Sorafenib also inhibits the isoenzymes CYP2B6 and CYP2C8 *in vitro*, and drug interactions with substrates of these may occur.

Sorafenib may increase exposure to docetaxel, doxorubicin, and irinotecan; variable effects on fluorouracil have been reported.

Pharmacokinetics

Sorafenib reaches peak plasma concentrations about 3 hours after an oral dose. Absorption is reduced by about 30% after a high-fat meal. Plasma protein binding is about 99.5%. Sorafenib is metabolised primarily in the liver via the cytochrome P450 isoenzyme CYP3A4. It also undergoes glucuronidation. The elimination half-life of sorafenib is about 25 to 48 hours. About 96% of a dose is excreted within 14 days, with 77%, mostly as unchanged drug, recovered in the faeces, and 19% in the urine as glucuronidated metabolites.

◊ References.

1. Clark JW, *et al.* Safety and pharmacokinetics of the dual action Raf kinase and vascular endothelial growth factor receptor inhibitor, BAY 43-9006, in patients with advanced, refractory solid tumors. *Clin Cancer Res* 2005; **11:** 5472–80.

Uses and Administration

Sorafenib is an inhibitor of multiple intracellular and cell surface kinases thought to be involved in angiogenesis. It is given as the tosilate but doses are expressed in terms of the base; sorafenib tosilate 274 mg is equivalent to about 200 mg of sorafenib. Sorafenib is used in the treatment of advanced renal cell carcinoma and hepatocellular carcinoma. The recommended oral dose is 400 mg twice daily, given at least 1 hour before or 2 hours after food. Treatment is continued until no clinical benefit is seen or until unacceptable toxicity occurs. Doses are reduced to 400 mg once daily if toxicity occurs; further reduction to a single dose of 400 mg every other day may be necessary.

Sorafenib is under investigation for the treatment of locally unresectable and metastatic melanoma.

◊ References.

1. Rini BI. Sorafenib. *Expert Opin Pharmacother* 2006; **7:** 453–61.
2. Escudier B, *et al.* TARGET Study Group. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007; **356:** 125–34. Correction. *ibid.*; **357:** 203.
3. McKeage K, Wagstaff AJ. Sorafenib: in advanced renal cancer. *Drugs* 2007; **67:** 475–83.
4. Grandinetti CA, Goldspiel BR. Sorafenib and sunitinib: novel targeted therapies for renal cell cancer. *Pharmacotherapy* 2007; **27:** 1125–44.
5. Takimoto CH, Awada A. Safety and anti-tumor activity of sorafenib (Nexavar) in combination with other anti-cancer agents: a review of clinical trials. *Cancer Chemother Pharmacol* 2008; **61:** 535–48.
6. Hiles JJ, Kolesar JM. Role of sunitinib and sorafenib in the treatment of metastatic renal cell carcinoma. *Am J Health-Syst Pharm* 2008; **65:** 123–31.
7. Simpson D, Keating GM. Sorafenib: in hepatocellular carcinoma. *Drugs* 2008; **68:** 251–8.

Administration in hepatic or renal impairment. Sorafenib is primarily metabolised in the liver. Hepatic impairment may reduce exposure to sorafenib, compared with patients with normal hepatic function. In patients with hepatocellular carcinoma, exposure is comparable in patients with mild and moderate (Child-Pugh A and B) impairment. Licensed product information states that no dose adjustment is needed in patients with mild to moderate impairment. No data are available on patients with severe (Child-Pugh C) hepatic impairment.

Licensed product information states that no dose adjustment is needed in patients with mild, moderate, or severe renal impairment, but that no data are available for patients on dialysis.

