9. Curran MP, Keating GM. Mycophenolate sodium delayed release: prevention of renal transplant rejection. *Drugs* 2005; **65**: 799–805.

10. Manzia TM, *et al.* Use of mycophenolate mofetil in liver transplantation: a literature review. *Transplant Proc* 2005; **37**: 2616–17.

11. Ciancio G, *et al.* Review of major clinical trials with mycophenolate mofetil in renal transplantation. *Transplantation* 2005; **80** (suppl 2): S191–S200.

12. Srinivas TR, *et al.* The impact of mycophenolate mofetil on long-term outcomes in kidney transplantation. *Transplantation* 2005; **80** (suppl 2): S211–S220.

13. Kobashigawa JA, Meiser BM. Review of major clinical trials with mycophenolate mofetil in cardiac transplantation. *Transplantation* 2005; **80** (suppl 2): S235–S243.

14. Kaplan B. Enteric-coated mycophenolate sodium (Myfortic): an overview of current and future use in transplantation. *Drugs* 2006; **66** (suppl 2): 1–8.

15. Kobashigawa JA, *et al.* Similar efficacy and safety of enteric-coated mycophenolate sodium (EC-MPS, Myfortic) compared with mycophenolate mofetil (MMF) in de novo heart transplant recipients: results of a 12-month, single-blind, randomized, parallel-group, multicenter study. *J Heart Lung Transplant* 2006; **25**: 935–41.

16. Zimmerhackl LB, *et al.* Mycophenolate mofetil (Cellcept) in pediatric renal transplantation. *Transplant Proc* 2006; **38**: 2038–40.

17. Schmeding M, *et al.* Mycophenolate mofetil in liver transplantation—is monotherapy safe? *Clin Transplant* 2006; **20** (suppl 17): 75–9.

Pemphigus and pemphigoid. Mycophenolate mofetil has been used successfully in the treatment of pemphigus and pemphigoid (p.1582), both with prednisolone[1-3] and alone.[4] In a randomised, non-blinded study,[5] adjuvant mycophenolate mofetil was found to be as effective as adjuvant azathioprine; corticosteroid-sparing effects were similar and there was a trend towards fewer adverse effects with mycophenolate.

1. Enk AH, Knop J. Mycophenolate is effective in the treatment of pemphigus vulgaris. *Arch Dermatol* 1999; **135**: 54–6.

2. Williams JV, *et al.* Use of mycophenolate mofetil in the treatment of paraneoplastic pemphigus. *Br J Dermatol* 2000; **142**: 506–8.

3. Powell AM, *et al.* An evaluation of the usefulness of mycophenolate mofetil in pemphigus. *Br J Dermatol* 2003; **149**: 138–45.

4. Bredlich R-O, *et al.* Mycophenolate mofetil monotherapy for pemphigus vulgaris. *Br J Dermatol* 1999; **141**: 934.

5. Beissert S, *et al.* A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of pemphigus. *Arch Dermatol* 2006; **142**: 1447–54.

Polymyositis and dermatomyositis. Mycophenolate mofetil has been reported to be of benefit in refractory cases of polymyositis and dermatomyositis (p.1510), allowing for tapering of corticosteroid doses.[1-3] Despite benefit in 6 out of 10 patients in another study,[4] 3 patients developed opportunistic infection, which was fatal in 1 case. While acknowledging that other factors may have had a role in this, the authors advised caution in the use of mycophenolate in dermatomyositis.

1. Gelber AC, *et al.* Mycophenolate mofetil in the treatment of severe skin manifestations of dermatomyositis: a series of 4 cases. *J Rheumatol* 2000; **27**: 1542–5.

2. Majithia V, Harisdangkul V. Mycophenolate mofetil (CellCept): an alternative therapy for autoimmune inflammatory myopathy. *Rheumatology (Oxford)* 2005; **44**: 386–9.

3. Edge JC, *et al.* Mycophenolate mofetil as an effective corticosteroid-sparing therapy for recalcitrant dermatomyositis. *Arch Dermatol* 2006; **142**: 65–9.

