Sirolimus *(BAN, USAN, rINN)*

AY-22989; AY-022989; NSC-226080; Rapamycin; Sirolimús; Sirolimusum; Sirolimuusi; Wy-090217. (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-hydroxy-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.

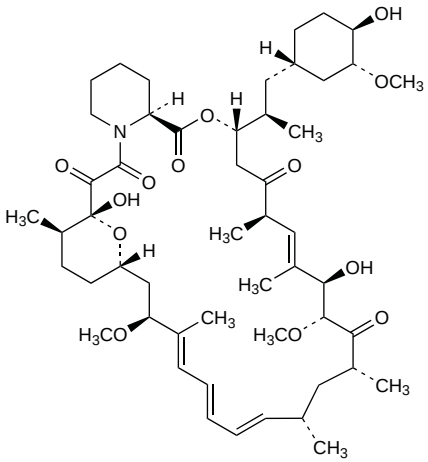
Сиролимус

$C_{51}H_{79}NO_{13}$ = 914.2.

CAS — 53123-88-9.

ATC — L04AA10.

ATC Vet — QL04AA10.



Adverse Effects and Precautions

The most frequent adverse effects of sirolimus include peripheral oedema, lymphocele, hypokalaemia, hypophosphataemia, hyperlipidaemia, hypercholesterolaemia, hyperglycaemia, tachycardia, venous thromboembolism, gastrointestinal disturbances, stomatitis, arthralgia, epistaxis, acne, rash, and bone necrosis. Anaemia, thrombocytopenia, neutropenia or leucopenia are common, especially at higher doses. Infections, including urinary-tract infections, pyelonephritis, CMV, Epstein-Barr virus, herpes zoster, and pneumocystis pneumonia, are also common, and antimicrobial prophylaxis for pneumonia is recommended for the first year after transplantation.

Thrombotic thrombocytopenic purpura and the haemolytic-uraemic syndrome may occur, as may hypersensitivity, including anaphylactic reactions, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis. There are reports of fluid accumulation, including lymphoedema, pleural effusions, and pericardial effusions. Pulmonary embolism, pulmonary haemorrhage, and pancreatitis may occur rarely. Renal impairment, proteinuria, or nephrotic syndrome may develop; renal function should be monitored, especially when given with ciclosporin. In patients with delayed graft function, sirolimus may delay recovery of renal function. There are reports of hepatotoxicity, and rarely, fatal hepatic necrosis. Excess mortality, graft loss, and hepatic artery thrombosis has been associated with the use of sirolimus in immunosuppressive regimens in liver transplant recipients and therefore use in such patients is not recommended. Interstitial lung disease has been reported, including some fatalities, although other cases resolved on stopping or reducing the dose of sirolimus. Abnormal wound healing after transplant surgery has been reported with the use of sirolimus, especially in those with a BMI greater than 30 kg/m^2; bronchial anastomotic dehiscence, including some fatal cases, has occurred in lung transplant recipients and use in the latter is not recommended. There is an increased risk of lymphoma and other malignancies with immunosuppression, and to minimise any risk of skin cancer, exposure to sunlight or ultraviolet light should be limited.

Sirolimus may have adverse effects on sperm parameters; azoospermia and infertility have been reported. These effects are usually reversible on stopping sirolimus.

Immunosuppressants may reduce the response to vaccines, and the use of live vaccines should be avoided. Intra-uterine devices should be used with caution during immunosuppressive therapy, as there is an increased risk of infection.

Hypersensitivity reactions and subacute thrombosis have occurred with use of the sirolimus-eluting stent; fatalities have been reported.

Effects on the kidneys. There are a number of reports of proteinuria and renal dysfunction associated with sirolimus. A review[1] concluded that the vast majority of evidence suggested that proteinuria was mediated by glomerular haemodynamic mechanisms due to withdrawal of other immunosuppressants in kidneys with chronic glomerular injury, as in those transplant patients with chronic allograft dysfunction. Whether sirolimus directly causes proteinuria and/or mediates direct glomerular toxicity remains to be resolved and further studies are needed.

1. Rangan GK. Sirolimus-associated proteinuria and renal dysfunction. *Drug Safety* 2006; **29:** 1153–61.

Effects on the lungs. Pulmonary toxicity, including interstitial pneumonitis,[1-7] and alveolar haemorrhage,[5,8,9] has been reported in association with sirolimus. There was some suggestion in one series that the incidence of interstitial pneumonitis might be higher in patients who switched from calcineurin inhibitors to sirolimus than in those who were started on sirolimus after transplantation.[6] Possible risk factors include giving a loading dose, late use of sirolimus compared with initial therapy, and higher sirolimus dose and trough concentrations; additional risk factors include allograft dysfunction, hypervolaemia, and male gender.[7] Acute respiratory distress has been reported in a 1-year-old heart transplant recipient 3 days after starting sirolimus.[10] Pulmonary alveolar proteinosis has also been reported in a renal transplant patient 2 years after starting sirolimus; symptoms resolved markedly upon stopping sirolimus.[11]

Similar toxicity has occurred with everolimus (p.1833).

