4. Ogata H, *et al.* A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. *Gut* 2006; **55:** 1255–62. Correction. *ibid.*; 1684. [dosage error in abstract]
5. Casson DH, *et al.* Topical tacrolimus may be effective in the treatment of oral and perineal Crohn's disease. *Gut* 2000; **47:** 436–40.
6. Hart AL, *et al.* Topical tacrolimus in the treatment of perianal Crohn's disease: exploratory randomized controlled trial. *Inflamm Bowel Dis* 2007; **13:** 245–53.
7. Gonzalez-Lama Y, *et al.* The role of tacrolimus in inflammatory bowel disease: a systematic review. *Dig Dis Sci* 2006; **51:** 1833–40.

Myasthenia gravis. Tacrolimus has been reported to be effective in the management of myasthenia gravis (p.629) in patients resistant to conventional therapy, or for whom standard therapy is contra-indicated.[1,2] In an open-label study, 79 patients with myasthenia gravis, who had undergone thymectomy and were on high doses of prednisone and ciclosporin, were switched from ciclosporin to tacrolimus. Initial doses of tacrolimus were 0.1 mg/kg daily, given in 2 divided doses. Dosage was subsequently adjusted to achieve plasma concentrations between 7 and 8 nanograms/mL; tacrolimus doses of 6 to 10 mg daily were needed. After 1 year doses were reduced to achieve concentrations of about 6 nanograms/mL. Doses of prednisone were reduced, and finally withdrawn in all but 2 patients; 73 patients received tacrolimus for more than 3 years. All patients were able to resume normal daily activities.[3] Tacrolimus is licensed for use for myasthenia gravis in some countries, in a usual dose of 3 mg once daily by mouth. Tacrolimus (initial daily dose 3 mg orally) was also reported to reduce corticosteroid dosage in another small study; treatment was continued long-term and efficacy was maintained for up to 3 years.[4] There is some suggestion that tacrolimus may be more effective in thymomatous myasthenia gravis than in non-thymomatous disease.[5]

Tacrolimus has also been used as first-line adjunctive therapy with prednisolone; it was reported to decrease the daily prednisolone dose, and the need for plasmapheresis and high-dose intravenous methylprednisolone.[6]

1. Evoli A, *et al.* Successful treatment of myasthenia gravis with tacrolimus. *Muscle Nerve* 2002; **25:** 111–14.
2. Shimojima Y, *et al.* Tacrolimus in refractory patients with myasthenia gravis: coadministration and tapering of oral prednisolone. *J Clin Neurosci* 2006; **13:** 39–44.
3. Ponseti JM, *et al.* Long-term results of tacrolimus in cyclosporine- and prednisone-dependent myasthenia gravis. *Neurology* 2005; **64:** 1641–3.
4. Tada M, *et al.* Long-term therapeutic efficacy and safety of low-dose tacrolimus (FK506) for myasthenia gravis. *J Neurol Sci* 2006; **247:** 17–20.
5. Mitsui T, *et al.* Beneficial effect of tacrolimus on myasthenia gravis with thymoma. *Neurologist* 2007; **13:** 83–6.
6. Nagane Y, *et al.* Efficacy of low-dose FK506 in the treatment of Myasthenia gravis—a randomized pilot study. *Eur Neurol* 2005; **53:** 146–50.

Ocular disorders. For mention of the use of tacrolimus in various disorders characterised by ocular lesions such as uveitis, see p.1810.

Organ and tissue transplantation. Tacrolimus has been used both for primary immunosuppression and for the control of graft rejection. Much of the initial experience with the drug was for liver grafts, (p.1815), but it is also used in the transplantation of heart (p.1812), kidney (p.1813), lung (p.1815), pancreas (p.1816), and intestines (p.1813). It has also been tried for the prophylaxis of graft-versus-host disease after bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p.1811).

A few selected references to the use of tacrolimus in transplantation are given below.