Preparations

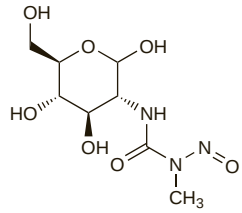
Proprietary Preparations (details are given in Part 3)
Arg.: Nexavar; ***Austral.:*** Nexavar; ***Chile:*** Nexavar; ***Cz.:*** Nexavar; ***Fr.:*** Nexavar; ***Gr.:*** Nexavar; ***Hung.:*** Nexavar; ***Indon.:*** Nexavar; ***Malaysia:*** Nexavar; ***Mex.:*** Nexavar; ***NZ:*** Nexavar; ***Port.:*** Nexavar; ***UK:*** Nexavar; ***USA:*** Nexavar.

Streptozocin *(USAN, rINN)*

Estreptozocina; NSC-85998; Streptotsosiini; Streptozocine; Streptozocinum; Streptozosin; Streptozotocin; U-9889. 2-Deoxy-2-(3-methyl-3-nitrosoureido)-D-glucopyranose.

Стрептозоцин

$C_8H_{15}N_3O_7$ = 265.2.
CAS — 18883-66-4.
ATC — L01AD04.
ATC Vet — QL01AD04.



Storage. Licensed product information recommends that the freeze-dried streptozocin preparation be stored at 2° to 8° and protected from light.

Adverse Effects, Treatment, and Precautions

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

Cumulative nephrotoxicity is common with streptozocin and may be severe and irreversible. Intra-arterial use may be associated with increased risk of nephrotoxicity.

Other adverse effects include severe nausea and vomiting and alterations in liver function or occasionally severe hepatotoxicity. Myelosuppression may occur but is rarely severe. Streptozocin may affect glucose metabolism. A diabetogenic effect has been reported; hypoglycaemia attributed to the release of insulin from damaged cells has also occurred.

Streptozocin is irritant to tissues and extravasation may lead to local ulceration and necrosis.

Streptozocin should be used with extreme care in patients with pre-existing renal impairment.

Handling and disposal. Methods for the destruction of streptozocin *waste* by reaction with hydrobromic acid in glacial acetic acid or by oxidation with a solution of potassium permanganate in sulfuric acid.[1] Residues produced by either method were free of mutagenic activity.

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73*. Lyon: WHO/International Agency for Research on Cancer, 1985.

Interactions

Streptozocin should not be given with other potentially nephrotoxic drugs. For increased doxorubicin toxicity when given with streptozocin see p.714.

Phenytoin. It has been suggested that because phenytoin appeared to protect the beta cells of the pancreas from the cytotoxic effects of streptozocin, its use with streptozocin should be avoided in patients being treated for pancreatic tumours.[1]

1. Koranyi L, Gero L. Influence of diphenylhydantoin on the effect of streptozotocin. *BMJ* 1979; **1:** 127.

Pharmacokinetics

After intravenous doses streptozocin is rapidly cleared from the blood and distributed to body tissues, particularly the liver, kidneys, intestines, and pancreas. It is extensively metabolised, mainly in the liver and perhaps the kidney, and excreted principally in the urine as metabolites and a small amount of unchanged drug. About 60 to 70% of an intravenous dose is excreted in urine within 24 hours. Some is also excreted via the lungs. Streptozocin itself does not cross the blood-brain barrier but its metabolites are found in the CSF.

Uses and Administration

Streptozocin is an antibiotic antineoplastic belonging to the nitrosoureas (see Carmustine, p.695) and is used, alone or with other antineoplastics, mainly in the treatment of pancreatic endocrine (islet-cell) tumours (p.643). It has been tried in other tumours including exocrine pancreatic cancer and prostate cancer. It is licensed for intravenous injection or infusion in doses of 1 g/m^2 weekly, increased if necessary after 2 weeks to up to 1.5 g/m^2. Alternatively doses of 500 mg/m^2 may be given daily for 5 days and repeated every 6 weeks.

Streptozocin has also been given by intra-arterial infusion (but see Adverse Effects above).

Full blood counts, and renal and hepatic function tests should be performed routinely during treatment; doses should be reduced or treatment withdrawn if renal toxicity occurs.