1. Morelon E, *et al.* Interstitial pneumonitis associated with sirolimus therapy in renal-transplant recipients. *N Engl J Med* 2000; **343:** 225–6.
2. Singer SJ, *et al.* Interstitial pneumonitis associated with sirolimus therapy in renal-transplant recipients. *N Engl J Med* 2000; **343:** 1815–16.
3. Morelon E, *et al.* Characteristics of sirolimus-associated interstitial pneumonitis in renal transplant patients. *Transplantation* 2001; **72:** 787–90.
4. Lennon A, *et al.* Interstitial pneumonitis associated with sirolimus (rapamycin) therapy after liver transplantation. *Transplantation* 2001; **72:** 1166–7.
5. Pham P-T T, *et al.* Sirolimus-associated pulmonary toxicity. *Transplantation* 2004; **77:** 1215–20.
6. Champion L, *et al.* Brief communication: sirolimus-associated pneumonitis: 24 cases in renal transplant recipients. *Ann Intern Med* 2006; **144:** 505–9.
7. Morath C, *et al.* Four cases of sirolimus-associated interstitial pneumonitis: identification of risk factors. *Transplant Proc* 2007; **39:** 99–102.
8. Vlahakis NE, *et al.* Sirolimus-associated diffuse alveolar hemorrhage. *Mayo Clin Proc* 2004; **79:** 541–5.
9. Khalife WI, *et al.* Sirolimus-induced alveolar hemorrhage. *J Heart Lung Transplant* 2007; **26:** 652–7.
10. Das BB, *et al.* Acute sirolimus pulmonary toxicity in an infant heart transplant recipient: case report and literature review. *J Heart Lung Transplant* 2007; **26:** 296–8.
11. Pedroso SL, *et al.* Pulmonary alveolar proteinosis: a rare pulmonary toxicity of sirolimus. *Transpl Int* 2007; **20:** 291–6.

Effects on the nervous system. Posterior reversible encephalopathy syndrome (a neurotoxic condition involving oedema of the white matter in the posterior parts of the brain and characterised by headache, confusion, and visual disturbances) has been reported after use of sirolimus.[1,2]

1. Bodkin CL, Eidelman BH. Sirolimus-induced posterior reversible encephalopathy. *Neurology* 2007; **68:** 2039–40.
2. Moskowitz A, *et al.* Posterior reversible encephalopathy syndrome due to sirolimus. *Bone Marrow Transplant* 2007; **39:** 653–4.

Thrombosis. There was an apparent clustering of reports of subacute thrombosis associated with the use of the sirolimus-eluting stent soon after its marketing approval in 2003.[1] However, subsequent studies[2] and additional data from 2063 patients[3] suggest that use of the sirolimus-eluting stent is not associated with an excess risk of subacute thrombosis compared with bare-metal stents.

1. Muni NI, Gross TP. Problems with drug-eluting coronary stents—the FDA perspective. *N Engl J Med* 2004; **351:** 1593–5.
2. Jeremias A, *et al.* Stent thrombosis after successful sirolimus-eluting stent implantation. *Circulation* 2004; **109:** 1930–2.
3. US Food and Drug Administration. FDA public health web notification: final update of information for physicians on sub-acute thromboses (SAT) and hypersensitivity reactions with use of the Cordis CYPHER sirolimus-eluting coronary stent (issued 18/10/04). Available at: http://www.fda.gov/cdrh/safety/cypher3.pdf (accessed 18/03/08)

Interactions

Inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole, HIV-protease inhibitors, the NNRTI delavirdine, and diltiazem may increase plasma concentrations of sirolimus. Conversely, inducers of this isoenzyme, such as nevirapine and rifampicin, may reduce plasma concentrations of sirolimus. Use of sirolimus with strong inhibitors or inducers of CYP3A4 and/or P-glycoprotein is not recommended. Grapefruit juice should not be taken with sirolimus. Ciclosporin can affect the rate and extent of sirolimus absorption and it is recommended that these drugs be given 4 hours apart. Use of sirolimus with a calcineurin inhibitor may also increase the risk of calcineurin inhibitor-induced haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, or thrombotic microangiopathy. Use of sirolimus with an ACE inhibitor may increase the risk of developing angioedema. See above for precautions about use with live vaccines.

Immunosuppressants. Concentrations of sirolimus, and area under the concentration-time curve were significantly higher when sirolimus and *ciclosporin* were given together than when the 2 drugs were given 4 hours apart,[1,2] and a synergistic effect has been suggested.[3] This effect may allow for lower doses[4] or early withdrawal[5] of ciclosporin, resulting in improved renal function and less nephrotoxicity. However, for the risk of increased thrombotic reactions see above.

