damage with a course of rituximab (2 doses); assessment was made at 24 weeks.[5] In a consensus statement, European and Canadian rheumatologists stated that re-treatment with rituximab may be considered after week 24 in those who respond to initial therapy.[6]

In the UK, NICE states that rituximab with methotrexate is a treatment option for adults with severe active rheumatoid arthritis who have had an inadequate response to DMARDs or are intolerant of them; previous therapy should have included at least one tumour necrosis factor α inhibitor. Treatment with rituximab and methotrexate should continue only if patients show an adequate response, and repeat courses should be given no more often than every 6 months; specialist supervision is advised.[7]

1. Edwards JCW, *et al.* Efficacy of B-cell—targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004; **350:** 2572–81.
2. Summers KM, Kockler DR. Rituximab treatment of refractory rheumatoid arthritis. *Ann Pharmacother* 2005; **39:** 2091–5.
3. Higashida J, *et al.* Safety and efficacy of rituximab in patients with rheumatoid arthritis refractory to disease modifying antirheumatic drugs and anti-tumor necrosis factor-α treatment. *J Rheumatol* 2005; **32:** 2109–15.
4. Looney RJ. B cell-targeted therapy for rheumatoid arthritis: an update on the evidence. *Drugs* 2006; **66:** 625–39.
5. Cohen SB, *et al.* Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. *Arthritis Rheum* 2006; **54:** 2793–2806.
6. Smolen JS, *et al.* Working Group on the Rituximab Consensus Statement. Consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007; **66:** 143–50.
7. NICE. Rituximab for the treatment of rheumatoid arthritis: Technology Appraisal 126 (issued August 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/word/TA126guidance.doc (accessed 13/05/08)

Scleroderma. Rituximab is under investigation for the management of scleroderma (p.1817).

Skin disorders. In addition to reports of efficacy in pemphigus (see above), rituximab has been reported to be of benefit in refractory cases of pemphigoid[1] and epidermolysis bullosa acquisita.[2,3]

1. Schmidt E, *et al.* Rituximab in autoimmune bullous diseases: mixed responses and adverse effects. *Br J Dermatol* 2007; **156:** 352–6.
2. Crichlow SM, *et al.* A successful therapeutic trial of rituximab in the treatment of a patient with recalcitrant, high-titre epidermolysis bullosa acquisita. *Br J Dermatol* 2007; **156:** 194–6.
3. Sadler E, *et al.* Treatment-resistant classical epidermolysis bullosa acquisita responding to rituximab. *Br J Dermatol* 2007; **157:** 417–19.

Systemic lupus erythematosus. Rituximab is under investigation for the treatment of SLE (p.1513).[1]

1. Sfikakis PP, *et al.* Rituximab anti-B-cell therapy in systemic lupus erythematosus: pointing to the future. *Curr Opin Rheumatol* 2005; **17:** 550–7.

Thrombotic microangiopathies. Rituximab has been reported[1-3] to be of benefit in relapsed or refractory thrombotic thrombocytopenic purpura (see under Plasma, p.1076).

1. Zheng X, *et al.* Remission of chronic thrombotic thrombocytopenic purpura after treatment with cyclophosphamide and rituximab. *Ann Intern Med* 2003; **138:** 105–8.
2. Reddy PS, *et al.* Rituximab in the treatment of relapsed thrombotic thrombocytopenic purpura. *Ann Hematol* 2005; **84:** 232–5.
3. Kosugi S, *et al.* Rituximab provided long-term remission in a patient with refractory relapsing thrombotic thrombocytopenic purpura. *Int J Hematol* 2005; **81:** 433–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: MabThera; ***Austral.:*** MabThera; ***Austria:*** MabThera; ***Belg.:*** MabThera; ***Braz.:*** MabThera; ***Canad.:*** Rituxan; ***Chile:*** MabThera; ***Cz.:*** MabThera; ***Denm.:*** MabThera; ***Fin.:*** MabThera; ***Fr.:*** MabThera; ***Ger.:*** MabThera; ***Gr.:*** MabThera; ***Hong Kong:*** MabThera; ***Hung.:*** MabThera; ***Indon.:*** MabThera; ***Irl.:*** MabThera; ***Israel:*** MabThera; ***Ital.:*** MabThera; ***Jpn:*** Rituxan; ***Malaysia:*** MabThera; ***Mex.:*** MabThera; ***Neth.:*** MabThera; ***Norw.:*** MabThera; ***NZ:*** MabThera; ***Philipp.:*** MabThera; ***Pol.:*** MabThera; ***Port.:*** MabThera; ***Rus.:*** MabThera (Ма6Тера); ***S.Afr.:*** MabThera; ***Singapore:*** MabThera; ***Spain:*** MabThera; ***Swed.:*** MabThera; ***Switz.:*** MabThera; ***Thai.:*** MabThera; ***Turk.:*** MabThera; ***UK:*** MabThera; ***USA:*** Rituxan; ***Venez.:*** MabThera.