1. European FK506 Multicentre Liver Study Group. Randomised trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection. *Lancet* 1994; **344:** 423–8.
2. The US Multicenter FK506 Liver Study Group. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression in liver transplantation. *N Engl J Med* 1994; **331:** 1110–15.
3. Gruessner RW. Tacrolimus in pancreas transplantation: a multicenter analysis. *Clin Transplant* 1997; **11:** 299–312.
4. Gruessner RWG, *et al.* Suggested guidelines for the use of tacrolimus in pancreas/kidney transplantation. *Clin Transplant* 1998; **12:** 260–2.
5. Margreiter R. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicentre study. *Lancet* 2002; **359:** 741–6.
6. O'Grady JG, *et al.* Tacrolimus versus microemulsified ciclosporin in liver transplantation: the TMC randomised controlled trial. *Lancet* 2002; **360:** 1119–25.
7. Scott LJ, *et al.* Tacrolimus: a further update of its use in the management of organ transplantation. *Drugs* 2003; **63:** 1247–97.
8. Kelly D, *et al.* Tacrolimus and steroids versus ciclosporin microemulsion, steroids, and azathioprine in children undergoing liver transplantation: randomised European multicentre trial. *Lancet* 2004; **364:** 1054–61.
9. Webster AC, *et al.* Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. *BMJ* 2005; **331:** 810–14.
10. McCormack PL, *et al.* Tacrolimus: in heart transplant recipients. *Drugs* 2006; **66:** 2269–79.
11. Haddad EM, *et al.* Cyclosporin versus tacrolimus for liver transplanted patients. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 18/03/08).
12. Wente MN, *et al.* Review of the clinical experience with a modified release form of tacrolimus [FK506E (MR4)] in transplantation. *Clin Transplant* 2006; **20** (suppl 17): 80–4.
13. Patel JK, Kobashigawa JA. Tacrolimus in heart transplant recipients: an overview. *BioDrugs* 2007; **21:** 139–43.
14. Joseph A, *et al.* Tacrolimus immunosuppression in high-risk corneal grafts. *Br J Ophthalmol* 2007; **91:** 51–5.

Psoriasis. Tacrolimus has been shown to be effective in the treatment of psoriasis (p.1583) when used orally[1] or topically.[2-4]

1. The European FK 506 Multicentre Psoriasis Study Group. Systemic tacrolimus (FK 506) is effective for the treatment of psoriasis in a double-blind, placebo-controlled study. *Arch Dermatol* 1996; **132:** 419–23.
2. Remitz A, *et al.* Tacrolimus ointment improves psoriasis in a microplaque assay. *Br J Dermatol* 1999; **141:** 103–7.
3. Clayton TH, *et al.* Topical tacrolimus for facial psoriasis. *Br J Dermatol* 2003; **149:** 419–20.
4. Brune A, *et al.* Tacrolimus ointment is effective for psoriasis on the face and intertriginous areas in pediatric patients. *Pediatr Dermatol* 2007; **24:** 76–80.

Pyoderma gangrenosum. There are reports of response to tacrolimus, given orally,[1-3] or topically,[4-9] or both,[10,11] in patients with pyoderma gangrenosum (p.1583). A small study[12] found topical tacrolimus 0.3% in carmellose sodium paste to be more effective than clobetasol propionate 0.05% for peristomal pyoderma gangrenosum.

Systemic absorption, resulting in tacrolimus blood concentrations equivalent to oral dosing, has been reported in patients with pyoderma gangrenosum in whom tacrolimus was applied directly onto ulcerated areas;[13,14] therapeutic drug monitoring has been suggested for patients treated with topical tacrolimus over large skin areas or with impaired skin barriers.