Sirolimus may decrease blood concentrations of *tacrolimus*.

1. Kaplan B, *et al.* The effects of relative timing of sirolimus and cyclosporine microemulsion formulation coadministration on the pharmacokinetics of each agent. *Clin Pharmacol Ther* 1998; **63:** 48–53.
2. Zimmerman JJ, *et al.* Pharmacokinetic interactions between sirolimus and microemulsion cyclosporine when orally administered jointly and 4 hours apart in healthy volunteers. *J Clin Pharmacol* 2003; **43:** 1168–76.
3. Kahan BD, Kramer WG. Median effect analysis of efficacy versus adverse effects of immunosuppressants. *Clin Pharmacol Ther* 2001; **70:** 74–81.
4. Reitamo S, *et al.* Efficacy of sirolimus (rapamycin) administered concomitantly with a subtherapeutic dose of cyclosporin in the treatment of severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2001; **145:** 438–45.
5. Johnson RWG, *et al.* Sirolimus allows early cyclosporine withdrawal in renal transplantation resulting in improved renal function and lower blood pressure. *Transplantation* 2001; **72:** 777–86.

Pharmacokinetics

Sirolimus is rapidly absorbed after doses of the oral solution, with a time to peak concentration of about 2 hours. Absorption is variably affected by food, especially high-fat meals. Sirolimus is extensively bound to plasma proteins. It is metabolised by the cytochrome P450 isoenzyme CYP3A4. Metabolism occurs by demethylation or hydroxylation, and the majority of a dose is excreted via the faeces, with only about 2% excreted in the urine. In healthy subjects, the bioavailability of a single dose of the tablet formulation is about 27% higher than the oral solution, bioavailability of which is only about 14%. However, this difference is less marked in renal transplant recipients, and when switching between formulations, licensed product information recommends giving the same dose, with trough concentrations verified 1 to 2 weeks later. The terminal half-life in stable renal transplant patients after multiple oral doses has been reported to be about 62 hours; the half-life in men was reported to be significantly longer than in women (about 72 hours compared with about 61 hours).

◊ References.

1. Mahalati K, Kahan BD. Clinical pharmacokinetics of sirolimus. *Clin Pharmacokinet* 2001; **40:** 573–85.

Genetic factors. Renal transplant recipients with at least one CYP3A5*1 allele had lower exposure to sirolimus than those patients homozygous for CYP3A5*3, and patients with CYP3A5*1/*1 and *1/*3 genotypes required significantly higher sirolimus daily dosage to achieve the same blood concentrations at steady state as the *3/*3 genotypes.[1] Determination of this cytochrome P450 isoenzyme polymorphism could be useful for individualising doses of sirolimus.

1. Le Meur Y, *et al.* CYP3A5*3 influences sirolimus oral clearance in de novo and stable renal transplant recipients. *Clin Pharmacol Ther* 2006; **80:** 51–60.

Therapeutic drug monitoring. The immunosuppressive efficacy and the occurrence and severity of adverse effects of sirolimus correlate with blood concentrations.[1] There is also a good correlation between sirolimus trough concentrations and the area under the concentration-time curve (AUC); the trough concentration is therefore a useful surrogate marker for sirolimus exposure.[2] When sirolimus is used with ciclosporin, whole blood trough concentrations of sirolimus between 4 and 12 nanograms/mL are associated with protection from acute rejection episodes and adverse events. Black patients may require higher doses of sirolimus to achieve a similar exposure to non-black patients; trough concentrations in the higher end of the range are recommended to reduce the risk of rejection.[3] When ciclosporin therapy is stopped, a target trough concentration of sirolimus of about 12 to 20 nanograms/mL is recommended (see also Uses and Administration, below).

Daily monitoring of sirolimus is not necessary due to the relatively long half-life of the drug (about 60 hours). Furthermore, sirolimus concentrations are variable early after transplantation due to physiological changes from surgery and concurrent dose adjustments in other immunosuppressants. The first sample should be taken about 4 days or more after the initial loading dose, and then weekly for the first month and every 2 weeks for the second month.[3] Monitoring is also necessary after changes in the dose of sirolimus or ciclosporin, or of their relative timing.[2,3]

After the first 2 months of dose titration, routine therapeutic drug monitoring is not considered necessary in all patients, although it is considered warranted in patients receiving concurrent CYP3A4 and/or P-glycoprotein inducers or inhibitors. Monitoring may also be needed in those at high risk of rejection, those displaying signs of toxicity, or those in whom compliance is a problem.[3] Patients with liver disease, hyperlipidaemia, or leucopenia should also have their sirolimus blood concentrations determined,[2] and concentrations in children should be monitored.[3] Licensed product information states that the recommended 24-hour trough concentrations for sirolimus are based on chromatographic assay methods, and that these values are not interchangeable with immunoassay methods.

