oral; Sandimmun; ***Ger.:*** Ciclorat; Immunosporin; Sandimmun; ***Gr.:*** Restasis; Sandimmun; ***Hong Kong:*** Gengraf; Sandimmun; ***Hung.:*** Sandimmun; ***India:*** Imusporin; Panimun Bioral; Sandimmun; ***Indon.:*** Sandimmun; ***Irl.:*** Neoral; Sandimmun; ***Israel:*** Deximune; Sandimmun; Sangcya; ***Ital.:*** Sandimmun; ***Jpn:*** Papilock; ***Malaysia:*** Gengraf; Sandimmun; ***Mex.:*** Immulem; Modusik-A; Restasis; Sandimmun; Supremunn; ***Neth.:*** Neoral; Sandimmune; ***Norw.:*** Sandimmun; ***NZ:*** Gengraf; Neoral; Sandimmun; ***Philipp.:*** Restasis; Sandimmun; ***Pol.:*** Equoral; Sandimmun; ***Port.:*** Ciclostar; Sandimmun; ***Rus.:*** Consupren (Консупрен); Sandimmun (Сандиммун); ***S.Afr.:*** Ciclohexal; Sandimmun; ***Singapore:*** Gengraf; ***Spain:*** Sandimmun; ***Swed.:*** Sandimmun; ***Switz.:*** Ciclosol; Sandimmun; ***Thai.:*** Consupren; Equoral; Gengraf; Restasis; Sanda; Sandimmun; ***Turk.:*** Gengraf; Sandimmun; ***UAE:*** Sigmasporin; ***UK:*** Neoral; Sandimmun; ***USA:*** Gengraf; Neoral; Restasis; Sandimmune; ***Venez.:*** Imusporin; Restasis; Sandimmun.

Daclizumab *(BAN, USAN, rINN)*

Dacliximab; Daclizumabum; Daklitsumabi; Daklizumab; Humanised Anti-Tac Antibody; Ro-24-7375. Immunoglobulin G 1, (human-mouse monoclonal 1H4 γ-chain, anti-human interleukin 2 receptor), disulfide with human-mouse monoclonal clone 1H4 light chain, dimer.

Даклизумаб

CAS — 152923-56-3.

ATC — L04AC01.

ATC Vet — QL04AC01.

Adverse Effects and Precautions

Severe acute hypersensitivity reactions have occurred rarely with daclizumab. These have included anaphylactoid-type reactions such as rash, urticaria, pruritus, hypotension, hypoxia, tachycardia, cardiac arrest, wheezing, dyspnoea, bronchospasm, pulmonary oedema, peripheral oedema, laryngeal oedema, and respiratory failure. Injection site reactions have also been reported. Reactions have been seen both on initial exposure and with subsequent therapy. Therapy should be permanently stopped if a severe reaction occurs.

Effects on mortality. Increased mortality was reported in cardiac transplant recipients given an immunosuppressive regimen of daclizumab with ciclosporin, mycophenolate mofetil, and corticosteroids. Some deaths were associated with severe infection and use with antilymphocyte immunoglobulins.[1,2]

1. Roche, USA. 2003 safety alert: Zenapax (daclizumab). Available at: http://www.fda.gov/medwatch/SAFETY/2003/zenapax.htm (accessed 15/01/08)
2. Hershberger RE, *et al.* Daclizumab to prevent rejection after cardiac transplantation. *N Engl J Med* 2005; **352:** 2705–13.

Pharmacokinetics

The recommended regimen of daclizumab (see below) should result in serum concentrations sufficient to saturate interleukin-2 receptors for about 90 days post-transplantation in adult patients, and 120 days in paediatric patients. The terminal elimination half-life of daclizumab has ranged from 11 to 38 days.