Preparations

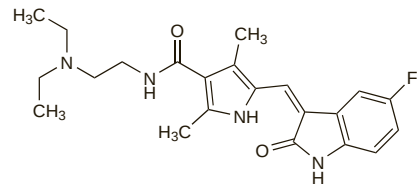
Proprietary Preparations (details are given in Part 3)
Canad.: Zanosar; ***Fr.:*** Zanosar; ***Gr.:*** Zanosar; ***Israel:*** Zanosar; ***USA:*** Zanosar.

Sunitinib Malate *(USAN, rINNM)*

Malato de sunitinib; PHA-290940AD; SU-010398; SU-011248 (sunitinib); Sunitinib, Malate de; Sunitinibi Malas. *N*-[2-(Diethylamino)ethyl]-5-[(*Z*)-(5-fluoro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide hydrogen (2*S*)-2-hydroxybutanedioate.

Сунитиниба Малат

$C_{22}H_{27}FN_4O_2{,}C_4H_6O_5$ = 532.6.
CAS — 557795-19-4 (sunitinib); 341031-54-7 (sunitinib malate).
ATC — L01XE04.
ATC Vet — QL01XE04.



(sunitinib)

Adverse Effects, Treatment, and Precautions

Common adverse effects of sunitinib include gastrointestinal disturbances, anorexia, headache, fatigue, fever, hypertension, hypothyroidism, mouth pain or irritation, dry mouth, mucosal inflammation, oedema, taste disturbances, arthralgia, and myalgia. Myelosuppression is common, and complete blood counts should be performed at the beginning of each treatment cycle. Other effects include dizziness, paraesthesia, dyspnoea, alopecia, Yellow skin discoloration and chromaturia can occur. Other dermatological effects include depigmentation of the hair or skin, dryness, rash, exfoliative dermatitis, or palmar-planter syndrome. Gastrointestinal perforation has been reported rarely; fatalities have been reported in patients with intra-abdominal malignancies.

Decreases in left ventricular ejection fraction (LVEF) have occurred with sunitinib; baseline and periodic evaluations of LVEF should be taken. Patients should be monitored for signs of congestive cardiac failure and therapy interrupted or stopped if they occur. Dose reductions may be necessary in patients who show no signs of heart failure but who show decreases in LVEF. Sunitinib may prolong the QT interval and should be used with caution in patients with a history of this, who are taking antiarrhythmics, or who have pre-existing cardiac disease, bradycardia, or electrolyte disturbances.

There is an increased risk of bleeding at all sites; epistaxis is the most common treatment-related bleeding event but fatal pulmonary haemorrhage has occurred in patients with lung cancer. Pulmonary embolism or venous thromboembolic events may occur. Patients under stresses such as surgery, trauma, or severe infection should be monitored for adrenal insufficiency. Increases in serum amylase and lipase concentrations have been seen and there are rare reports of pancreatitis and hepatic failure. There are also rare reports of seizures and reversible posterior leukoencephalopathy syndrome.

Effects on the cardiovascular system. A retrospective review in 75 patients given repeating cycles of sunitinib in phase I/II studies of its efficacy for gastrointestinal stromal tumours found that cardiovascular events occurred in 8, of whom 6 developed congestive heart failure.[1] Of 36 patients given the subsequently approved dose, 10 had reductions in left ventricular ejection fraction of at least 10%. Hypertension developed in 35 of the 75 patients, and it was suggested that left ventricular dysfunction might be due to a combination of hypertension and a direct toxic effect on heart muscle.

For the relative risk of developing hypertension with sunitinib, and the view that this may be an effect common to angiogenesis inhibitors, see under Sorafenib, p.770.

1. Chu TF, *et al.* Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet* 2007; **370:** 2011–19.

Effects on the kidneys. For a report of haemolytic-uraemic syndrome after the use of bevacizumab and sunitinib, see Effects on the Kidneys, under Bevacizumab, p.685.