1. Abu-Elmagd K, *et al.* Resolution of severe pyoderma gangrenosum in a patient with streaking leukocyte factor disease after treatment with tacrolimus (FK 506). *Ann Intern Med* 1993; **119:** 595–8.
2. D'Incà R, *et al.* Tacrolimus to treat pyoderma gangrenosum resistant to cyclosporine. *Ann Intern Med* 1998; **128:** 783–4.
3. Lyon CC, *et al.* Recalcitrant pyoderma gangrenosum treated with systemic tacrolimus. *Br J Dermatol* 1999; **140:** 562–4.
4. Schuppe H-C, *et al.* Topical tacrolimus for pyoderma gangrenosum. *Lancet* 1998; **351:** 832.
5. Reich K, *et al.* Topical tacrolimus for pyoderma gangrenosum. *Br J Dermatol* 1998; **139:** 755–7.
6. Vidal D, Alomar A. Successful treatment of periostomal pyoderma gangrenosum using topical tacrolimus. *Br J Dermatol* 2004; **150:** 387–8.
7. Lally A, *et al.* Penile pyoderma gangrenosum treated with topical tacrolimus. *Arch Dermatol* 2005; **141:** 1175–6.
8. Chiba T, *et al.* Topical tacrolimus therapy for pyoderma gangrenosum. *J Dermatol* 2005; **32:** 199–203.
9. Kontos AP, *et al.* An open-label study of topical tacrolimus ointment 0.1% under occlusion for the treatment of pyoderma gangrenosum. *Int J Dermatol* 2006; **45:** 1383–5.
10. Jolles S, *et al.* Combination oral and topical tacrolimus in therapy-resistant pyoderma gangrenosum. *Br J Dermatol* 1999; **140:** 564–5.
11. Deckers-Kocken JM, Pasmans SG. Successful tacrolimus (FK506) therapy in a child with pyoderma gangrenosum. *Arch Dis Child* 2005; **90:** 531.
12. Lyon CC, *et al.* Topical tacrolimus in the management of peristomal pyoderma gangrenosum. *J Dermatol Treat* 2001; **12:** 13–17.
13. Ghislain P-D, *et al.* Efficacy and systemic absorption of topical tacrolimus used in pyoderma gangrenosum. *Br J Dermatol* 2004; **150:** 1052–3.
14. Pitarch G, *et al.* Systemic absorption of topical tacrolimus in pyoderma gangrenosum. *Acta Derm Venereol* 2006; **86:** 64–5.

Reperfusion and revascularisation procedures. References to the use of tacrolimus-eluting stents.

1. García-Tejada J, *et al.* Carbo-stent liberador de tacrolimus Janus : resultados inmediatos y seguimiento clínico a medio plazo. *Rev Esp Cardiol* 2007; **60:** 197–200.
2. Han Y-L, *et al.* Midterm outcomes of prospective, randomized, single-center study of the Janus tacrolimus-eluting stent for treatment of native coronary artery lesions. *Chin Med J (Engl)* 2007; **120:** 552–6.

Rheumatoid arthritis. In a small, open-label study[1] of 12 patients with rheumatoid arthritis (p.11) refractory to other disease-modifying antirheumatic drugs including ciclosporin, 7 had significant response to tacrolimus after treatment for 6 months, with 4 of these patients maintaining this response after 2 years of therapy. In a larger controlled study,[2] tacrolimus improved disease activity in patients with rheumatoid arthritis resistant to methotrexate. Similarly, an open-label multicentre study involving 80 patients with active disease inadequately responsive to methotrexate alone, addition of tacrolimus 3 mg daily by mouth to methotrexate therapy produced a clinical improvement in about half. The regimen was considered to be generally well tolerated.[3] Tacrolimus in an oral dose of 3 mg once daily has been licensed for use in refractory rheumatoid arthritis in some countries; elderly patients may be given 1.5 mg once daily.[4,5]

1. Gremillion RB, *et al.* Tacrolimus (FK506) in the treatment of severe, refractory rheumatoid arthritis: initial experience in 12 patients. *J Rheumatol* 1999; **26:** 2332–6.
2. Furst DE, *et al.* Efficacy of tacrolimus in rheumatoid arthritis patients who have been treated unsuccessfully with methotrexate: a six-month, double-blind, randomized, dose-ranging study. *Arthritis Rheum* 2002; **46:** 2020–8.
3. Kremer JM, *et al.* Tacrolimus in rheumatoid arthritis patients receiving concomitant methotrexate: a six-month, open-label study. *Arthritis Rheum* 2003; **48:** 2763–8.
4. Curran MP, Perry CM. Tacrolimus: in patients with rheumatoid arthritis. *Drugs* 2005; **65:** 993–1001.
5. Kawai S, Yamamoto K. Safety of tacrolimus, an immunosuppressive agent, in the treatment of rheumatoid arthritis in elderly patients. *Rheumatology (Oxford)* 2006; **45:** 441–4.

Scleroderma. There are reports of response to tacrolimus in patients with scleroderma (p.1817).