4. Rowin J, *et al.* Mycophenolate mofetil in dermatomyositis: is it safe? *Neurology* 2006; **66**: 1245–7.

Primary biliary cirrhosis. Despite initial reports[1] of benefit with mycophenolate mofetil in the treatment of primary biliary cirrhosis (p.2408), a small study found no clinical benefit when it was given to patients with incomplete responses to ursodeoxycholic acid.[2]

1. Jones EA. Rationale for trials of long-term mycophenolate mofetil therapy for primary biliary cirrhosis. *Hepatology* 2002; **35**: 258–62.

2. Talwalkar JA, *et al.* Mycophenolate mofetil for the treatment of primary biliary cirrhosis in patients with an incomplete response to ursodeoxycholic acid. *J Clin Gastroenterol* 2005; **39**: 168–71.

Psoriasis. Mycophenolate mofetil has proved successful in some cases of psoriasis (p.1583) refractory to conventional therapies,[1-3] and topical application (as a 2% cream) has been investigated.[4]

1. Grundmann-Kollmann M, *et al.* Treatment of chronic plaque-stage psoriasis and psoriatic arthritis with mycophenolate mofetil. *J Am Acad Dermatol* 2000; **42**: 835–7.

2. Geilen CC, *et al.* Mycophenolate mofetil as a systemic antipsoriatic agent: positive experience in 11 patients. *Br J Dermatol* 2001; **144**: 583–6.

3. Zhou Y, *et al.* Mycophenolate mofetil (CellCept) for psoriasis: a two-center, prospective, open-label clinical trial. *J Cutan Med Surg* 2003; **7**: 193–7.

4. Wohlrab J, *et al.* Topical application of mycophenolate mofetil in plaque-type psoriasis. *Br J Dermatol* 2001; **144**: 1263–4.

Rheumatoid arthritis. Mycophenolate mofetil has been tried in rheumatoid arthritis (p.11); reports suggest it may effectively suppress synovial inflammation.[1]

1. McMurray RW, Harisdangkul V. Mycophenolate mofetil: selective T cell inhibition. *Am J Med Sci* 2002; **323**: 194–6.

Sarcoidosis. Mycophenolate mofetil has been used as an adjunct in the successful treatment of patients with mucocutaneous sarcoidosis (p.1512)[1] and neurosarcoidosis.[2] It was reported to have a significant corticosteroid-sparing effect in an adolescent with renal involvement,[3] and was effective in a case of severe, relapsing, corticosteroid-dependent gastrointestinal sarcoidosis.[4]

1. Kouba DJ, *et al.* Mycophenolate mofetil may serve as a steroid-sparing agent for sarcoidosis. *Br J Dermatol* 2003; **148**: 147–8.

2. Chaussenot A, *et al.* Neurosarcoïdose et mycophénolate mofétil. *Rev Neurol (Paris)* 2007; **163**: 471–5.

3. Moudgil A, *et al.* Successful steroid-sparing treatment of renal limited sarcoidosis with mycophenolate mofetil. *Pediatr Nephrol* 2006; **21**: 281–5.

4. O'Connor AS, *et al.* Pancreatitis and duodenitis from sarcoidosis: successful therapy with mycophenolate mofetil. *Dig Dis Sci* 2003; **48**: 2191–5.

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

References.

1. Nihtyanova SI, *et al.* Mycophenolate mofetil in diffuse cutaneous systemic sclerosis—a retrospective analysis. *Rheumatology (Oxford)* 2007; **46**: 442–5.

2. Vanthuyne M, *et al.* A pilot study of mycophenolate mofetil combined to intravenous methylprednisolone pulses and oral low-dose glucocorticoids in severe early systemic sclerosis. *Clin Exp Rheumatol* 2007; **25**: 287–92.

3. Shenin M, *et al.* The use of mycophenolate mofetil for the treatment of systemic sclerosis. *Endocr Metab Immune Disord Drug Targets* 2008; **8**: 11–14.

