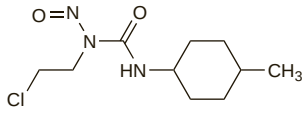
3. Sternberg CN, *et al.* Phase III trial of satraplatin, an oral platinum plus prednisone vs. prednisone alone in patients with hormone-refractory prostate cancer. *Oncology* 2005; **68:** 2–9.
4. Sternberg CN. Satraplatin in the treatment of hormone-refractory prostate cancer. *BJU Int* 2005; **96:** 990–4.
5. McKeage MJ. Satraplatin in hormone-refractory prostate cancer and other tumour types: pharmacological properties and clinical evaluation. *Drugs* 2007; **67:** 859–69.

Semustine *(USAN, rINN)*

Methyl Lomustine; Methyl-CCNU; NSC-95441; Semustiini; Semustin; Semustina; Sémustine; Semustinum; WR-220076. 1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea.

Семустин

$C_{10}H_{18}ClN_3O_2$ = 247.7.
CAS — 13909-09-6.
ATC — L01AD03.
ATC Vet — QL01AD03.



Pharmacopoeias. In *Chin.*

Adverse Effects, Treatment, and Precautions

As for Carmustine, p.694.

Effects on the kidneys. Nephrotoxicity has been reported in patients receiving high cumulative doses of semustine. Severe renal damage was reported in 6 of 17 children given semustine after radiotherapy for brain tumours; all 6 children had received a total dose above 1.5 g/m^2 in contrast to those not so affected, who had received lower doses.[1] A decrease in kidney size was seen in 2 patients who had received lower cumulative doses. There had been no evidence during treatment that patients were losing renal function. Similarly others have reported an increased risk of renal abnormalities in patients given a cumulative dose of 1.4 g/m^2 or more.[2] Some 25% of patients given higher doses were so affected, while those given lower doses were not. Overall, however, the problem may not be particularly frequent: in one study it was considered that only 4 of 857 patients treated with semustine over 6 years might have had delayed renal insufficiency possibly related to semustine.[3]

1. Harmon WE, *et al.* Chronic renal failure in children treated with methyl-CCNU. *N Engl J Med* 1979; **300:** 1200–3.
2. Micetich KC, *et al.* Nephrotoxicity of semustine (methyl-CC-NU) in patients with malignant melanoma receiving adjuvant chemotherapy. *Am J Med* 1981; **71:** 967–72.
3. Nichols WC, Moertel CG. Nephrotoxicity of methyl-CCNU. *N Engl J Med* 1979; **301:** 1181.

Pharmacokinetics

Semustine is well absorbed from the gastrointestinal tract after oral doses, and is rapidly metabolised. The metabolites are reported to possess prolonged plasma half-lives, and cross the blood-brain barrier into the CSF. It is excreted in urine as metabolites: up to 60% of a dose is excreted in this way within 48 hours. Small amounts may be excreted in faeces and via the lungs as carbon dioxide.

Uses and Administration

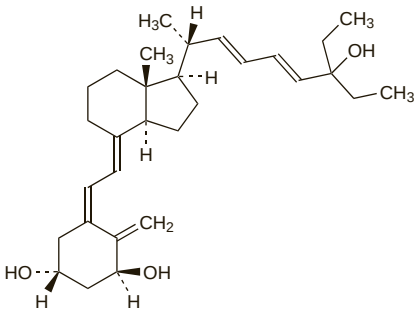
Semustine is a nitrosourea with actions and uses similar to those of carmustine (p.695) and lomustine (p.741).

Seocalcitol *(BAN, rINN)*

EB-1089; Séocalcitol; Seocalcitolum. (5*Z*,7*E*,22*E*,24*E*)-24a,26a,27a-Trihomo-9,10-secocholesta-5,7,10(19),22,24-pentaene-1α,3β,25-triol.

Сеокальцитол

$C_{30}H_{46}O_3$ = 454.7.
CAS — 134404-52-7.



Profile

Seocalcitol is a vitamin D analogue that has been investigated for the treatment of hepatocellular carcinoma.

Sizofiran *(rINN)*

Schizophyllan; Sizofirán; Sizofiranum. Poly[3→-(*O*-β-D-glucopyranosyl-(1→3)-*O*-[β-D-glucopyranosyl-(1→6)]-*O*-β-D-glucopyranosyl-(1→3)-*O*-β-D-glucopyranosyl)→1].