Uses and Administration

Daclizumab is a humanised monoclonal murine antibody that functions as an interleukin-2 receptor antagonist by binding to the alpha chain (CD25 antigen, Tac subunit) of the interleukin-2 receptor on the surface of activated T-lymphocytes. It is used in the prevention of acute graft rejection after kidney transplantation as part of an immunosuppressive regimen that includes ciclosporin and corticosteroids. It is given in a dose of 1 mg/kg intravenously over 15 minutes within 24 hours before surgery and repeated at intervals of 2 weeks for a total of 5 doses. The required dose is diluted in 50 mL of sodium chloride 0.9%, and may be infused either centrally or peripherally. Daclizumab is also under investigation for its immunosuppressant properties in other forms of transplantation (see below) and in various diseases with an auto-immune component.

Administration in children. The dose for daclizumab in children aged 1 year and over is the same as in adults (see Uses and Administration, above).

Multiple sclerosis. Daclizumab has been tried[1-4] in patients with relapsing-remitting or secondary progressive multiple sclerosis; benefit has been reported.

1. Bielekova B, *et al.* Humanized anti-CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon β. *Proc Natl Acad Sci U S A* 2004; **101:** 8705–8.
2. Rose JW, *et al.* Treatment of multiple sclerosis with an anti-interleukin-2 receptor monoclonal antibody. *Ann Neurol* 2004; **56:** 864–7.
3. Rose JW, *et al.* Daclizumab phase II trial in relapsing and remitting multiple sclerosis: MRI and clinical results. *Neurology* 2007; **69:** 785–9.
4. Martin R. Humanized anti-CD25 antibody treatment with daclizumab in multiple sclerosis. *Neurodegener Dis* 2008; **5:** 23–6.

Ocular disorders. There have been reports of benefit with daclizumab in ocular inflammatory disorders[1] including scleritis, ocular cicatricial pemphigoid, and uveitis, all of which had been resistant to conventional therapy.

1. Papaliodis GN, *et al.* Treatment of ocular inflammatory disorders with daclizumab. *Ophthalmology* 2003; **110:** 786–9.

Organ and tissue transplantation. Daclizumab is used as induction therapy to reduce the incidence of acute rejection episodes after kidney transplantation (p.1813);[1-4] it is usually given as part of an immunosuppressive regimen that includes a calcineurin inhibitor and corticosteroids.

There are reports of successful corticosteroid withdrawal and corticosteroid-free regimens using daclizumab.[5] An attempt at using daclizumab to avoid use of ciclosporin after renal transplantation was unsuccessful, with a high rate of overall acute rejection in the daclizumab group.[6]

Daclizumab has also been investigated for the prevention of acute rejection after heart,[7] liver,[8,9] and lung[10] transplantation (see p.1812) but increased mortality has followed its use in patients receiving heart grafts[11] (see also under Adverse Effects and Precautions, above).

Daclizumab has also been tried in the management of acute graft-versus-host disease (GVHD; see Haematopoietic Stem Cell Transplantation, p.1811). While some consider it a viable alternative for corticosteroid-refractory acute GVHD,[12] others found that when daclizumab was used with corticosteroids to treat acute GVHD, this combination had a significantly deleterious effect on patient survival.[13]

Controlled studies that directly compare 2 doses of daclizumab with the standard 5-dose regimen in kidney transplantation are lacking; despite this, many centres use a 2-dose regimen.[14] In a small, retrospective analysis[15] of simultaneous kidney-pancreas transplant recipients (p.1816), patients receiving 1 to 3 doses of daclizumab in addition to triple therapy had a significantly higher incidence of rejection than those receiving 4 to 5 doses. There was no difference in patient or graft survival. A larger multicentre study[16,17] found that simultaneous kidney-pancreas recipients given daclizumab 2 mg/kg every 14 days for 2 doses had a similar incidence of rejection to those given the standard 5-dose regimen; mean time to onset of rejection was delayed in the 2-dose regimen but there was no beneficial effect of daclizumab on graft survival at 3 years. A small comparative study[18] in heart transplant recipients found 2 doses of daclizumab to be at least as effective as the 5-dose regimen; no significant differences were observed for mortality. A novel 3-dose regimen has been investigated in liver transplantation.[19]

