of Fluorouracil, p.723). Increased plasma concentrations of phenytoin, and symptoms of toxicity during use with tegafur and uracil, have been reported.

Pharmacokinetics

Tegafur is well absorbed from the gastrointestinal tract after oral doses. After an intravenous dose it is reported to have a prolonged plasma half-life of 6 to 16 hours. Tegafur appears to be slowly metabolised in the liver to fluorouracil (p.723), and some intracellular conversion to fluorouracil may also occur. Tegafur crosses the blood-brain barrier and is found in the CSF.

◊ References.

1. Etienne-Grimaldi M-C, *et al.* A clinical pharmacokinetic analysis of tegafur-uracil (UFT) plus leucovorin given in a new twice-daily oral administration schedule. *Clin Pharmacokinet* 2007; **46:** 953–63.

Uses and Administration

Tegafur is considered to be an orally active prodrug of fluorouracil (p.723). It has been used in the management of malignant neoplasms including those of the breast, gallbladder, gastrointestinal tract, head and neck, liver, and pancreas. Tegafur has been given orally in doses up to 1 g/m^2 daily. It is often given with uracil (UFT; p.2407). Tegafur 300 mg/m^2 daily, with uracil 672 mg/m^2 daily, may be given in 3 divided oral doses, together with calcium folinate, in the management of metastatic colorectal cancer. Doses are given for a cycle of 28 days, followed by 7 days without treatment. The drugs should be taken 1 hour before or after meals, and doses modified according to toxicity. Doses of tegafur 1 to 3 g/m^2 daily for 5 days have been given intravenously.

Administration. Tegafur is an orally active prodrug of fluorouracil. Although it has been given as a single agent, it is more often used with drugs that modify its bioavailability and toxicity.[1] These include uracil (p.2407) and gimestat (5-chlorodihydropyrimidine, CDHP), which can increase fluorouracil concentrations by inhibition of dihydropyrimidine dehydrogenase, the enzyme responsible for its further catabolism,[1-3] and oxonic acid (otastat), which inhibits another enzyme, orotate pyrimidine phosphoribosyl transferase, thought to play a role in the gastrointestinal toxicity of fluorouracil and its prodrugs.[2]

UFT consists of tegafur and uracil in the optimal molar ratio 1:4.[1] It is available for the treatment of colorectal cancer (p.665)—for doses, see above. A preliminary analysis of a large study comparing oral UFT and calcium folinate therapy with intravenous fluorouracil and calcium folinate found both regimens to be well tolerated with similar levels of toxicity.[4] Adjuvant therapy with UFT appears to improve survival in patients with adenocarcinoma of the lung[5] and node-negative breast cancer.[6]

S-1 (TS-1, *Taiho Jpn*) is a combination of tegafur, gimestat and the potassium salt of oxonic acid in the molar ratio 10:4:10. It has been tried in gastric and colorectal cancers,[2,3,7,8] and initial results have suggested comparable activity to fluorouracil and calcium folinate in induction regimens, but the incidence of diarrhoea and stomatitis was reduced.

1. Adjei AA. A review of the pharmacology and clinical activity of new chemotherapy agents for the treatment of colorectal cancer. *Br J Clin Pharmacol* 1999; **48:** 265–77.
2. Sakata Y, *et al.* Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) in advanced gastric cancer patients. *Eur J Cancer* 1998; **34:** 1715–20.
3. Sugimachi K, *et al.* An early phase II study of oral S-1, a newly developed 5-fluorouracil derivative for advanced and recurrent gastrointestinal cancers. *Oncology* 1999; **57:** 202–10.
4. Smith R, *et al.* UFT plus calcium folinate vs 5-FU plus calcium folinate in colon cancer. *Oncology (Huntingt)* 1999; **13** (suppl 3): 44–7.
5. Kato H, *et al.* A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *N Engl J Med* 2004; **350:** 1713–21.
6. Noguchi S, *et al.* Postoperative adjuvant therapy with tamoxifen, tegafur plus uracil, or both in women with node-negative breast cancer: a pooled analysis of six randomized controlled trials. *J Clin Oncol* 2005; **23:** 2172–84.
7. Osugi H, *et al.* Oral fluoropyrimidine anticancer drug TS-1 for gastric cancer patients with peritoneal dissemination. *Oncol Rep* 2002; **9:** 811–15.
8. Shibahara K, *et al.* Retrospective study of S-1 versus tegafur/uracil and oral leucovorin in patients with metastatic colorectal cancer. *Anticancer Res* 2008; **28:** 1779–83.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Ftorafur; UFT; ***Hong Kong:*** Futraful; ***Hung.:*** Ftorafur; ***Indon.:*** Futraful; ***Ital.:*** Citofur†; ***Jpn:*** Futraful; ***Rus.:*** Ftorafur (Фторафур); ***Spain:*** Utefos; ***Thai.:*** UFUR.