Bayesian forecasting has also been proposed as an accurate predictor of sirolimus pharmacokinetics.[4,5]

1. Mahalati K, Kahan BD. Clinical pharmacokinetics of sirolimus. *Clin Pharmacokinet* 2001; **40:** 573–85.
2. Oellerich M, Armstrong VW. The role of therapeutic drug monitoring in individualizing immunosuppressive drug therapy: recent developments. *Ther Drug Monit* 2006; **28:** 720–5.
3. Stenton SB, *et al.* Sirolimus: the evidence for clinical pharmacokinetic monitoring. *Clin Pharmacokinet* 2005; **44:** 769–86.
4. Dansirikul C, *et al.* A Bayesian approach for population pharmacokinetic modelling of sirolimus. *Br J Clin Pharmacol* 2006; **62:** 420–34.
5. Djebli N, *et al.* Sirolimus population pharmacokinetic/pharmacogenetic analysis and Bayesian modelling in kidney transplant recipients. *Clin Pharmacokinet* 2006; **45:** 1135–48.

Uses and Administration

Sirolimus is a macrolide compound obtained from *Streptomyces hygroscopicus* and has potent immunosuppressant properties. Sirolimus binds to a protein (FK binding protein-12; FKBP-12; FKPB-12) and this complex inhibits the activation of the mammalian target of rapamycin (mTOR), a key regulatory kinase for cell cycle progression thus suppressing cytokine-driven T-cell proliferation.

Sirolimus is used for the prevention of graft rejection in kidney transplantation (p.1813), and is being investigated for induction of remission in some auto-immune diseases. Sirolimus-releasing stents have been developed to reduce restenosis after coronary artery stent placement. They are also used in the treatment of severe claudication and critical limb ischaemia of infrapopliteal lesions (which is the most severe form of arterial disease in the leg).

For prevention of graft rejection, sirolimus is given with ciclosporin and corticosteroids as soon as possible after transplantation. A loading dose of 6 mg is given orally, followed by a maintenance dose of 2 mg daily, 4 hours after ciclosporin. In patients 13 years of age or more who weigh less than 40 kg a loading dose of 3 mg/m^2, followed by initial maintenance doses of 1 mg/m^2 daily, is recommended. It is recommended that the dose of sirolimus should be adjusted to obtain whole blood trough concentrations of 4 to 12 nanograms/mL (by chromatographic assay), and the doses of ciclosporin and corticosteroids gradually reduced. After 2 to 3 months, ciclosporin should be gradually stopped over 4 to 8 weeks, and the dose of sirolimus adjusted to obtain trough concentrations of about 12 to 20 nanograms/mL. In the USA, ciclosporin may be continued for up to 4 months; sirolimus trough concentrations of 16 to 24 nanograms/mL have been recommended for the first year after transplantation; thereafter, the concentrations should be 12 to 20 nanograms/mL. In patients at high immunological risk (defined as black [Afro-Caribbean] patients and/or repeat renal transplant patients), sirolimus may be used with ciclosporin and corticosteroids for the first year after transplantation. The recommended loading dose is 15 mg, followed by an initial maintenance dose of 5 mg daily; adjustments thereafter are made on the basis of whole blood trough concentrations. In patients in whom ciclosporin withdrawal is unsuccessful or cannot be attempted, sirolimus should not be used for more than 3 months after transplantation.

Sirolimus has been shown to possess antifungal and antineoplastic properties. It is under investigation for gene regulation in gene therapy.

Administration. A study in renal transplant recipients judged the tablet and oral solution formulations of sirolimus to be therapeutically equivalent.[1] Licensed product information states that while 2 mg of oral solution has been shown to be clinically equivalent to 2 mg of the oral tablet formulation, and the two are hence interchangeable, it is not known whether higher doses of the oral solution are clinically equivalent to the same doses as tablets. When switching patients between formulations, it is recommended to give the same dose and verify the sirolimus trough concentrations 1 to 2 weeks later; verification of trough concentrations is also recommended when switching between different tablet strengths.

1. Mathew TH, *et al.* A comparative study of sirolimus tablet versus oral solution for prophylaxis of acute renal allograft rejection. *J Clin Pharmacol* 2006; **46:** 76–87.