1. Vincenti F, *et al.* Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. *N Engl J Med* 1998; **338:** 161–5.
2. Nashan B, *et al.* Reduction of acute renal allograft rejection by daclizumab. *Transplantation* 1999; **67:** 110–15.
3. Bumgardner GL, *et al.* Results of 3-year phase III clinical trials with daclizumab prophylaxis for prevention of acute rejection after renal transplantation. *Transplantation* 2001; **72:** 839–45.
4. Ciancio G, *et al.* Daclizumab induction, tacrolimus, mycophenolate mofetil and steroids as an immunosuppression regimen for primary kidney transplant recipients. *Transplantation* 2002; **73:** 1100–6.
5. ter Meulen CG, *et al.* Steroid-withdrawal at 3 days after renal transplantation with anti-IL-2 receptor α therapy: a prospective, randomized, multicenter study. *Am J Transplant* 2004; **4:** 803–10.
6. Åsberg A, *et al.* Calcineurin inhibitor avoidance with daclizumab, mycophenolate mofetil, and prednisolone in DR-matched de novo kidney transplant recipients. *Transplantation* 2006; **82:** 62–8.
7. Beniaminovitz A, *et al.* Prevention of rejection in cardiac transplantation by blockade of the interleukin-2 receptor with a monoclonal antibody. *N Engl J Med* 2000; **342:** 613–19.
8. Niemeyer G, *et al.* Long-term safety, tolerability and efficacy of daclizumab (Zenapax) in a two-dose regimen in liver transplant recipients. *Am J Transplant* 2002; **2:** 454–60.
9. Figueras J, *et al.* Daclizumab induction and maintenance steroid-free immunosuppression with mycophenolate mofetil and tacrolimus to prevent acute rejection of hepatic allografts. *Transpl Int* 2006; **19:** 641–8.
10. Garrity ER, *et al.* Low rate of acute lung allograft rejection after the use of daclizumab, an interleukin 2 receptor antibody. *Transplantation* 2001; **71:** 773–7.
11. Hershberger RE, *et al.* Daclizumab to prevent rejection after cardiac transplantation. *N Engl J Med* 2005; **352:** 2705–13.
12. Bordigoni P, *et al.* Daclizumab, an efficient treatment for steroid-refractory acute graft-versus-host disease. *Br J Haematol* 2006; **135:** 382–5.
13. Lee SJ, *et al.* Effect of up-front daclizumab when combined with steroids for the treatment of acute graft-versus-host disease: results of a randomized trial. *Blood* 2004; **104:** 1559–64.
14. van Gelder T, *et al.* Anti-interleukin-2 receptor antibodies in transplantation: what is the basis for choice? *Drugs* 2004; **64:** 1737–41.
15. Bruce DS, *et al.* Multicenter survey of daclizumab induction in simultaneous kidney-pancreas transplant recipients. *Transplantation* 2001; **72:** 1637–43.
16. Stratta RJ, *et al.* One-year outcomes in simultaneous kidney-pancreas transplant recipients receiving an alternative dosing regimen of daclizumab. *Transplant Proc* 2004; **36:** 1080–1.
17. Stratta RJ, *et al.* A prospective, randomized, multicenter study evaluating the safety and efficacy of two dosing regimens of daclizumab compared to no antibody induction in simultaneous kidney-pancreas transplantation: results at 3 years. *Transplant Proc* 2005; **37:** 3531–4.
18. Ortiz V, *et al.* Induction therapy with daclizumab in heart transplantation—how many doses? *Transplant Proc* 2006; **38:** 2541–3.
19. Washburn WK, *et al.* A novel three-dose regimen of daclizumab in liver transplant recipients with hepatitis C: a pharmacokinetic and pharmacodynamic study. *Liver Transpl* 2006; **12:** 585–91.

