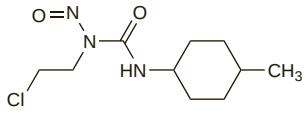
3. Sternberg CN, *et al.* Phase III trial of satraplatin, an oral platinum plus prednisone vs. prednisone alone in patients with hormone-refractory prostate cancer. *Oncology* 2005; **68:** 2–9.
4. Sternberg CN. Satraplatin in the treatment of hormone-refractory prostate cancer. *BJU Int* 2005; **96:** 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

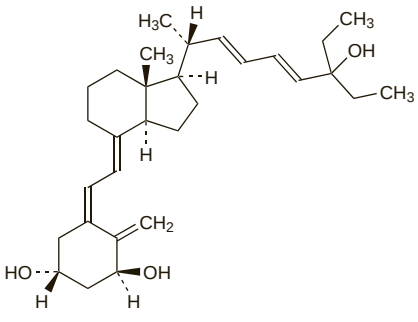
Semustine is a nitrosourea with actions and uses similar to those of carmustine (p.695) and lomustine (p.741).

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

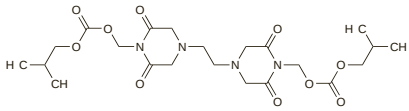
Proprietary Preparations (details are given in Part 3)
Jpn: Sonifilan.

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.

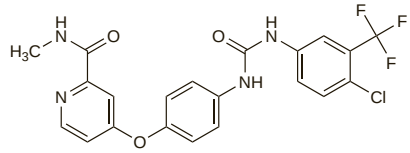
1. Okamoto T, *et al.* Long-term administration of oral low-dose topoisomerase II inhibitors, MST-16 and VP-16, for refractory or relapsed non-Hodgkin's lymphoma. *Acta Haematol (Basel)* 2000; **104:** 128–30.
2. Inoue Y, *et al.* Durable remission by sobuzoxane in an HIV-seronegative patient with human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