Roquinimex *(USAN, rINN)*

FCF-89; LS-2616; Roquinimexum. 1,2-Dihydro-4-hydroxy-*N*,1-dimethyl-2-oxo-3-quinolinecarboxanilide.

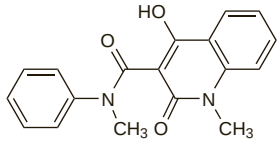
Рохинимекс

$C_{18}H_{16}N_2O_3$ = 308.3.

CAS — 84088-42-6.

ATC — L03AX02.

ATC Vet — QL03AX02.



Profile

Roquinimex is an immunomodulator reported to stimulate various immune functions including macrophage cytotoxicity. It has been investigated for its potential against malignant neoplasms including as adjuvant therapy after bone marrow transplantation in acute leukaemia, to prolong the time to relapse. Roquinimex has also been investigated in immune and auto-immune disorders including multiple sclerosis. However serious cardiovascular toxicity after roquinimex therapy has led to several studies being terminated.

◊ References.

1. Coutant R, *et al.* Low dose linomide in type I juvenile diabetes of recent onset: a randomised placebo-controlled double blind trial. *Diabetologia* 1998; **41:** 1040–6.
2. Simonsson B, *et al.* Roquinimex (Linomide) vs placebo in AML after autologous bone marrow transplantation. *Bone Marrow Transplant* 2000; **25:** 1121–7.
3. Tan IL, *et al.* Linomide in the treatment of multiple sclerosis: MRI results from prematurely terminated phase-III trials. *Multiple Sclerosis* 2000; **6:** 99–104.
4. Noseworthy JH, *et al.* Linomide in relapsing and secondary progressive MS. Part 1: trial design and clinical results. *Neurology* 2000; **54:** 1726–33.

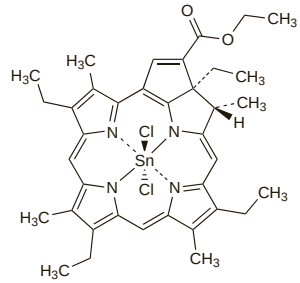
Rostaporfin *(USAN, rINN)*

Rostaporfina; Rostaporfine; Rostaporfinum; SnET2; Tin Ethyl Etiopurpurin; Tin etiopurpurin dichloride. (*OC*-6-13)-Dichloro[ethyl (18*RS*,19*SR*)-3,4,20,21-tetradehydro-4,9,14,19-tetraethyl-18,19-dihydro-3,8,13,18-tetramethyl-20-phorbinecarboxylato (2-)-N^{23},N^{24},N^{25},N^{26}]tin.

Ростапорфин

$C_{37}H_{42}Cl_2N_4O_2Sn$ = 764.4.

CAS — 284041-10-7; 114494-17-6.



and enantiomer

Profile

Rostaporfin is a photosensitiser that is under investigation in the photodynamic therapy of neovascular (wet) age-related macular degeneration (p.785). It has also been investigated for photodynamic therapy of malignant neoplasms.

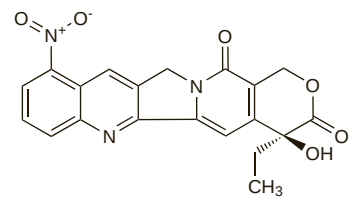
Rubitecan *(USAN, rINN)*

9-NC; 9-Nitrocamptothecin; RFS-2000; Rubitécan; Rubitecán; Rubitecanum. 9-Nitro-20(*S*)-camptothecin.

Рубитекан

$C_{20}H_{15}N_3O_6$ = 393.3.

CAS — 91421-42-0.



Profile

Like irinotecan (p.737), rubitecan is a topoisomerase I inhibitor related to camptothecin. It can be given orally and has been investigated for its antineoplastic properties particularly in the treatment of pancreatic cancer. It is also under investigation for the treatment of paediatric patients infected with HIV.

◊ References.

1. Clark JW. Rubitecan. *Expert Opin Invest Drugs* 2006; **15:** 71–9.

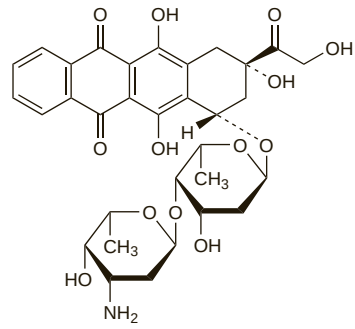
Sabarubicin *(rINN)*

MEN-10755; Sabarubicina; Sabarubicine; Sabarubicinum. (7*S*,9*S*)-7-{[4-*O*-(3-Amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl]oxy}-6,9,11-trihydroxy-9-(hydroxyacetyl)-7,8,9,10-tetrahydrotetracene-5,12-dione.