Сизофиран

$(C_{24}H_{40}O_{20})_n$.
CAS — 9050-67-3.

Profile

Sizofiran is a polysaccharide obtained from cultures of the basidiomycete fungus *Schizophyllum commune*. It is reported to have antineoplastic and immunomodulating activity and is given with radiotherapy in malignant neoplasms of the cervix (p.663). It is given by intramuscular injection in usual doses of 40 mg weekly. It has also been tried with chemotherapy or radiotherapy in other malignant neoplasms. Hypersensitivity reactions, including anaphylactoid shock, may occur.

Preparations

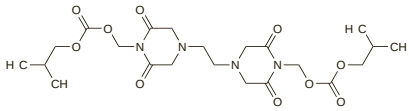
Proprietary Preparations (details are given in Part 3)
Jpn: Sonifilan.

Sobuzoxane *(rINN)*

MST-16; Sobuzoxano; Sobuzoxanum. 4,4′-Ethylenebis[1-(hydroxymethyl)-2,6-piperazinedione] bis(isobutyl carbonate).

Собузоксан

$C_{22}H_{34}N_4O_{10}$ = 514.5.
CAS — 98631-95-9.



Profile

Sobuzoxane is an orally active inhibitor of topoisomerase II that has been used for its antineoplastic properties in the treatment of non-Hodgkin's lymphomas and adult T-cell leukaemia/lymphoma. Adverse effects include myelosuppression, bleeding tendency, renal and hepatic dysfunction, gastrointestinal disturbances, alopecia, headache, and fever.

◊ References.

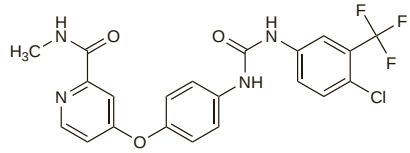
1. Okamoto T, *et al.* Long-term administration of oral low-dose topoisomerase II inhibitors, MST-16 and VP-16, for refractory or relapsed non-Hodgkin's lymphoma. *Acta Haematol (Basel)* 2000; **104:** 128–30.
2. Inoue Y, *et al.* Durable remission by sobuzoxane in an HIV-seronegative patient with human herpesvirus 8-negative primary effusion lymphoma. *Int J Hematol* 2004; **79:** 271–5.

Sorafenib *(USAN, rINN)*

BAY-43-9006; Sorafénib; Sorafenibum. 4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-*N*^{2}-methylpyridine-2-carboxamide.

Сорафениб

$C_{21}H_{16}ClF_3N_4O_3$ = 464.8.
CAS — 284461-73-0.
ATC — L01XE05.
ATC Vet — QL01XE05.



Sorafenib Tosilate *(rINNM)*

BAY-54-9085; Sorafénib, Tosilate de; Sorafenib, tosilato de; Sorafenib Tosylate *(USAN)*; Sorafenibi Tosilas. 4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-*N*^{2}-methylpyridine-2-carboxamide 4-methylbenzenesulfonate.

Сорафениба Тозилат

$C_{21}H_{16}ClF_3N_4O_3$, $C_7H_8O_3S$ = 637.0.
CAS — 475207-59-1.
ATC — L01XE05.
ATC Vet — QL01XE05.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641. Dermatological toxicities such as palmar-plantar syndrome and rash are the most common adverse effects with sorafenib. Treatment may include topical therapies, or dose adjustment, or temporary interruption of sorafenib. Mild to moderate hypertension can occur, which may be manageable with antihypertensive therapy, but severe or persistent hypertension or hypertensive crisis despite treatment, may force sorafenib to be stopped. Blood pressure should be regularly monitored. There is an increased risk of bleeding with sorafenib and fatalities have been reported; if severe enough to need intervention, the drug should be permanently stopped. Leucopenia, lymphopenia, anaemia, neutropenia, and thrombocytopenia are common. Hypophosphataemia and transient disturbances in liver function tests can occur. Elevations in lipase and amylase concentrations are very common. Pancreatitis has been reported. Other adverse effects include alopecia, pruritus, dry skin, erythema, acne, flushing, exfoliative dermatitis, hoarseness, gastrointestinal disturbances, arthralgia, myalgia, asthenia, pain, and peripheral neuropathy. Tinnitus, depression, and erectile dysfunction are often reported, as are pyrexia, flu-like illness, and weight decrease. Gastrointestinal perforation has been reported rarely; therapy should be stopped if it occurs. Reversible posterior leukoencephalopathy has also occurred rarely. Sorafenib therapy should be interrupted or stopped in patients who develop cardiac ischaemia and/or infarction.

