Profile

Ranpirnase is a ribonuclease reported to have antineoplastic properties. It is under investigation in the treatment of malignant mesothelioma. Ranpirnase has also been investigated in the management of solid tumours. It is also reported to have activity *in vitro* against HIV.

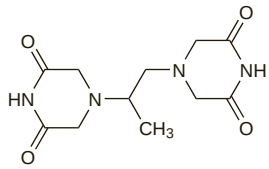
Razoxane *(BAN, rINN)*

ICI-59118; ICRF-159; NSC-129943; Ratsoksaani; Razoxan; Razoxano; Razoxanum. (±)-4,4′-Propylenebis(piperazine-2,6-dione).

Разоксан

$C_{11}H_{16}N_4O_4$ = 268.3.

CAS — 21416-87-5.



Profile

Razoxane is an antineoplastic with inhibitory activity during the pre-mitotic and early mitotic phases of cell growth (G_2-M). It enhances the effects of radiotherapy. It has been used with radiotherapy in the treatment of sarcomas, including Kaposi's sarcoma. Razoxane has also been tried in other malignant diseases including acute leukaemias and non-Hodgkin's lymphomas. However, it is no longer widely used. Razoxane was formerly used in psoriasis, but its carcinogenic properties militate against such use, as discussed below.

In the treatment of sarcomas it has generally been given orally in doses of 125 mg twice daily; higher doses have been given in the management of acute leukaemias and Kaposi's sarcoma. The peripheral blood count should be monitored during treatment.

The principal adverse effects of razoxane include bone-marrow depression, gastrointestinal disturbances, skin reactions, and alopecia. It may enhance the adverse effects of radiotherapy. Razoxane therapy has been associated with the development of secondary malignancies: it is contra-indicated in the treatment of non-malignant conditions.

Dexrazoxane (p.1443) is the (+)-enantiomer of razoxane. It is used to reduce anthracycline-induced cardiotoxicity.

Malignant neoplasms. References to the use of razoxane with radiotherapy.

1. Rhomberg W, *et al.* Radiotherapy vs radiotherapy and razoxane in the treatment of soft tissue sarcomas: final results of a randomized study. *Int J Radiat Oncol Biol Phys* 1996; **36:** 1077–84.
2. Rhomberg W, *et al.* A small prospective study of chordomas treated with radiotherapy and razoxane. *Strahlenther Onkol* 2003; **179:** 249–53.

Skin disorders, non-malignant. Razoxane was formerly used in the systemic treatment of psoriasis, and has been found to be extremely effective, with an initial response rate of 97% overall. It was found to be of use in all forms of cutaneous psoriasis and psoriatic arthropathy.[1] However, the development of acute myeloid leukaemias and other malignancies in patients given razoxane[2-5] has led to its being contra-indicated in non-malignant conditions.

For a discussion of psoriasis and its management, see p.1583.

1. Horton JJ, Wells RS. Razoxane: a review of 6 years' therapy in psoriasis. *Br J Dermatol* 1983; **109:** 669–73.
2. Horton JJ, *et al.* Epitheliomas in patients receiving razoxane therapy for psoriasis. *Br J Dermatol* 1983; **109:** 675–8.
3. Lakhani S, *et al.* Razoxane and leukaemia. *Lancet* 1984; **ii:** 288–9.
4. Caffrey EA, *et al.* Acute myeloid leukaemia after treatment with razoxane. *Br J Dermatol* 1985; **113:** 131–4.
5. Zuiable AG, *et al.* Razoxane and T-cell lymphoma. *Br J Dermatol* 1989; **121:** 149.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Cardioxane.

Rituximab *(BAN, USAN, rINN)*

IDEC-102; IDEC-C2B8; Rituksimab; Rituksimabi; Rituximabum. Immunoglobulin G1 (human-mouse monoclonal IDEC-C2B8 γ1-chain anti-human antigen CD 20), disulfide with human-mouse monoclonal IDEC-C2B8 κ-chain, dimer.

Ритуксимаб

CAS — 174722-31-7.

ATC — L01XC02.

ATC Vet — QL01XC02.