Systemic lupus erythematosus. Mycophenolate mofetil by mouth plus prednisolone, given for 12 months, was found to be as effective as oral cyclophosphamide plus prednisolone, for 6 months, followed by azathioprine plus prednisolone for 6 months,[1] in the treatment of Chinese patients with diffuse proliferative *lupus nephritis* (see Systemic Lupus Erythematosus, p.1513). However, some[2,3] have cautioned about generalising these findings to other patients since mycophenolate was compared with oral and not intravenous pulsed cyclophosphamide, which is considered the standard of care in those with diffuse proliferative disease. Patients with poorer prognoses were also considered to have been excluded or underrepresented in the study, and follow-up was short. However, in a 24-week unblinded study[4] oral mycophenolate mofetil was more effective in inducing complete remission than intermittent intravenous cyclophosphamide when used as induction therapy for active lupus nephritis and appeared to be better tolerated. Also, there have been reports of benefit with mycophenolate mofetil in patients with various forms of refractory lupus nephritis, including proliferative disease and membranous nephropathy,[5-7] and some consider it a good therapeutic alternative.[8,9] A review[10] concluded that limited data support induction with cyclophosphamide followed by maintenance with azathioprine or mycophenolate; in selected patients induction with mycophenolate is a reasonable alternative. Meta-analyses concluded that daily oral mycophenolate mofetil, in average or median doses of 1 to 2 g, was more effective than pulsed intravenous or oral cyclophosphamide,[11] and that mycophenolate reduced the risk of failure to induce remission during induction therapy when compared with cyclophosphamide.[12] However, the role of racial and ethnic differences in lupus remain poorly understood, and enrolment of varying ethnic populations in studies can significantly affect results of therapy.[13] Furthermore, it has been pointed out that subjects in studies included in one meta-analysis had relatively preserved renal function, and results cannot be generalised to patients with moderate to severe renal impairment and rapidly progressive glomerulonephritis.[14] While acknowledging data of mycophenolate use in children are limited, another review[15] concluded that from data in adults, mycophenolate is an acceptable alternative to intravenous cyclophosphamide in the induction phase for newly diagnosed patients with mild to moderate nephritis and intact renal function; it may also be suitable if there is concern about a patient's future fertility. However, the optimal dose and length of induction treatment with mycophenolate are still unknown.

Mycophenolate mofetil has been used to control extra-renal manifestations of SLE,[16,17] although it was ineffective in a small number of patients with severe refractory cutaneous disease.[18] Oral mycophenolate sodium 1.44 g daily has been reported to be effective in the treatment of patients with subacute cutaneous lupus erythematosus resistant to standard therapy.[19]

1. Chan TM, *et al.* Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. *N Engl J Med* 2000; **343**: 1156–62.

2. Falk RJ. Treatment of lupus nephritis—a work in progress. *N Engl J Med* 2000; **343**: 1182–3.

3. Karassa FB, Isenberg DA. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. *N Engl J Med* 2001; **344**: 382–3. Correction. *ibid.*; 1176.

4. Ginzler EM, *et al.* Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005; **353**: 2219–28.

5. Kingdon EJ, *et al.* The safety and efficacy of MMF in lupus nephritis: a pilot study. *Lupus* 2001; **10**: 606–11.

6. Kapitsinou PP, *et al.* Lupus nephritis: treatment with mycophenolate mofetil. *Rheumatology (Oxford)* 2004; **43**: 377–80.

7. Spetie DN, *et al.* Mycophenolate therapy of SLE membranous nephropathy. *Kidney Int* 2004; **66**: 2411–15.

8. Ginzler EM, Aranow C. Mycophenolate mofetil in lupus nephritis. *Lupus* 2005; **14**: 59–64.

9. Pisoni CN, *et al.* Mycophenolate mofetil in systemic lupus erythematosus: efficacy and tolerability in 86 patients. *J Rheumatol* 2005; **32**: 1047–52.

10. Lenz O, *et al.* Defining the role of mycophenolate mofetil in the treatment of proliferative lupus nephritis. *Drugs* 2005; **65**: 2229–36.

11. Moore RA, Derry S. Systematic review and meta-analysis of randomised trials and cohort studies of mycophenolate mofetil in lupus nephritis. *Arthritis Res Ther* 2006; **8**: R182.

12. Walsh M, *et al.* Mycophenolate mofetil for induction therapy of lupus nephritis: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2007; **2**: 968–75.

13. Dooley MA. Mycophenylate [sic] mofetil: what role in the treatment of lupus? *Lupus* 2006; **15**: 179–82.

14. Contreras G, Sosnov J. Role of mycophenolate mofetil in the treatment of lupus nephritis. *Clin J Am Soc Nephrol* 2007; **2**: 879–82.

15. Paredes A. Can mycophenolate mofetil substitute cyclophosphamide treatment of pediatric lupus nephritis? *Pediatr Nephrol* 2007; **22**: 1077–82.