Effects on the nervous system. Coma has been reported with sunitinib; therapy was immediately stopped and the patient regained consciousness within 24 hours.[1]

1. Arnaud L, *et al.* Transient sunitinib-induced coma in a patient with fibromyxoid sarcoma. *J Clin Oncol* 2008; **26:** 1569–71.

Effects on the skin. A patient developed palmar-plantar syndrome and rashes resembling seborrhoeic dermatitis while taking sunitinib. Therapy was stopped and the rash was treated with a topical corticosteroid; blisters on the palms and soles resolved with desquamation.[1]

1. Tsai K-Y, *et al.* Hand-foot syndrome and seborrheic dermatitis-like rash induced by sunitinib in a patient with advanced renal cell carcinoma. *J Clin Oncol* 2006; **24:** 5786–8.

Effects on thyroid function. Hypothyroidism is common after sunitinib therapy. A cohort study found that 36% of patients developed hypothyroidism after an average of 50 weeks of therapy. The incidence of hypothyroidism increased with the duration of therapy, and the effect was not transient; patients needed replacement therapy with levothyroxine. Mild thyrotoxicosis may precede the onset of hypothyroidism. Although the mechanism is not clear, the drug may cause destructive thyroiditis. Patients should be screened for hypothyroidism and serum concentrations of thyroid-stimulating hormone (TSH) measured at suggested intervals of 2 to 3 months.[1]

1. Desai J, *et al.* Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. *Ann Intern Med* 2006; **145:** 660–4.

Tumour lysis syndrome. Tumour lysis syndrome has been reported after treatment with sunitinib; electrolytes and renal function should be closely monitored.[1,2]

1. Nicholaou T, *et al.* Tumour lysis syndrome in a patient with renal-cell carcinoma treated with sunitinib malate. *Lancet* 2007; **369:** 1923–4.
2. Saylor PJ, Reid TR. Tumor lysis syndrome after treatment of a gastrointestinal stromal tumor with the oral tyrosine kinase inhibitor sunitinib. *J Clin Oncol* 2007; **25:** 3544–6.

Interactions

Sunitinib is metabolised primarily by the cytochrome P450 isoenzyme CYP3A4 to produce an active metabolite, which is further metabolised by CYP3A4. Ketoconazole increased exposure to sunitinib, and use with other potent inhibitors of CYP3A4 (such as other azole antifungals, macrolide antibacterials, HIV-protease inhibitors, or grapefruit juice) may also increase sunitinib concentrations. Conversely, use with rifampicin decreased exposure to sunitinib, and inducers of CYP3A4 (such as dexamethasone, phenytoin, carbamazepine, phenobarbital, or St John's wort) may decrease plasma sunitinib concentrations. If the use of alternative drugs is not feasible, dose adjustments of sunitinib may be necessary (see Uses and Administration, below).

◊ The US manufacturer of *bevacizumab* has recommended that it should not be used with sunitinib after several patients receiving the combination had developed microangiopathic haemolytic anaemia.[1]

1. Genentech, USA. Important drug warning subject: microangiopathic hemolytic anemia (MAHA) in patients treated with Avastin (bevacizumab) and sunitinib malate (issued July 2008). Available at: http://www.fda.gov/medwatch/safety/2008/MAHA_DHCP.pdf (accessed 30/07/08)

Pharmacokinetics

Maximum plasma concentrations occur 6 to 12 hours after an oral dose of sunitinib. Bioavailability is unaffected by food. Sunitinib is metabolised mainly via the cytochrome P450 isoenzyme CYP3A4 to its primary active metabolite, which itself is then further metabolised via CYP3A4. Plasma protein binding of sunitinib and its metabolite is about 95% and 90%, respectively; plasma elimination half-lives are 40 to 60 hours, and 80 to 110 hours, respectively. Sunitinib is excreted mainly in faeces; about 16% is found in urine, as unchanged drug and metabolites.