Administration in children. Sirolimus is not licensed for use in children under 13 years of age. For doses in children aged 13 years or older, and weighing under 40 kg, see Uses and Administration, above. In the UK, the *BNFC* recommends local treatment protocols be consulted for details of doses to be used in children; official guidance from NICE recommends that sirolimus be used as a component of immunosuppressive regimens in children and adolescents only if intolerance necessitates the withdrawal of a calcineurin inhibitor.[1]

1. NICE. Immunosuppressive therapy for renal transplantation in children and adolescents (Technology Appraisal 99, issued April 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/TA099guidance.pdf (accessed 07/02/08)

Administration in hepatic impairment. Exposure to sirolimus and half-life are both increased in patients with mild to moderate hepatic impairment (Child-Pugh category A or B). UK licensed product information states that in patients with hepatic impairment, it is not necessary to modify the loading dose of sirolimus, but whole blood trough concentrations should be closely monitored in these patients. US licensed product information states that the maintenance dose should be reduced by about one-third in patients with mild to moderate hepatic impairment.

A study[1] involving 9 patients with severe hepatic impairment (Child-Pugh category C) indicated that an initial dosage reduction of about 60% followed by therapeutic drug monitoring might be suitable in these patients. For patients with severe hepatic impairment UK and US licensed product information state that the maintenance dose should be reduced by about one half.

1. Zimmerman JJ, *et al.* Pharmacokinetics of sirolimus (rapamycin) in subjects with severe hepatic impairment. *J Clin Pharmacol* 2008; **48:** 285–92.

Kaposi's sarcoma. Transplant recipients are susceptible to the development of Kaposi's sarcoma (p.675) as a result of long-term immunosuppressive therapy. In 15 renal transplant recipients with biopsy-proven Kaposi's sarcoma, therapy with ciclosporin and mycophenolate was stopped, and sirolimus started. After 1 month, cutaneous lesions had regressed in 12 patients and after 6 months biopsy specimens were negative for Kaposi's sarcoma.[1] While stopping ciclosporin or mycophenolate has led to remission of Kaposi's sarcoma,[2] sirolimus may have an antineoplastic action independent of its immunosuppressive effect.[1] In renal transplant recipients, those who received sirolimus-based therapy after ciclosporin withdrawal at month 3 had a reduced incidence of both skin and non-skin (including Kaposi's sarcoma) malignancies at 5 years after transplantation, compared with those who continued with sirolimus and ciclosporin therapy.[3]

1. Stallone G, *et al.* Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *N Engl J Med* 2005; **352:** 1317–23.
2. Dantal J, Soulillou J-P. Immunosuppressive drugs and the risk of cancer after organ transplantation. *N Engl J Med* 2005; **352:** 1371–3.
3. Campistol JM, *et al.* Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. *J Am Soc Nephrol* 2006; **17:** 581–9.

Lymphangioleiomyomatosis. Improvements in left lung function have been noted in a patient with lymphangioleiomyomatosis treated with sirolimus after transplantation of the right lung.[1] For mention of the use of medroxyprogesterone in this rare disease, see Respiratory Disorders, p.2114.

1. Egan JJ, *et al.* Sirolimus for lymphangioleiomyomatosis lesions. *N Engl J Med* 2008; **358:** 1963–4.

Organ and tissue transplantation. Sirolimus is used for the prophylaxis of graft rejection in kidney transplantation (p.1813), initially as an adjunct to calcineurin inhibitor-based regimens. It is increasingly used for corticosteroid or calcineurin inhibitor withdrawal, although long-term data are lacking, and the safety of ciclosporin withdrawal in high-risk patients has not been adequately studied and is not recommended. Sirolimus has been investigated for liver (p.1815), heart (p.1812), pancreas (p.1816), and lung (p.1815) transplantation, although safety has not been established. In *de novo* renal transplant patients, there was an increased risk of rejection in those given sirolimus and mycophenolate and corticosteroids with an interleukin-2 receptor antibody, compared with those not given an interleukin-2 receptor antibody. In a small study of heart transplant recipients switched from standard immunosuppressive therapy with a calcineurin inhibitor, mycophenolate mofetil, and corticosteroids, to sirolimus with mycophenolate mofetil, there was an increased incidence of acute rejection; target sirolimus and mycophenolate concentrations may have been insufficient to maintain adequate immunosuppression.