Skin disorders. There are reports of successful treatment with daclizumab in psoriasis (p.1583),[1,2] pemphigus vulgaris,[3] bullous pemphigoid[4] (see Pemphigus and Pemphigoid, p.1582), and epidermolysis bullosa acquisita[5] (p.1579). Cutaneous manifestations of adult T-cell leukaemia/lymphoma have also been reported to respond to daclizumab.[6]

1. Wohlrab J, *et al.* Treatment of recalcitrant psoriasis with daclizumab. *Br J Dermatol* 2001; **144:** 209–10.
2. Dichmann S, *et al.* Humanized monoclonal anti-CD25 antibody as a novel therapeutic option in HIV-associated psoriatic erythroderma. *J Am Acad Dermatol* 2002; **47:** 635–6.
3. Renkl A, *et al.* A novel therapeutic option in pemphigus vulgaris: humanized monoclonal anti-CD25 antibody. *Br J Dermatol* 2004; **150:** 1220–2.
4. Mockenhaupt M, *et al.* Daclizumab: a novel therapeutic option in severe bullous pemphigoid. *Acta Derm Venereol* 2005; **85:** 65–6.
5. Egan CA, *et al.* Treatment of epidermolysis bullosa acquisita with the humanised anti-Tac mAb daclizumab. *Clin Immunol* 2001; **101:** 146–51.
6. Osborne GEN, *et al.* Novel treatment of Sézary-like syndrome due to adult T-cell leukaemia/lymphoma with daclizumab (humanized anti-interleukin-2 receptor α antibody). *Br J Dermatol* 2006; **155:** 617–20.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Zenapax; ***Austral.:*** Zenapax; ***Austria:*** Zenapax; ***Belg.:*** Zenapax†; ***Braz.:*** Zenapax; ***Canad.:*** Zenapax; ***Chile:*** Zenapax; ***Cz.:*** Zenapax; ***Denm.:*** Zenapax; ***Fin.:*** Zenapax; ***Fr.:*** Zenapax; ***Ger.:*** Zenapax; ***Gr.:*** Zenapax; ***Hong Kong:*** Zenapax; ***Hung.:*** Zenapax; ***Irl.:*** Zenapax; ***Israel:*** Zenapax; ***Ital.:*** Zenapax; ***Mex.:*** Zenapax; ***Neth.:*** Zenapax; ***NZ:*** Zenapax; ***Philipp.:*** Zenapax; ***Pol.:*** Zenapax; ***Port.:*** Zenapax; ***S.Afr.:*** Zenapax; ***Singapore:*** Zenapax†; ***Spain:*** Zenapax; ***Swed.:*** Zenapax; ***Switz.:*** Zenapax; ***Thai.:*** Zenapax; ***Turk.:*** Zenapax; ***UK:*** Zenapax; ***USA:*** Zenapax; ***Venez.:*** Zenapax.

Everolimus *(USAN, rINN)*

Évérolimus; Everolimús; Everolimusum; NVP-RAD-001; RAD-001; SDZ-RAD; SDZ-RAD-666. (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,-17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,-26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-{(1*R*)-2-[(1*S*,3*R*,4*R*)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4*H*,6*H*,31*H*)-pentone.

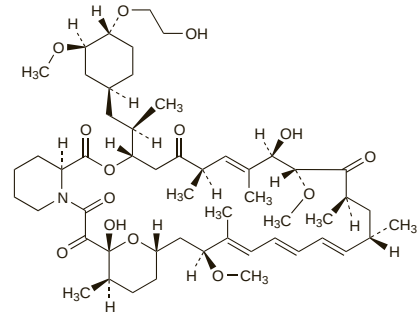
Эверолимус

$C_{53}H_{83}NO_{14}$ = 958.2.

CAS — 159351-69-6.

ATC — L04AA18.

ATC Vet — QL04AA18.



Adverse Effects

Leucopenia, thrombocytopenia, and anaemia occur commonly with everolimus. Haemolysis has been reported rarely. Other common adverse effects include hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, hypertension, lymphocele, venous thromboembolism, and gastrointestinal upsets. Pneumonia, pneumonitis, hepatitis, jaundice, renal tubular necrosis, and pyelonephritis may occur. Acne and oedema occur frequently; rashes and myalgia occur rarely.

Effects on the lungs. Pulmonary toxicity is a well-known adverse effect in patients given sirolimus (p.1841) and similar toxicity has occurred[1] in patients given everolimus.

1. Expósito V, *et al.* Everolimus-related pulmonary toxicity in heart transplant recipients. *J Heart Lung Transplant* 2008; **27:** 797–800.

Interactions

Everolimus is metabolised in the liver and to some extent in the gastrointestinal wall; plasma concentrations may be affected by