Adverse Effects, Treatment, and Precautions

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

Infusion of rituximab has been associated with a cytokine release syndrome of fever, chills, and rigors, usually within 2 hours of beginning therapy (see also below). Other reported symptoms include pruritus, urticaria, rashes, dyspnoea, bronchospasm, angioedema, transient hypotension, and flushing. Asthenia, headache, rhinitis, myalgia, dizziness, and hypertension may also be associated with infusion reactions. Severe cases may be associated with tumour lysis syndrome, acute renal failure, respiratory failure, and death. Hypersensitivity reactions manifest similarly to the cytokine release syndrome, but usually occur within minutes of starting infusion. Mucocutaneous reactions, some fatal, and including Stevens-Johnson syndrome or toxic epidermal necrolysis have also occurred.

Patients with an extensive tumour burden, pulmonary tumour infiltration or pulmonary insufficiency may be at increased risk of severe reactions and should be treated with caution and possibly a decreased initial infusion rate. Therapy should be interrupted in patients who develop severe symptoms and only resumed, at half the previous rate, once all signs and symptoms have resolved. Premedication with analgesics, antihistamines, and possibly corticosteroids is recommended in all patients before receiving rituximab.

Reactivation of hepatitis B virus (HBV) has occurred in some patients; fulminant hepatitis, hepatic failure, and fatalities have been reported. Patients at high risk of HBV infection should be screened before starting rituximab therapy and carriers should be monitored for signs of active infection or hepatitis during and for several months after therapy. Rituximab should be stopped if viral hepatitis develops. Other serious infections, which may be fatal, can occur with rituximab. Cases of progressive multifocal leukoencephalopathy, some fatal, have been reported with rituximab.

Haematological adverse effects including lymphopenia, leucopenia, neutropenia, thrombocytopenia, and anaemia have occurred in some patients; effects are considered mild and reversible. Complete blood and platelet counts should be monitored regularly. Exacerbation of heart failure and angina pectoris has also been reported, and other cardiac events include arrhythmias and tachycardia. Gastrointestinal disturbances may also occur. Abdominal pain, bowel obstruction, and perforation, in some cases fatal, have been reported with rituximab combination chemotherapy.

◊ References.

1. Mohrbacher A. B cell non-Hodgkin's lymphoma: rituximab safety experience. *Arthritis Res Ther* 2005; **7** (suppl 3): S19–S25.
2. Kimby E. Tolerability and safety of rituximab (MabThera). *Cancer Treat Rev* 2005; **31:** 456–73.

Effects on the blood. Late-onset neutropenia (defined as neutropenia occurring 30 days after the last dose) has been reported in patients receiving rituximab.[1]

1. Rios-Fernández R, *et al.* Late-onset neutropenia following rituximab treatment in patients with autoimmune diseases. *Br J Dermatol* 2007; **157:** 1271–3.

Effects on the eyes. About 20 minutes after the start of a rituximab infusion, a patient developed bilateral conjunctivitis without pain, lachrymation, or discharge. No other clinical manifestations of a hypersensitivity reaction were apparent, and the conjunctivitis resolved spontaneously, about 30 minutes after the end of the infusion. No recurrence was evident with subsequent rituximab therapy.[1]

1. Marinella MA. Bilateral conjunctivitis due to rituximab. *Ann Pharmacother* 2007; **41:** 1318.

Effects on the gastrointestinal tract. In November 2006 the manufacturer noted that 47 cases of bowel obstruction (9 fatal) and 37 cases of gastrointestinal perforation (4 fatal) had been reported in patients given rituximab.[1] Interpretation of data was difficult due to confounding factors; however, a contributory role of rituximab could not be excluded. The mean time to onset of symptoms was 6 days (range 1 to 77 days) for documented perforation. Complaints of abdominal pain, especially early in a course of rituximab treatment, should prompt thorough diagnostic evaluation and treatment.