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

1. Vasquez EM. Sirolimus: a new agent for prevention of renal allograft rejection. *Am J Health-Syst Pharm* 2000; **57:** 437–51.
2. Kahan BD. Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomised multicentre study. *Lancet* 2000; **356:** 194–202.
3. Ingle GR, *et al.* Sirolimus: continuing the evolution of transplant immunosuppression. *Ann Pharmacother* 2000; **34:** 1044–55.
4. Johnson RW. Sirolimus (Rapamune) in renal transplantation. *Curr Opin Nephrol Hypertens* 2002; **11:** 603–7.
5. Radovancevic B, Vrtovec B. Sirolimus therapy in cardiac transplantation. *Transplant Proc* 2003; **35** (suppl): 171S–176S.
6. Trotter JF. Sirolimus in liver transplantation. *Transplant Proc* 2003; **35** (suppl): 193S–200S.
7. MacDonald AS. Rapamycin in combination with cyclosporine or tacrolimus in liver, pancreas, and kidney transplantation. *Transplant Proc* 2003; **35** (suppl): 201S–208S.
8. Neff GW, *et al.* Ten years of sirolimus therapy in orthotopic liver transplant recipients. *Transplant Proc* 2003; **35** (suppl): 209S–216S.
9. Dupont P, Warrens AN. The evolving role of sirolimus in renal transplantation. *QJM* 2003; **96:** 401–9.
10. Kahan BD. Sirolimus: a ten-year perspective. *Transplant Proc* 2004; **36:** 71–5.
11. Lo A, *et al.* Comparison of sirolimus-based calcineurin inhibitor-sparing and calcineurin inhibitor-free regimens in cadaveric renal transplantation. *Transplantation* 2004; **77:** 1228–35.
12. Kuypers DRJ. Benefit-risk assessment of sirolimus in renal transplantation. *Drug Safety* 2005; **28:** 153–81.
13. Mehrabi A, *et al.* The role and value of sirolimus administration in kidney and liver transplantation. *Clin Transplant* 2006; **20** (Suppl 17): 30–43.
14. Mulay AV, *et al.* Conversion from calcineurin inhibitors to sirolimus for chronic renal allograft dysfunction: a systematic review of the evidence. *Transplantation* 2006; **82:** 1153–62.
15. Augustine JJ, *et al.* Use of sirolimus in solid organ transplantation. *Drugs* 2007; **67:** 369–91.
16. House AA, *et al.* Sirolimus use in recipients of expanded criteria donor kidneys. *Drugs* 2008; **68** (suppl 1): 41–9.

Psoriasis. Sirolimus has been investigated both systemically[1,2] and topically[3,4] in the treatment of psoriasis (p.1583).

1. Reitamo S, *et al.* A double-blind study in patients with severe psoriasis to assess the clinical activity and safety of rapamycin (sirolimus) alone or in association with a reduced dose of cyclosporine. *Br J Dermatol* 1999; **141:** 978–9.
2. Reitamo S, *et al.* Efficacy of sirolimus (rapamycin) administered concomitantly with a subtherapeutic dose of cyclosporin in the treatment of severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2001; **145:** 438–45.
3. Ormerod AD, *et al.* Penetration, safety and efficacy of the topical immunosuppressive sirolimus in psoriasis. *Br J Dermatol* 1999; **141:** 975.
4. Ormerod AD, *et al.* Treatment of psoriasis with topical sirolimus: preclinical development and a randomized, double-blind trial. *Br J Dermatol* 2005; **152:** 758–64.

Reperfusion and revascularisation procedures. Restenosis is a particular problem after percutaneous coronary revascularisation procedures (p.1181) and various drugs have been tried for its prevention. Coronary stents that elute sirolimus effectively reduce restenosis[1-8] and have been widely used. There is some suggestion that sirolimus-eluting stents may be superior to paclitaxel-eluting stents in terms of clinical outcome and rates of restenosis,[9-12] although not all studies have noted differences.[13] The risk of late stent thrombosis may be increased with drug eluting stents,[14] although the evidence is controversial,[15] and their role in complex interventions is not yet established.[16,17] Oral sirolimus may also be effective in preventing restenosis.[18-21]

1. Morice M-C, *et al.* A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002; **346:** 1773–80.
2. Moses JW, *et al.* Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003; **349:** 1315–23.

3. Lemos PA, *et al.* Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndromes: insights from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *J Am Coll Cardiol* 2003; **41:** 2093–9.
4. Holmes DR, *et al.* Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. *Circulation* 2004; **109:** 634–40.
5. Vishnevetsky D, *et al.* Sirolimus-eluting coronary stent. *Am J Health-Syst Pharm* 2004; **61:** 449–56.
6. Cheng-Lai A, Frishman WH. Sirolimus-eluting coronary stents: novel devices for the management of coronary artery disease. *Am J Ther* 2004; **11:** 218–28.
7. Spaulding C, *et al.* A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007; **356:** 989–97.
8. Kastrati A, *et al.* Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007; **356:** 1030–9.
9. Windecker S, *et al.* Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med* 2005; **353:** 653–62.
10. Dibra A, *et al.* Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. *N Engl J Med* 2005; **353:** 663–70.
11. Hofma SH, *et al.* One year clinical follow up of paclitaxel eluting stents for acute myocardial infarction compared with sirolimus eluting stents. *Heart* 2005; **91:** 1176–80.
12. Stettler C, *et al.* Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet* 2007; **370:** 937–48.
13. Galløe AM, *et al.* SORT OUT II Investigators. Comparison of paclitaxel- and sirolimus-eluting stents in everyday clinical practice: the SORT OUT II randomized trial. *JAMA* 2008; **299:** 409–16.
14. Stone GW, *et al.* Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007; **356:** 998–1008.
15. Mauri L, *et al.* Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007; **356:** 1020–9.
16. Beohar N, *et al.* Outcomes and complications associated with off-label and untested use of drug-eluting stents. *JAMA* 2007; **297:** 1992–2000.
17. Win HK, *et al.* Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. *JAMA* 2007; **297:** 2001–9.
18. Hausleiter J, *et al.* Randomized, double-blind, placebo-controlled trial of oral sirolimus for restenosis prevention in patients with in-stent restenosis: the Oral Sirolimus to Inhibit Recurrent In-stent Stenosis (OSIRIS) trial. *Circulation* 2004; **110:** 790–5.
19. Waksman R, *et al.* Oral rapamycin to inhibit restenosis after stenting of de novo coronary lesions: the Oral Rapamune to Inhibit Restenosis (ORBIT) study. *J Am Coll Cardiol* 2004; **44:** 1386–92.
20. Rodriguez AE, *et al.* ORAR II Investigators. Oral rapamycin after coronary bare-metal stent implantation to prevent restenosis: the Prospective, Randomized Oral Rapamycin in Argentina (ORAR II) Study. *J Am Coll Cardiol* 2006; **47:** 1522–9.
21. Rodriguez AE, *et al.* Role of oral rapamycin to prevent restenosis in patients with de novo lesions undergoing coronary stenting: results of the Argentina single centre study (ORAR trial). *Heart* 2005; **91:** 1433–7.