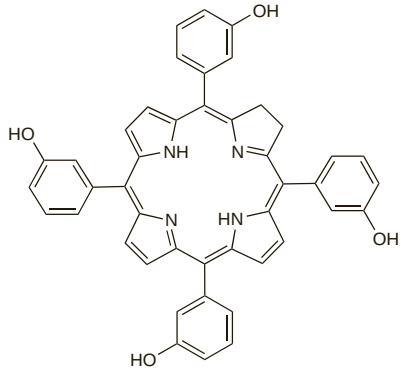
Multi-ingredient: ***Arg.:*** Asofurtal; UFT; ***Austria:*** UFT; ***Belg.:*** UFT; ***Braz.:*** UFT; ***Denm.:*** Uftoral; ***Fr.:*** UFT; ***Ger.:*** UFT; ***Gr.:*** UFT; ***Hong Kong:*** UFT; ***Hung.:*** UFT; ***Israel:*** UFT†; ***Ital.:*** UFT; ***Jpn:*** UFT; ***Malaysia:*** UFT; ***Mex.:*** UFT; ***Neth.:*** UFT; ***Norw.:*** UFT; ***NZ:*** Orzel†; ***Philipp.:*** Tefudex; UFT; ***Port.:*** UFT; ***Rus.:*** UFT (УФТ); ***S.Afr.:*** UFT; ***Singapore:*** UFT; ***Spain:*** UFT; ***Swed.:*** UFT; ***Thai.:*** UFT; ***Turk.:*** UFT; ***UK:*** Uftoral.

Temoporfin *(BAN, USAN, rINN)*

EF-9; mTHPC; Temoporfiini; Temoporfina; Témoporfine; Temoporfinum; *meso*-Tetrahydroxyphenylchlorin; *meta*-Tetrahydroxyphenylchlorin. 3,3′,3″,3‴-(7,8-Dihydroporphyrin-5,10,15,20-tetryl)tetraphenol; 7,8-Dihydro-5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrin.

Темопорфин

$C_{44}H_{32}N_4O_4$ = 680.7.
CAS — 122341-38-2.
ATC — L01XD05.
ATC Vet — QL01XD05.



Adverse Effects and Precautions

Adverse effects of temoporfin include photosensitivity, local inflammatory reactions, and gastrointestinal disturbances. Patients should be advised to avoid direct sunlight or bright indoor light for 15 days, and to protect the injection site from light for at least 3 months if extravasation has occurred.

Porphyria. The use of temoporfin is contra-indicated in patients with porphyria.

Interactions

Use of temoporfin with other drugs causing photosensitivity should be avoided as the reaction may be increased; this has been reported with topical fluorouracil.

Pharmacokinetics

Peak plasma concentrations of temoporfin are reached about 2 to 4 hours after intravenous infusion. Thereafter, elimination is bi-exponential, with a terminal plasma half-life of about 65 hours. Plasma protein binding is about 85%. *Animal* data indicate that temoporfin is metabolised in the liver and excreted in the faeces via the bile.

Uses and Administration

Temoporfin is a porphyrin derivative. It is used palliatively as a photosensitiser in the photodynamic therapy (see under Porfimer Sodium, p.764) of refractory squamous cell carcinoma of the head and neck (p.666), that cannot be treated with radiotherapy, surgery, or systemic chemotherapy. It is also under investigation in the treatment of various other malignant neoplasms. Temoporfin is given by slow intravenous injection over at least 6 minutes, at a dose of 150 micrograms/kg. This is followed 96 hours later by activation using a laser tuned to a wavelength of 652 nanometres for about 200 seconds, sufficient to supply a dose of 20 J/cm^2. Treatment may be repeated once after 4 weeks if necessary.

◊ References.