1. Roche, Canada. Reports of bowel obstruction and gastrointestinal perforation with RITUXAN (rituximab) (issued 10th November 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2006/rituxan_3_hpc-cps-eng.php (accessed 30/07/08)

Effects on the lungs. Pulmonary reactions have been reported with rituximab use,[1] including reversible interstitial pneumonia[2-4] and interstitial fibrosis.[5] A fatal intra-alveolar haemorrhage in 1 patient was attributed to a hypersensitivity reaction to rituximab.[6]

1. Wagner SA, *et al.* Rituximab-induced interstitial lung disease. *Am J Hematol* 2007; **82:** 916–19.
2. Burton C, *et al.* Interstitial pneumonitis related to rituximab therapy. *N Engl J Med* 2003; **348:** 2690–1.
3. Jullien V, *et al.* Une pneumopathie alvéolo-interstitielle hypoxémiante associée à la prise de rituximab. *Rev Mal Respir* 2004; **21:** 407–10.
4. Swords R, *et al.* Interstitial pneumonitis following rituximab therapy for immune thrombocytopenic purpura (ITP). *Am J Hematol* 2004; **77:** 103–4.
5. Leon RJ, *et al.* Rituximab-induced acute pulmonary fibrosis. *Mayo Clin Proc* 2004; **79:** 949, 953.
6. Alexandrescu DT, *et al.* Fatal intra-alveolar hemorrhage after rituximab in a patient with non-Hodgkin lymphoma. *Leuk Lymphoma* 2004; **45:** 2321–5.

Effects on the nervous system. As of December 2006, the FDA had received a total of 24 reports of progressive multifocal leukoencephalopathy (PML) in patients given rituximab.[1] PML is a fatal demyelinating disease that follows reactivation of latent JC or PK polyomavirus (also known as papovavirus) in the CNS; the virus is present in about 80% of adults. In the first 12 cases reported to the FDA, 10 patients tested positive for the JC virus and 1 had confirmed BK virus.

1. FDA. Rituximab (marketed as Rituxan): progressive multifocal leukoencephalopathy (PML). *FDA Drug Safety Newsletter* 2007; **1:** 3–5. Available at: http://www.fda.gov/cder/dsn/2007_fall/2007_fall.pdf (accessed 07/02/08)

Infusion-related reactions. By November 1998 there had been 74 cases of serious infusion-related reactions to rituximab reported worldwide, with 8 fatal cases.[1] An estimated 12 000 to 14 000 patients had been treated.

The reaction usually occurs within the first 2 hours of infusion and the underlying mechanism is believed to be a severe cytokine release syndrome, with some elements of tumour lysis syndrome.[1-3] In one series of cases tumour necrosis factor-α and interleukin-6 levels were found to peak 90 minutes after the onset of the infusion, and these elevated cytokine levels coincided with infusion-related symptoms.[2] The reaction is usually most marked after the first infusion and subsequent infusions are usually tolerated, emphasising that this is not a true hypersensitivity reaction.[4]

Patients with a high tumour burden (lesions over 10 cm in diameter or more than 500 000 circulating malignant cells/mm^3), a history of pulmonary infiltration or insufficiency, or underlying cardiac disease are believed to be at greater risk of severe reactions.[1,2,4] The UK CSM recommends that premedication with an analgesic and an antihistamine should always be given before rituximab, and corticosteroids should be considered.[1] However, serious or fatal reactions have occurred despite such premedication.[3,4] Alternative infusion schedules and/or combination therapy with chemotherapeutic drugs may be required to decrease the tumour burden before rituximab therapy.[2,4]

1. Committee on Safety of Medicines/Medicines Control Agency. Rituximab (MabThera): serious infusion-related adverse reactions. *Current Problems* 1999; **25:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 26/04/06)
2. Winkler U, *et al.* Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukaemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). *Blood* 1999; **94:** 2217–24.
3. Lim L-C, *et al.* Fatal cytokine release syndrome with chimeric anti-CD20 monoclonal antibody rituximab in a 71-year-old patient with chronic lymphocytic leukaemia. *J Clin Oncol* 1999; **17:** 1962–3.
4. Byrd JC, *et al.* Rituximab therapy in hematologic malignancy patients with circulating blood tumor cells: association with increased infusion-related side effects and rapid blood tumor clearance. *J Clin Oncol* 1999; **17:** 791–5.