Uveitis. Sirolimus has been reported to be effective in the treatment of patients with refractory uveitis.[1]

1. Shanmuganathan VA, *et al.* The efficacy of sirolimus in the treatment of patients with refractory uveitis. *Br J Ophthalmol* 2005; **89:** 666–9.

Preparations

Proprietary Preparations (details are given in Part 3)

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

Tacrolimus *(BAN, USAN, rINN)*

FK-506; FR-900506; Tacrolimús; Tacrolimusum; Takrolimus; Takrolimuusi; Tsukubaenolide. (−)-(3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26a*S*)-8-Allyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-{(*E*)-2-[(1*R*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylvinyl}-14,16,-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-3*H*-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4*H*,23*H*)-tetrone monohydrate.

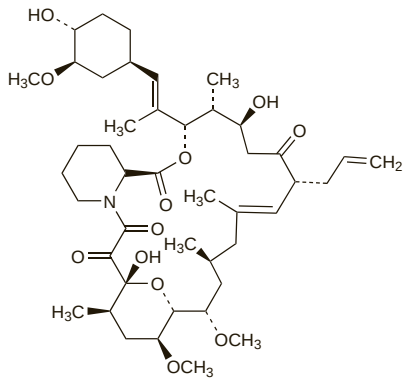
Такролимус

$C_{44}H_{69}NO_{12},H_2O$ = 822.0.

CAS — 104987-11-3 (anhydrous tacrolimus); 109581-93-3 (tacrolimus monohydrate).

ATC — D11AX14; L04AD02.

ATC Vet — QD11AX14; QL04AD02.



Adverse Effects, Treatment, and Precautions

The most common adverse effects after **systemic** use of tacrolimus include tremor, headache, paraesthesias, nausea and diarrhoea, hypertension, insomnia, and impaired renal function. Disturbances of serum electrolytes, notably hyperkalaemia, and hyperglycaemic conditions, including diabetes mellitus, occur frequently. Hyperlipidaemia, hypercholesterolaemia, and hypertriglyceridaemia are common. Anaemia, leucopenia, and thrombocytopenia also occur commonly. Other common adverse effects include mood changes, anxiety, confusion, dizziness, tinnitus, visual disturbances, peripheral neuropathies, and convulsions; constipation, dyspepsia, gastrointestinal perforation and ulceration, and gastrointestinal haemorrhage; dyspnoea, parenchymal lung disorders, pleural effusions, pharyngitis, cough, nasal congestion and inflammation; alopecia, acne, skin rashes, and pruritus; and arthralgia, muscle cramps, asthenia, febrile disorders, oedema, and liver dysfunction. Tachycardia is common; ventricular arrhythmias, cardiac arrest, heart failure, palpitations, and ECG changes are less frequent. Cardiomyopathies, including ventricular hypertrophy have also been reported; most cases have been reversible, and occurring primarily in children with tacrolimus blood concentrations much higher than the recommended maximum levels. Coagulation disorders, neutropenia, and pancytopenia have occurred, as have asthma, acute respiratory distress syndrome, hypoproteinaemia, deep limb venous thrombosis, paralytic ileus, acute and chronic pancreatitis, and haemolytic uraemic syndrome. Coma, CNS haemorrhage, encephalopathy, amnesia, and speech and language abnormalities have also been reported. There are rare reports of thrombotic thrombocytopenic purpura, hypoprothrombinaemia, and hirsutism. Toxic epidermal necrolysis, Stevens Johnson syndrome, hepatic artery thrombosis, and veno-occlusive liver disease have occurred rarely.