Uses and Administration

Sunitinib malate is an inhibitor of several receptor tyrosine kinases. It is used for the treatment of gastrointestinal stromal tumours (see Soft-tissue Sarcoma, p.676) after disease progression during imatinib treatment, or in patients intolerant to imatinib. It is also used for the treatment of advanced and/or metastatic renal cell carcinoma (p.667).

Sunitinib is given orally as the malate, but doses are expressed in terms of the base; sunitinib malate 66.8 mg is equal to about 50 mg of sunitinib. The recommended dose is 50 mg once daily, for 4 weeks of a 6-week treatment cycle. Doses may be increased or decreased in steps of 12.5 mg, based on individual tolerability. UK licensed product information recommends that the daily dose should not normally exceed 75 mg nor be decreased below 25 mg.

Use of inhibitors or inducers of CYP3A4 may increase or decrease sunitinib plasma concentrations. If no alternative is available, a dose reduction of sunitinib to a minimum of 37.5 mg daily should be considered if it is given with a strong CYP3A4 inhibitor. Doses can be increased to a maximum of 87.5 mg daily if sunitinib is given with a CYP3A4 inducer; the patient should be closely monitored for toxicity.

◊ References.

1. Motzer RJ, *et al.* Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006; **24:** 16–24.
2. Faivre S, *et al.* Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J Clin Oncol* 2006; **24:** 25–35.
3. Motzer RJ, *et al.* Sunitinib malate for the treatment of solid tumours: a review of current clinical data. *Expert Opin Invest Drugs* 2006; **15:** 553–61.
4. Motzer RJ, *et al.* Sunitinib in patients with metastatic renal cell carcinoma. *JAMA* 2006; **295:** 2516–24.
5. Deeks ED, Keating GM. Sunitinib. *Drugs* 2006; **66:** 2255–66.
6. Demetri GD, *et al.* Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006; **368:** 1329–38.
7. Motzer RJ, *et al.* Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007; **356:** 115–24.
8. Goodman VL, *et al.* Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. *Clin Cancer Res* 2007; **13:** 1367–73.
9. O'Brien MF, *et al.* Sunitinib therapy in renal cell carcinoma. *BJU Int* 2008; **101:** 1339–42.
10. Socinski MA. The current status and evolving role of sunitinib in non-small cell lung cancer. *J Thorac Oncol* 2008; **3** (suppl 2): S119–S123.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Sutent; ***Austral.:*** Sutent; ***Braz.:*** Sutent; ***Cz.:*** Sutent; ***Fr.:*** Sutent; ***Gr.:*** Sutent; ***Hung.:*** Sutent; ***Malaysia:*** Sutent; ***NZ:*** Sutent; ***Port.:*** Sutent; ***UK:*** Sutent; ***USA:*** Sutent.

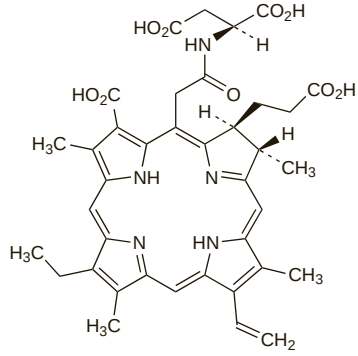
Talaporfin Sodium *(USAN, rINNM)*

LS-11; Monoaspartyl Chlorin e6 (talaporfin); Natrii Talaporfinum; NPe-6 (talaporfin); Talaporfina sódica; Talaporfine Sodique; Taporfin Sodium. Tetrasodium *N*-{[(7*S*,8*S*)-3-carboxy-7-(2-carboxyethyl)-13-ethenyl-18-ethyl-7,8-dihydro-2,8,12,17-tetramethyl-21*H*,23*H*-porphin-5-yl]acetyl}-L-aspartate.

Натрий Талапорфин

$C_{38}H_{41}N_5Na_4O_9$ = 803.7.

CAS — 110230-98-3 (talaporfin); 220201-34-3 (talaporfin sodium).