Pregnancy. Giving 4 cycles of rituximab (with doxorubicin, vincristine, and prednisolone) to a pregnant woman with lymphoma, from 21 weeks of gestation until delivery at 35 weeks, resulted in no adverse effects to either the mother or the infant.[1] In another report, a 31-year-old woman was diagnosed with non-Hodgkin's lymphoma during pregnancy. She received 6 cycles of rituximab with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Two months after treatment, she spontaneously delivered a premature but healthy infant. Patient and child were clinically assessed every 3 months; the infant's B cells were severely diminished at birth but recovered over 6 to 12 weeks. Rituximab concentrations in both mother and child also decreased as expected. No adverse effects were seen during 16 months of follow-up.[2] In 2 case reports of rituximab use during the first trimester of pregnancy, no significant adverse effects on the neonates were seen; transient granulocytopenia and lymphopenia were reported.[3,4] A 35-year-old woman diagnosed with Burkitt's lymphoma in week 15 of pregnancy received 4 weekly

infusions of rituximab starting in week 16, followed by four courses of rituximab with CHOP, and then 2 courses of CHOP alone. In week 41, a healthy infant was delivered by caesarean section. Both the mother and child had very high serum concentrations of rituximab at birth with a complete absence of B cells; rituximab levels in the cord blood serum were three times that in the mother's serum. However, B-cell recovery was reported to be rapid, and no overt infectious complications were seen in the child up to the age of 26 months; growth and developmental status were also normal.[5] Nonetheless, licensed product information advises against rituximab use during pregnancy, given the potential for B-cell depletion in the fetus; women of child-bearing potential should use effective contraceptive methods during treatment and for up to 12 months after therapy.

1. Herold M, *et al.* Efficacy and safety of a combined rituximab chemotherapy during pregnancy. *J Clin Oncol* 2001; **19:** 3439.
2. Decker M, *et al.* Rituximab plus CHOP for treatment of diffuse large B-cell lymphoma during second trimester of pregnancy. *Lancet Oncol* 2006; **7:** 693–4. Correction. *ibid.*; 706.
3. Kimby E, *et al.* Safety of rituximab therapy during the first trimester of pregnancy: a case history. *Eur J Haematol* 2004; **72:** 292–5.
4. Ojeda-Uribe M, *et al.* Administration of rituximab during the first trimester of pregnancy without consequences for the newborn. *J Perinatol* 2006; **26:** 252–5.
5. Friedrichs B, *et al.* The effects of rituximab treatment during pregnancy on a neonate. *Haematologica* 2006; **91:** 1426–7.

Pharmacokinetics

The mean maximum plasma concentration of rituximab has been reported to increase with successive infusions; however, considerable interindividual variation is seen. Serum concentrations are negatively correlated with tumour burden and the number of circulating B-cells. The mean terminal half-life is about 20 days. Rituximab is bound to B lymphocytes, and is detectable in the body for 3 to 6 months after treatment.

Uses and Administration

Rituximab is a chimeric monoclonal antibody to CD20 antigen used in the treatment of non-Hodgkin's lymphomas (p.656). It is used as monotherapy in relapsed or refractory low-grade or follicular lymphoma, or as first-line treatment with combination chemotherapy, such as CVP (cyclophosphamide, vincristine, and prednisolone). Rituximab monotherapy may also be used in patients with low-grade stable disease after first-line treatment with CVP chemotherapy. It is also indicated for maintenance therapy in patients with refractory or relapsed follicular lymphoma who respond to induction chemotherapy that may or may not have contained rituximab. Rituximab is also used with CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) or other anthracycline-based regimens for CD20-positive diffuse large B-cell non-Hodgkin's lymphoma. Rituximab also forms part of the combination regimen employing ibritumomab tiuxetan (p.730). Rituximab with methotrexate is used in adults with moderate to severely active rheumatoid arthritis (p.11) who have had an inadequate response to DMARDs, including tumour necrosis factor inhibitors.

Rituximab is given by intravenous infusion, diluted in sodium chloride 0.9% or glucose 5% to a final concentration of between 1 and 4 mg/mL. The first infusion is given initially at a rate of 50 mg/hour; subsequently this may be increased in increments of 50 mg/hour every 30 minutes to a maximum of 400 mg/hour, if well tolerated. Subsequent doses may be begun at a rate of 100 mg/hour, and increased in increments of 100 mg/hour every 30 minutes to a maximum of 400 mg/hour.