Skin disorders. Topical tacrolimus has been used to treat various skin disorders. Aside from its licensed use in eczema (above), and use in psoriasis and pyoderma gangrenosum (see above), there are reports of benefit in granuloma annulare,[1,2] lichen sclerosus,[3] lichen striatus,[4] pityriasis alba,[5] pityriasis lichenoides,[6] seborrhoeic dermatitis,[7] as well as the skin manifestations of angiolymphoid hyperplasia,[8] pruritus due to primary biliary cirrhosis,[9] and facial cutaneous lupus erythematosus.[10]

1. Harth W, Linse R. Topical tacrolimus in granuloma annulare and necrobiosis lipoidica. *Br J Dermatol* 2004; **150:** 792–4.
2. Jain S, Stephens CJM. Successful treatment of disseminated granuloma annulare with topical tacrolimus. *Br J Dermatol* 2004; **150:** 1042–3.
3. Hengge UR, *et al.* Multicentre, phase II trial on the safety and efficacy of topical tacrolimus ointment for the treatment of lichen sclerosus. *Br J Dermatol* 2006; **155:** 1021–8.
4. Sorgentini C, *et al.* Lichen striatus in an adult: successful treatment with tacrolimus. *Br J Dermatol* 2004; **150:** 776–7.
5. Rigopoulos D, *et al.* Tacrolimus ointment 0.1% in pityriasis alba: an open-label, randomized, placebo-controlled study. *Br J Dermatol* 2006; **155:** 152–5.
6. Simon D, *et al.* Successful treatment of pityriasis lichenoides with topical tacrolimus. *Br J Dermatol* 2004; **150:** 1033–5.
7. Braza TJ, *et al.* Tacrolimus 0.1% ointment for seborrhoeic dermatitis: an open-label pilot study. *Br J Dermatol* 2003; **148:** 1242–4.
8. Mashiko M, *et al.* A case of angiolymphoid hyperplasia with eosinophilia successfully treated with tacrolimus ointment. *Br J Dermatol* 2006; **154:** 803–4.
9. Aguilar-Bernier M, *et al.* Successful treatment of pruritus with topical tacrolimus in a patient with primary biliary cirrhosis. *Br J Dermatol* 2005; **152:** 808–9.
10. Tzung T-Y, *et al.* Tacrolimus vs. clobetasol propionate in the treatment of facial cutaneous lupus erythematosus: a randomized, double-blind, bilateral comparison study. *Br J Dermatol* 2007; **156:** 191–2.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Prograf; Protopic; Tacraf; Tacro-Tic; Tacroinmun; ***Austral.:*** Prograf; ***Austria:*** Prograf; Protopic; ***Belg.:*** Progaft; Protopic; ***Braz.:*** Prograf; Protopic; ***Canad.:*** Prograf; Protopic; ***Chile:*** Cromidin; Prograf; Protopic; T-Inmun; ***Cz.:*** Advagraf; Prograf; Protopic; Protopy; ***Denm.:*** Prograf; Protopic; ***Fin.:*** Prograf; Protopic; ***Fr.:*** Advagraf; Prograf; Protopic; ***Ger.:*** Prograf; Protopic; ***Gr.:*** Prograf; Protopic; ***Hong Kong:*** Prograf; Protopic; ***Hung.:*** Prograf; Protopic; ***India:*** Mustopic; PanGraf; Tacroz†; ***Indon.:*** Protopic; ***Irl.:*** Prograf; Protopic; ***Israel:*** Prograf; Protopic; ***Ital.:*** Prograf; Protopic; ***Jpn:*** Prograf; Protopic; ***Malaysia:*** Prograf; Protopic; ***Mex.:*** Limustin; Proalid; Prograf; ***Neth.:*** Prograf; Progaft; Protopic; Protopy; ***Norw.:*** Prograf; Protopic; ***NZ:*** Prograf; ***Philipp.:*** Prograf; Protopic; ***Pol.:*** Prograf; Protopic; ***Port.:*** Prograf; Protopic; Protopy; ***Rus.:*** Prograf (Програф); ***S.Afr.:*** Prograf; ***Singapore:*** Prograf; Protopic; ***Spain:*** Prograf; Protopic; ***Swed.:*** Prograf; Protopic; ***Switz.:*** Prograf; Protopic; ***Thai.:*** Prograf; Protopic; ***Turk.:*** Prograf; ***UK:*** Advagraf; Prograf; Protopic; ***USA:*** Prograf; Protopic; ***Venez.:*** Prograf.

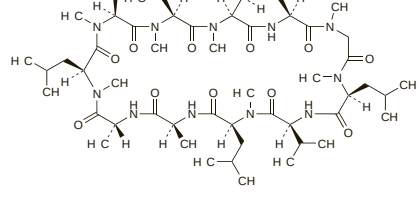
Voclosporin *(USAN, rINN)*

ISA-247; ISATX-247; LX-211; R-1524; Voclosporina; Voclosporine; Voclosporinum. Cyclo{L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-[(2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)nona-6,8-dienoyl]-(2*S*)-2-aminobutanoyl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl}.