Сабарубицин

$C_{32}H_{37}NO_{13}$ = 643.6.

CAS — 211100-13-9.



Profile

Sabarubicin, an anthracycline, is an analogue of doxorubicin (p.712). It acts as a potent topoisomerase II inhibitor and is under investigation for the treatment of various solid tumours, such as cancers of the lung, ovary, breast, and prostate. Myelosuppression is the main adverse effect.

◊ References.

1. Bos AM, *et al.* Pharmacokinetics of MEN-10755, a novel anthracycline disaccharide analogue, in two phase I studies in adults with advanced solid tumours. *Cancer Chemother Pharmacol* 2001; **48:** 361–9.
2. Schrijvers D, *et al.* Phase I study of MEN-10755, a new anthracycline in patients with solid tumours: a report from the European Organization for Research and Treatment of Cancer, Early Clinical Studies Group. *Ann Oncol* 2002; **13:** 385–91.
3. Jones K. MEN-10755. Menarini. *Curr Opin Investig Drugs* 2003; **4:** 1473–8.
4. Caponigro F, *et al.* A phase II study of sabarubicin (MEN-10755) as second line therapy in patients with locally advanced or metastatic platinum/taxane resistant ovarian cancer. *Invest New Drugs* 2005; **23:** 85–9.
5. Fiedler W, *et al.* A study from the EORTC new drug development group: open label phase II study of sabarubicin (MEN-10755) in patients with progressive hormone refractory prostate cancer. *Eur J Cancer* 2006; **42:** 200–204.

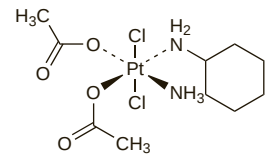
Satraplatin *(USAN, rINN)*

BMS-182751; BMY-45594; JM-216; Satraplatine; Satraplatino; Satraplatinum. (*OC*-6-43)-Bis(acetato)amminedichloro(cyclohexylamine)platinum.

Сатраплатин

$C_{10}H_{22}Cl_2N_2O_4Pt$ = 500.3.

CAS — 129580-63-8.



Profile

Satraplatin is an analogue of cisplatin (p.698) with generally similar properties, but which is well absorbed after oral dosage. It is under investigation for its antineoplastic properties in the treatment of various solid tumours.

◊ References.

1. Kelland LR. An update on satraplatin: the first orally available platinum anticancer drug. *Expert Opin Invest Drugs* 2000; **9:** 1373–82.
2. Vouillamoz-Lorenz S, *et al.* Pharmacokinetics of satraplatin (JM216), an oral platinum (IV) complex under daily oral administration for 5 or 14 days. *Anticancer Res* 2003; **23:** 2757–65.

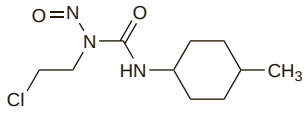
3. Sternberg CN, *et al.* Phase III trial of satraplatin, an oral platinum plus prednisone vs. prednisone alone in patients with hormone-refractory prostate cancer. *Oncology* 2005; **68:** 2–9.
4. Sternberg CN. Satraplatin in the treatment of hormone-refractory prostate cancer. *BJU Int* 2005; **96:**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

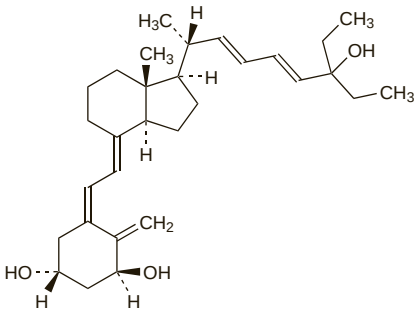
Semustine is a nitrosourea with actions and uses similar to those of carmustine (p.695) and lomustine (p.741).

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

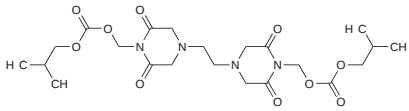
Proprietary Preparations (details are given in Part 3)
Jpn: Sonifilan.

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.

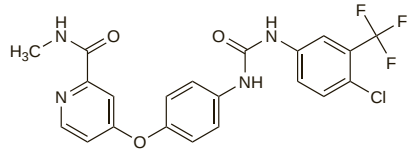
1. Okamoto T, *et al.* Long-term administration of oral low-dose topoisomerase II inhibitors, MST-16 and VP-16, for refractory or relapsed non-Hodgkin's lymphoma. *Acta Haematol (Basel)* 2000; **104:** 128–30.
2. Inoue Y, *et al.* Durable remission by sobuzoxane in an HIV-seronegative patient with human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