In the UK for the treatment of refractory or relapsed follicular **lymphoma**, rituximab is given as a single agent in a usual dose of 375 mg/m^2 once weekly for 4 doses; in the USA 8 doses may be given. Patients in either country may be re-treated after relapse for a further 4 doses. When given with combination chemotherapy such as CVP (for follicular lymphoma) or CHOP (for diffuse large B-cell lymphoma), rituximab 375 mg/m^{2}is given on day 1 of the chemotherapy cycle, after the corticosteroid component of the regimen, for a total of 8 cycles. In patients previously treated with 6 to 8 cycles of CVP chemotherapy and who have not progressed, rituximab 375 mg/m^2 may be given once weekly for 4 doses, repeated every 6 months, for up to 16 doses. For maintenance treatment in those who have responded to induction chemotherapy, rituximab 375 mg/m^2 is given once every 3 months until disease progression or for a maximum period of 2 years.

In the regimen with ibritumomab tiuxetan, rituximab is usually given at a dose of 250 mg/m^2.

In the treatment of **rheumatoid arthritis**, rituximab is given in a dose of 1 g, for 2 doses; the infusions are separated by 2 weeks. It is given with methotrexate, and corticosteroids are recommended before each infusion to reduce the incidence and severity of infusion reactions.

Rituximab is also under investigation for the treatment of a number of **other conditions** including chronic lymphocytic leukaemia, multiple sclerosis, ANCA-associated vasculitis, and SLE, including lupus nephritis.

Administration. Rituximab has been used intralesionally in the treatment of cutaneous B-cell lymphoma. There are reports of benefit, with long-term remission in some patients,[1] but rapid recurrence in others.[2] In a study of 8 patients, intralesional rituximab was given to 6 patients, in doses of 10 to 30 mg per lesion, 3 times weekly; if clinical remission was incomplete, another cycle of 3 injections was given 1 month later. Two patients were treated intravenously with weekly infusions for 4 weeks. Complete remission was seen in all 8 patients. No relapse was seen in those given intravenous therapy, but recurrences were seen in 4 of the 6 patients treated intralesionally. Moderate pain was reported during intralesional injection.[3]

1. Paul T, *et al.* Intralesional rituximab for cutaneous B-cell lymphoma. *Br J Dermatol* 2001; **144:** 1239–43.
2. Roguedas AM, *et al.* Intralesional therapy with anti-CD20 monoclonal antibody rituximab: local and systemic efficacy in primary cutaneous B-cell lymphoma. *Br J Dermatol* 2005; **152:** 541–4.
3. Kerl K, *et al.* Intralesional and intravenous treatment of cutaneous B-cell lymphomas with the monoclonal anti-CD20 antibody rituximab: report and follow-up of eight cases. *Br J Dermatol* 2006; **155:** 1197–1200.

Administration in children. Although not licensed in the UK or the USA for use in children, there are reports of benefit in children with various diseases, such as auto-immune haemolytic anaemia, idiopathic thrombocytopenic purpura (see also below), and post-transplantation lymphoproliferative disease,[1] as well as rheumatoid arthritis, and SLE.[2] Standard doses of 375 mg/m^2 weekly have usually been given, in most cases for a median course of 4 doses.

1. Giulino LB, *et al.* Treatment with rituximab in benign and malignant hematologic disorders in children. *J Pediatr* 2007; **150:** 338–44.
2. El-Hallak M, *et al.* Clinical effects and safety of rituximab for treatment of refractory pediatric autoimmune diseases. *J Pediatr* 2007; **150:** 376–82.

Eye disorders. Orbital pseudolymphomas are uncommon benign tumours which usually affect the lachrymal gland, orbital soft tissue, or extra-ocular muscles. Clinical presentation includes painless onset of ptosis, proptosis, diplopia, or eyelid swelling. There are reports of durable response to rituximab.[1]

1. Witzig TE, *et al.* Treatment of benign orbital pseudolymphomas with the monoclonal anti-CD20 antibody rituximab. *Mayo Clin Proc* 2007; **82:** 692–9.

Glomerular kidney disease. In a report of 5 patients with corticosteroid-resistant nephrotic syndrome, 4 patients had a complete remission and 1 patient had a partial remission after treatment with rituximab in standard doses for 4 weeks. Complete remission was maintained in 3 patients, despite tapering of corticosteroids and calcineurin inhibitors.[1]

1. Bagga A, *et al.* Rituximab in patients with the steroid-resistant nephrotic syndrome. *N Engl J Med* 2007; **356:** 2751–2.