(talaporfin)

Profile

Talaporfin sodium is a photosensitiser that is used for the photodynamic therapy (see under Porfimer Sodium, p.764) of lung cancer. It is also under investigation for the treatment of other tumours.

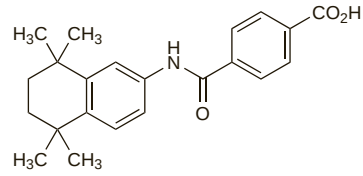
Tamibarotene *(rINN)*

AM-80; Tamibarotène; Tamibaroteno; Tamibarotenum. *N*-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)terephthalamic acid.

Тамибаротен

$C_{22}H_{25}NO_3$ = 351.4.

CAS — 94497-51-5.



Profile

Tamibarotene is a synthetic retinoid that is given orally for the treatment of relapsed or refractory acute promyelocytic leukaemia.

Malignant neoplasms. Tamibarotene has been used to induce remission in patients with acute promyelocytic leukaemia (see Acute Myeloid Leukaemias, p.652) who relapsed after successful remission induction with tretinoin.[1,2] Twenty-four patients received tamibarotene at a daily oral dose of 6 mg/m^2; 14 patients obtained complete remission after a median of 41 days.[1] Reported adverse effects include hypercholesterolaemia, hypertriglyceridaemia,[1,3] cheilitis, xerosis, gastrointestinal disturbances, bone pain, headache, dermatitis, liver damage, and leucocytosis; in one case, retinoic acid syndrome occurred.[1]

1. Tobita T, *et al.* Treatment with a new synthetic retinoid, Am80, of acute promyelocytic leukemia relapsed from complete remission induced by all-trans retinoic acid. *Blood* 1997; **90:** 967–73.
2. Shinjo K, *et al.* Good prognosis of patients with acute promyelocytic leukemia who achieved second complete remission (CR) with a new retinoid, Am80, after relapse from CR induced by all-trans-retinoic acid. *Int J Hematol* 2000; **72:** 470–3.
3. Takeuchi M, *et al.* Relapsed acute promyelocytic leukemia previously treated with all-trans retinoic acid: clinical experience with a new synthetic retinoid, Am-80. *Leuk Lymphoma* 1998; **31:** 441–51.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Amnolake.

Tamoxifen Citrate *(BANM, USAN, rINNM)* ⊗

Citrato de tamoxifeno; ICI-46474; Tamoksifeenisitraatti; Tamoksifen Sitrat; Tamoksifeno citratas; Tamoxifen citrát; Tamoxifencitrat; Tamoxifén-citrát; Tamoxifène, citrate de; Tamoxifeni citras. (*Z*)-2-[4-(1,2-Diphenylbut-1-enyl)phenoxy]ethyldimethylamine citrate.

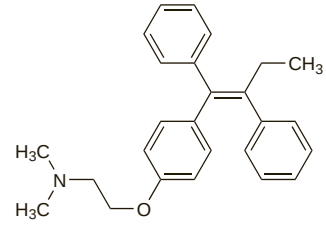
Тамоксифена Цитрат

$C_{26}H_{29}NO,C_6H_8O_7$ = 563.6.

CAS — 10540-29-1 (tamoxifen); 54965-24-1 (tamoxifen citrate).

ATC — L02BA01.

ATC Vet — QL02BA01.



(tamoxifen)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Tamoxifen Citrate). A white or almost white, polymorphic, crystalline powder. Slightly soluble in water and in acetone; soluble in methyl alcohol.

USP 31 (Tamoxifen Citrate). A white, fine, crystalline powder. Very slightly soluble in water, in alcohol, in acetone, and in chloroform; soluble in methyl alcohol. Protect from light.

Adverse Effects

The most frequent adverse effects of tamoxifen are hot flushes. Other adverse effects include fluid retention, nausea, gastrointestinal intolerance, vaginal bleeding or discharge, pruritus vulvae, rashes, dry skin, and alopecia. There have also been reports of dizziness, head-