1. Kubler AC, *et al.* Photodynamic therapy of primary nonmelanomatous skin tumours of the head and neck. *Lasers Surg Med* 1999; **25:** 60–8.
2. Baas P, *et al.* Photodynamic therapy with *meta*-tetrahydroxyphenylchlorin for basal cell carcinoma: a phase I/II study. *Br J Dermatol* 2001; **145:** 75–8.
3. Kubler AC, *et al.* Treatment of squamous cell carcinoma of the lip using Foscan-mediated photodynamic therapy. *Int J Oral Maxillofac Surg* 2001; **30:** 504–9.
4. Javaid B, *et al.* Photodynamic therapy (PDT) for oesophageal dysplasia and early carcinoma with mTHPC (m-tetrahydroxyphenyl chlorin): a preliminary study. *Lasers Med Sci* 2002; **17:** 51–6.
5. Friedberg JS, *et al.* A phase I study of Foscan-mediated photodynamic therapy and surgery in patients with mesothelioma. *Ann Thorac Surg* 2003; **75:** 952–9.
6. Copper MP, *et al.* Meta-tetra(hydroxyphenyl)chlorin photodynamic therapy in early-stage squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg* 2003; **129:** 709–11.
7. D'Cruz AK, *et al.* mTHPC-mediated photodynamic therapy in patients with advanced, incurable head and neck cancer: a multicenter study of 128 patients. *Head Neck* 2004; **26:** 232–40.
8. Etienne J, *et al.* Photodynamic therapy with green light and mtetrahydroxyphenyl chlorin for intramucosal adenocarcinoma and high-grade dysplasia in Barrett's esophagus. *Gastrointest Endosc* 2004; **59:** 880–9. Correction. *ibid.*; **60:** 1042.
9. Hopper C, *et al.* mTHPC-mediated photodynamic therapy for early oral squamous cell carcinoma. *Int J Cancer* 2004; **111:** 138–46.
10. Lou PJ, *et al.* Interstitial photodynamic therapy as salvage treatment for recurrent head and neck cancer. *Br J Cancer* 2004; **91:** 441–6.
11. Campbell SM, *et al.* Photodynamic therapy using meta-tetrahydroxyphenylchlorin (Foscan) for the treatment of vulval intraepithelial neoplasia. *Br J Dermatol* 2004; **151:** 1076–80.
12. Naim R. Photodynamische Therapie mit m-THPC (Foscan): Behandlung von Plattenepithelkarzinomen im Kopf-Hals-Bereich. *HNO* 2008; **56:** 490–2.

Preparations

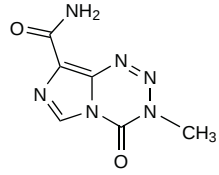
Proprietary Preparations (details are given in Part 3)
Belg.: Foscan; ***Cz.:*** Foscan; ***Denm.:*** Foscan; ***Ger.:*** Foscan; ***Gr.:*** Foscan; ***Israel:*** Foscan; ***Neth.:*** Foscan; ***Port.:*** Foscan; ***UK:*** Foscan.

Temozolomide *(BAN, USAN, rINN)*

CCRG-81045; M&B-39831; NSC-362856; Sch-52365; Temotsolomidi; Temozolomid; Temozolomida; Témozolomide; Temozolomidum. 3,4-Dihydro-3-methyl-4-oxoimidazo[5,1-*d*][1,2,-3,5]tetrazine-8-carboxamide.

Темозоломид

$C_6H_6N_6O_2$ = 194.2.
CAS — 85622-93-1.
ATC — L01AX03.
ATC Vet — QL01AX03.



Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641. Myelosuppression is common with temozolomide and is dose-limiting. The nadir of cell counts usually occurs 21 to 28 days after treatment, with recovery within the next 1 to 2 weeks. Patients over 70 years of age are thought to be more susceptible to severe myelosuppression. Prolonged pancytopenia may result in aplastic anaemia, and fatalities have been reported. Opportunistic infections can occur; *Pneumocystis jirovecii* pneumonia has been reported in patients

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.

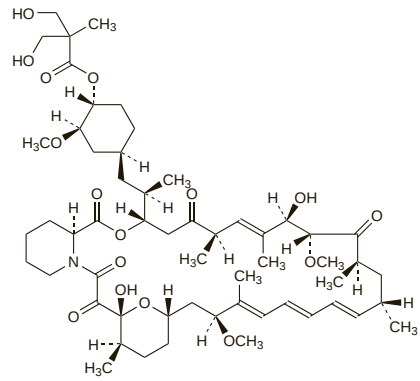
Temsirolimus *(BAN, USAN, rINN)*

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.