Haemolytic anaemia. Rituximab has been used in the treatment of severe refractory auto-immune haemolytic anaemia (p.1043) of various causes, including warm,[1,2] cold,[3-5] and mixed[6,7] disease.

1. Quartier P, *et al.* Treatment of childhood autoimmune haemolytic anaemia with rituximab. *Lancet* 2001; **358:** 1511–13.
2. Gottardo NG, *et al.* Successful induction and maintenance of long-term remission in a child with chronic relapsing autoimmune hemolytic anemia using rituximab. *Pediatr Hematol Oncol* 2003; **20:** 557–61.
3. Sparling TG, *et al.* Remission of cold hemagglutinin disease induced by rituximab therapy. *Can Med Assoc J* 2001; **164:** 1405.
4. Engelhardt M, *et al.* Severe cold hemagglutinin disease (CHD) successfully treated with rituximab. *Blood* 2002; **100:** 1922–3.
5. Berentsen S, *et al.* Rituximab for primary chronic cold agglutinin disease: a prospective study of 37 courses of therapy in 27 patients. *Blood* 2004; **103:** 2925–8.
6. Morselli M, *et al.* Mixed warm and cold autoimmune hemolytic anemia: complete recovery after 2 courses of rituximab treatment. *Blood* 2002; **99:** 3478–9.
7. Webster D, *et al.* Prompt response to rituximab of severe hemolytic anemia with both cold and warm autoantibodies. *Am J Hematol* 2004; **75:** 258–9.

Haemorrhagic disorders. Although data are limited, reports suggest that rituximab may be an effective alternative for the treatment of acquired haemophilia (p.1048) after established therapies have failed.[1,2]

1. Maillard H, *et al.* Rituximab in postpartum-related acquired hemophilia. *Am J Med* 2006; **119:** 86–8.
2. Stachnik JM. Rituximab in the treatment of acquired hemophilia. *Ann Pharmacother* 2006; **40:** 1151–7.

Idiopathic thrombocytopenic purpura. Rituximab has been reported[1-3] to be effective in patients, including children and infants, with idiopathic thrombocytopenic purpura (p.1505) refractory to standard treatments. However, a review[4] cautioned against the indiscriminate use of rituximab in this patient population, given the lack of controlled data.

1. Zaja F, *et al.* The B-cell compartment as the selective target for the treatment of immune thrombocytopenias. *Haematologica* 2003; **88:** 538–46.
2. Bengtson KL, *et al.* Successful use of anti-CD20 (rituximab) in severe, life-threatening childhood immune thrombocytopenic purpura. *J Pediatr* 2003; **143:** 670–3.
3. Wang J, *et al.* Chronic immune thrombocytopenic purpura in children: assessment of rituximab treatment. *J Pediatr* 2005; **146:** 217–21.
4. Arnold DM, *et al.* Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. *Ann Intern Med* 2007; **146:** 25–33.

Malignant neoplasms. Reviews.

1. NICE. Rituximab for aggressive non-Hodgkin's lymphoma (issued September 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/65_rituximab_nonhodgkins_fullguidance.pdf (accessed 30/07/08)
2. Avivi I, *et al.* Clinical use of rituximab in haematological malignancies. *Br J Cancer* 2003; **89:** 1389–94.
3. Cvetković RS, Perry CM. Rituximab: a review of its use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. *Drugs* 2006; **66:** 791–820.
4. Held G, *et al.* Rituximab for the treatment of diffuse large B-cell lymphomas. *Expert Rev Anticancer Ther* 2006; **6:** 1175–86.
5. van Oers MH. Rituximab maintenance in indolent lymphoma: indications and controversies. *Curr Oncol Rep* 2007; **9:** 378–83.
6. Schulz H, *et al.* Chemotherapy plus rituximab versus chemotherapy alone for B-cell non-Hodgkin's lymphoma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 24/07/08).
7. Molina A. A decade of rituximab: improving survival outcomes in non-Hodgkin's lymphoma. *Annu Rev Med* 2008; **59:** 237–50.