Tacrolimus injection is formulated with polyoxyl castor oil: anaphylactoid reactions have occurred, and appropriate means for their management should be available in patients given the injection. Use of tacrolimus should be avoided in patients hypersensitive to macrolides.

Dosage reduction may be necessary in patients with hepatic impairment. Care is also required in patients with pre-existing renal impairment, and dosage reduction may prove advisable in such patients. Monitoring of blood concentrations of tacrolimus is recommended in all patients, especially during episodes of diarrhoea as concentrations may be significantly affected. Renal and hepatic function, blood pressure, serum glucose electrolytes, haematological and cardiac function, as well as neurological and visual status, coagulation values, and plasma protein should be monitored regularly. As with other immunosuppressants, patients receiving tacrolimus are at increased risk of infection and malignancy. Intra-uterine devices should be used with caution during immunosuppressive therapy as there is an increased risk of infection. Use of live vaccines should be avoided for the same reason. Tacrolimus may affect visual or neurological function, and patients so affected should not drive or operate dangerous machinery.

Topical tacrolimus has been associated with local irritation and skin disorders including an increased incidence of herpes simplex and zoster infections; headache and 'flu-like' symptoms have also been reported. Facial flushing and skin irritation has been reported after consumption of alcohol. Exposure of the skin to sunlight should be minimised and the use of artificial sources of ultraviolet light avoided. Carcinogenicity studies in *animals* have reported an increase in the incidence of lymphoma and skin cancers associated with topical tacrolimus and rare cases of skin malignancy and lymphoma have been reported in patients (see also below).

Skin infections should be treated before starting therapy with topical tacrolimus. It should not be used in immunocompromised patients or those with conditions that might increase systemic absorption of tacrolimus. It must also not be applied to pre-malignant or malignant skin conditions; some malignant skin conditions may mimic eczema.

Breast feeding. Tacrolimus is distributed into breast milk. Tacrolimus concentrations were measured in milk from a liver transplant recipient on a dose of 100 micrograms/kg daily. The authors estimated that the infant would ingest only 0.06% (0.06 micrograms/kg daily) of the mother's weight-adjusted dose. No adverse effects were noted in the infant at 2.5 months of age.[1]

Licensed product information recommends that women should avoid breast feeding while taking tacrolimus.

1. French AE, *et al.* Milk transfer and neonatal safety of tacrolimus. *Ann Pharmacother* 2003; **37:** 815–18.

Carcinogenicity. The systemic use of tacrolimus increases the risk of malignancy.

Carcinogenicity studies in *animals* have also reported an increase in the incidence of malignancies associated with the topical calcineurin inhibitors, tacrolimus and pimecrolimus. As of December 2004 the FDA had received reports of 19 cases of lymphoma or cutaneous tumours associated with topical tacrolimus, of which 4 cases were a recurrence or aggravation of a pre-existing malignancy, and 3 other cases were confounded by other possible risk factors. At this same date, the FDA had also received reports of 10 cases of malignancy in patients treated with topical pimecrolimus, including 6 cutaneous tumours. Although the potential for systemic immunosuppression from topical use was unknown and the role of the drug in these cases was uncertain, the FDA recommended that topical calcineurin inhibitors should only be used as a second-line drug for short-term and intermittent treatment of eczema, and that they should not be used in immunocompromised patients or in children younger than 2 years of age.[1,2] Similar warnings have been issued in the European Union.[3] However, there has been some debate about the risk of malignancy associated with the topical use of these drugs, and a number of groups[4-6] have examined the evidence used by the FDA. They found that after topical application in humans the serum concentrations of these drugs were usually low or undetectable, that there was no evidence of systemic immunosuppression as measured by response to childhood immunisation and delayed hypersensitivity, no evidence of an increase in malignancy in clinical studies or compared with the general population, and that none of the reported lymphoma cases resembled the usual presentation and histology seen with systemic immunosuppression-associated lymphoma. They concluded that based on available data the risk of cancer from topical calcineurin inhibitors was theoretical and unknown. A review[7] of skin cancer risk found that there was no conclusive evidence from *rodent* studies to suggest that topical calcineurin inhibitors were associated with an increase in skin cancers, or a potentiation of UV-associated immunosuppression and carcinogenicity. There was also no evidence of an increased risk of skin cancer in human studies. In general, there seems to be agreement that long-term data are still needed to determine the carcinogenic risk, if there is any, from topical tacrolimus and pimecrolimus. Until long-term safety data are available some[8] consider that it would be prudent if topical calcineurin inhibitors were:

- not used in children under 2 years of age
- not used continuously for more than 6 weeks, with an application-free period of up to 2 weeks
- avoided in immunocompromised patients
- avoided in patients with neoplasia
- avoided in those with skin disorders liable to lead to increased systemic absorption