Вокльоспорин

$C_{63}H_{111}N_{11}O_{12}$ = 1214.6.

CAS — 515814-01-4.



Profile

Voclosporin is an analogue of ciclosporin (p.1822) that is under investigation for the treatment of uveitis, psoriasis, and for the prevention of rejection in organ transplantation.

◊ References.

1. Dumont FJ. ISAtx-247 (Isotechnika/Roche). *Curr Opin Investig Drugs* 2004; **5:** 542–50.
2. Anonymous. ISA 247: trans-ISA 247, trans-R 1524, ISA(TX)247, ISAtx 247, ISATx247, LX 211, LX211, R 1524, R-1524. *Drugs R D* 2007; **8:** 103–12.
3. Papp K, *et al.* Efficacy of ISA247 in plaque psoriasis: a randomised, multicentre, double-blind, placebo-controlled phase III study. *Lancet* 2008; **371:** 1337–42.

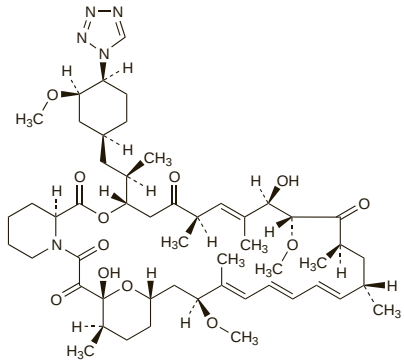
Zotarolimus *(USAN, rINN)*

ABT-578; Zotarolimusum. (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*)-9,27-Dihydroxy-10,21-dimethoxy-3-{(2*R*)-1-[(1*S*,3*R*,4*S*)-3-methoxy-4-(1*H*-tetrazol-1-yl)cyclohexyl]propan-2-yl}-6,8,12,14,20,26-hexamethyl-3,4,9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-octadecahydro-5*H*-23,27-epoxypyrido[2,1-*c*][1,4]oxaazahentriacontine-1,5,11,28,29(6*H*,31*H*)-pentone.

Зотаролимус

$C_{52}H_{79}N_5O_{12}$ = 966.2.

CAS — 221877-54-9.



Profile

Zotarolimus is an analogue of sirolimus (p.1841) that is used in the form of a drug-eluting stent to reduce the risk of restenosis after percutaneous coronary stenting.

Reperfusion and revascularisation procedures. References to the use of zotarolimus-eluting stents.

1. Burke SE, *et al.* Zotarolimus (ABT-578) eluting stents. *Adv Drug Deliv Rev* 2006; **58:** 437–46.
2. Fajadet J, *et al.* ENDEAVOR II Investigators. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. *Circulation* 2006; **114:** 798–806.
3. Kandzari DE, Leon MB. Overview of pharmacology and clinical trials program with the zotarolimus-eluting endeavor stent. *J Interv Cardiol* 2006; **19:** 405–13.
4. Korovesis S, *et al.* Subacute thrombosis following implantation of zotarolimus-eluting stent. *Hellenic J Cardiol* 2006; **47:** 310–2.
5. Kandzari DE, *et al.* ENDEAVOR III Investigators. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. *J Am Coll Cardiol* 2006; **48:** 2440–7.
6. Chen Y-W, *et al.* Zotarolimus, a novel sirolimus analogue with potent anti-proliferative activity on coronary smooth muscle cells and reduced potential for systemic immunosuppression. *J Cardiovasc Pharmacol* 2007; **49:** 228–35.
7. Gershlick A, *et al.* ENDEAVOR Investigators. Zotarolimus-eluting stents in patients with native coronary artery disease: clinical and angiographic outcomes in 1,317 patients. *Am J Cardiol* 2007; **100** (suppl 2): S45–S55.
8. Meredith IT, *et al.* Four-year clinical follow-up after implantation of the endeavor zotarolimus-eluting stent: ENDEAVOR I, the first-in-human study. *Am J Cardiol* 2007; **100** (suppl 2): S56–S61.
9. Jain AK, *et al.* Real-world safety and efficacy of the endeavor zotarolimus-eluting stent: early data from the E-Five Registry. *Am J Cardiol* 2007; **100** (suppl 2): S77–S83.