Pemphigus. Rituximab has been reported to be of benefit in pemphigus vulgaris (p.1582) and 17 cases have been reviewed.[1] It was used in patients with severe and widespread disease that had not responded to usual therapy with corticosteroids and immunosuppressants. A dose of 375 mg/m^2 once weekly was used and most patients were given a course of 4 doses. Most patients showed some improvement from rituximab, including 9 who were free of clinical disease for more than 6 months and 5 who had a partial response. However, although concomitant therapy could be reduced in 8 patients, only 2 were able to stop systemic corticosteroids and immunosuppressants; in 6 cases this information was not reported. Rituximab might therefore be useful for remission induction when corticosteroids have not been effective, but long-term follow-up is needed. Rituximab with normal immunoglobulins has also been reported to be effective in patients with refractory pemphigus vulgaris.[2]

Rituximab has been reported to be of benefit in pemphigus foliaceus,[3,4] a less common variant of pemphigus. A single cycle of 4 weekly infusions of rituximab was reported to achieve complete remission in 12 of 14 patients with pemphigus vulgaris and 6 of 7 patients with pemphigus foliaceus; 2 patients in the former group achieved delayed complete remission. Of these 20 patients, 6 with pemphigus vulgaris and 3 with pemphigus foliaceus had a relapse; 2 of these 9 patients were given a second course of rituximab and again achieved complete remission. After 34 months of follow-up, 18 patients were free of disease, and 8 of these were not receiving any systemic therapy.[5]

1. El Tal AK, *et al.* Rituximab: a monoclonal antibody to CD20 used in the treatment of pemphigus vulgaris. *J Am Acad Dermatol* 2006; **55:** 449–59.
2. Ahmed AR, *et al.* Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. *N Engl J Med* 2006; **355:** 1772–9.
3. Goebeler M, *et al.* Rapid response of treatment-resistant pemphigus foliaceus to the anti-CD20 antibody rituximab. *Br J Dermatol* 2003; **149:** 899–901.
4. Arin MJ, *et al.* Anti-CD20 monoclonal antibody (rituximab) in the treatment of pemphigus. *Br J Dermatol* 2005; **153:** 620–5.
5. Joly P, *et al.* A single cycle of rituximab for the treatment of severe pemphigus. *N Engl J Med* 2007; **357:** 545–52.

Rheumatoid arthritis. Rituximab is of benefit in patients with rheumatoid arthritis (p.11) refractory to standard therapy.[1-3] The ability of rituximab to prevent articular damage, its efficacy for extra-articular manifestations, the efficacy and safety of repeated courses, and long-term effects on the immune system remain to be determined.[4] Radiographic data from a placebo-controlled study showed a trend towards less progression of structural joint

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.

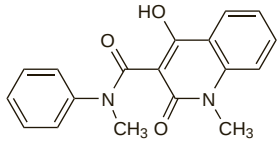
Рохинимекс

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

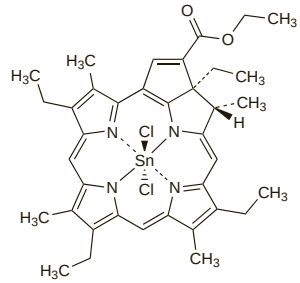
Rostaporfin *(USAN, rINN)*

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.

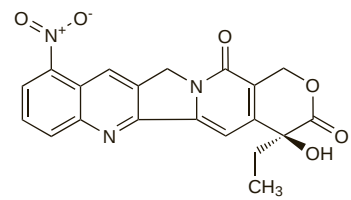
Rubitecan *(USAN, rINN)*

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.

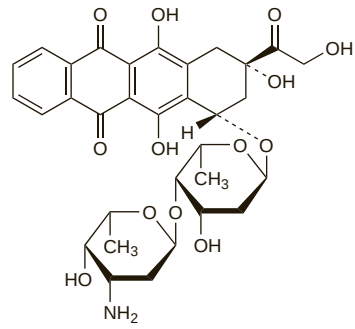
Sabarubicin *(rINN)*

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.

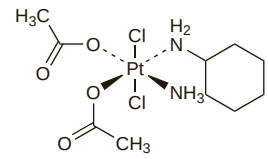
Satraplatin *(USAN, rINN)*

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.