◊ References.

1. Robert C, *et al.* Cutaneous side-effects of kinase inhibitors and blocking antibodies. *Lancet Oncol* 2005; **6:** 491–500.
2. Strumberg D, *et al.* Pooled safety analysis of BAY 43-9006 (sorafenib) monotherapy in patients with advanced solid tumours: is rash associated with treatment outcome? *Eur J Cancer* 2006; **42:** 548–56.
3. Veronese ML, *et al.* Mechanisms of hypertension associated with BAY 43-9006. *J Clin Oncol* 2006; **24:** 1363–9.
4. Yang C-H, *et al.* Hand-foot skin reaction in patients treated with sorafenib: a clinicopathological study of cutaneous manifestations due to multitargeted kinase inhibitor therapy. *Br J Dermatol* 2008; **158:** 592–6.

Effects on the cardiovascular system. A meta-analysis[1] of data involving 4599 patients indicated that 23.4% of those given sorafenib developed hypertension; about 5% of sorafenib-treated patients developed severe (grade 3 or 4) hypertension. This represented a relative risk of developing high blood pressure 6.1 times that of patients not given sorafenib. Hypertension may also develop with other angiogenesis inhibitors; relative risk has been shown to be similar with high-dose bevacizumab, and there is evidence of a slightly smaller risk (incidence of hypertension 22.5%, relative risk 3.89) with sunitinib.

1. Wu S, *et al.* Incidence and risk of hypertension with sorafenib in patients with cancer: a systematic review and meta-analysis. *Lancet Oncol* 2008; **9:** 117–23.

Interactions

For a general discussion of antineoplastic drug interactions, see p.642. Sorafenib is metabolised by the cytochrome P450 isoenzyme CYP3A4. Rifampicin can reduce exposure to sorafenib. Other inducers of this enzyme (such as carbamazepine, dexamethasone, St John's wort, phenobarbital, and phenytoin) may also reduce blood concentrations of sorafenib. However, ketoconazole did not alter exposure to sorafenib and other drugs that inhibit CYP3A4 are considered unlikely to alter the metabolism of sorafenib.

In vitro studies have indicated that sorafenib itself inhibits the cytochrome P450 isoenzymes CYP3A4, CYP2C19, and CYP2D6, but use of sorafenib with midazolam, or omeprazole, or dextromethorphan did not alter the exposure to any of these drugs; interactions with drugs that are substrates of these enzymes are considered unlikely.

Sorafenib inhibits the cytochrome P450 isoenzyme CYP2C9 *in vitro*, and may increase concentrations of its substrates. The effect of warfarin on mean PT-INR was not altered by sorafenib; however, patients taking warfarin or phenprocoumon with sorafenib should have their INR regularly checked.

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

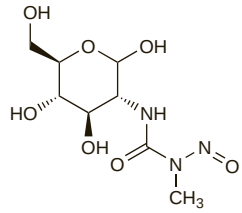
Proprietary Preparations (details are given in Part 3)
Arg.: Nexavar; ***Austral.:*** Nexavar; ***Chile:*** Nexavar; ***Cz.:*** Nexavar; ***Fr.:*** Nexavar; ***Gr.:*** Nexavar; ***Hung.:*** Nexavar; ***Indon.:*** Nexavar; ***Malaysia:*** Nexavar; ***Mex.:*** Nexavar; ***NZ:*** Nexavar; ***Port.:*** Nexavar;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

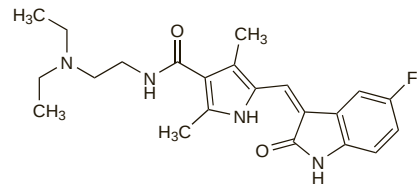
Proprietary Preparations (details are given in Part 3)
Canad.: Zanosar; ***Fr.:*** Zanosar; ***Gr.:*** Zanosar; ***Israel:*** Zanosar; ***USA:*** Zanosar.

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.