16. Karim MY, *et al.* Mycophenolate mofetil for systemic lupus erythematosus refractory to other immunosuppressive agents. *Rheumatology (Oxford)* 2002; **41**: 876–82.

17. Pisoni CN, *et al.* Mycophenolate mofetil and systemic lupus erythematosus: an overview. *Lupus* 2005; **14** (suppl): s9–s11.

18. Pisoni CN, *et al.* Skin manifestations of systemic lupus erythematosus refractory to multiple treatment modalities: poor results with mycophenolate mofetil. *Clin Exp Rheumatol* 2005; **23**: 393–6.

19. Kreuter A, *et al.* Mycophenolate sodium for subacute cutaneous lupus erythematosus resistant to standard therapy. *Br J Dermatol* 2007; **156**: 1321–7.

Vasculitic syndromes. Mycophenolate mofetil has been tried in a number of the vasculitic syndromes, including Churg-Strauss syndrome (p.1501), polyarteritis nodosa and microscopic polyangiitis (p.1510), Takayasu's arteritis (p.1514), and Wegener's granulomatosis (p.1515).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: CellCept; Imuxgen; Munotras; Myfortic; *Austral.*: CellCept; Myfortic; *Austria*: CellCept; Myfortic; *Belg.*: CellCept; Myfortic; *Braz.*: CellCept; Myfortic; Refrat†; *Canad.*: CellCept; Myfortic; *Chile*: CellCept; Myfortic; *Cz.*: CellCept; Myfenax; Myfortic; *Denm.*: CellCept; Myfortic; *Fin.*: CellCept; Myfortic; *Fr.*: CellCept; Myfortic; *Ger.*: CellCept; Myfortic; *Gr.*: CellCept; Myfortic; *Hong Kong*: CellCept; Myfortic; *Hung.*: CellCept; Myfortic; *India*: Cellmune; Mycept; *Indon.*: CellCept; Myfortic; *Irl.*: CellCept; Myfortic; *Israel*: CellCept; Myfortic; *Ital.*: CellCept; Myfortic; *Jpn*: CellCept; *Malaysia*: CellCept; Myfortic; *Mex.*: CellCept; Myfortic; *Neth.*: CellCept; Myfortic; *Norw.*: CellCept; Myfortic; *NZ*: CellCept; Myfortic; *Philipp.*: CellCept; Myfortic; *Pol.*: CellCept; Myfortic; *Port.*: CellCept; Myfortic; *Rus.*: Myfortic (Майфортик); *S.Afr.*: CellCept; Myfortic; *Singapore*: CellCept; *Spain*: CellCept; Myfortic; *Swed.*: CellCept; Myfortic; *Switz.*: CellCept; Myfortic; *Thai.*: CellCept; Myfortic; *Turk.*: CellCept; UK: CellCept; Myfortic; *USA*: CellCept; Myfortic; *Venez.*: CellCept; Myfortic.
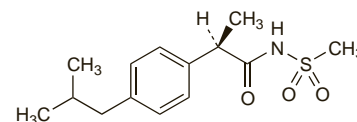
Reparixin *(USAN, rINN)*

DF-1681Y; Reparixina; Réparixine; Reparixinum; Repertaxin. (2R)-2-[4-(2-Methylpropyl)phenyl]-N-methylsulfonylpropanamide.

Репариксин

$C_{14}H_{21}NO_3S = 283.4$.

CAS — 266359-83-5.

Reparixin Lysine *(rINNM)*

Reparixin L-Lysine; Reparixina lisina; Réparixine Lysine; Reparixinum Lysinum; Repertaxin L-Lysine. Reparixin compound with L-lysine (1:1); .

Репариксин Лизин

$C_{14}H_{21}NO_3S,C_6H_{14}N_2O_2$; = 429.6.

CAS — 266359-93-7.

Profile

Reparixin is an inhibitor of interleukin-8. Reparixin and reparixin lysine are under investigation for the prevention of delayed graft function in organ transplantation.

Sirolimus (BAN, USAN, rINN)

AY-22989; AY-022989; NSC-226080; Rapamycin; Sirolimús; Sirolimusum; Sirolimuusi; Wy-090217. (3S,6R,7E,9R,10R,12R,-14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,10,12,13,14,21,22,-23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-{(1R)-2-[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methyl-ethyl}-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine-1,5,11,28,29-(4H,6H,31H)-pentone.
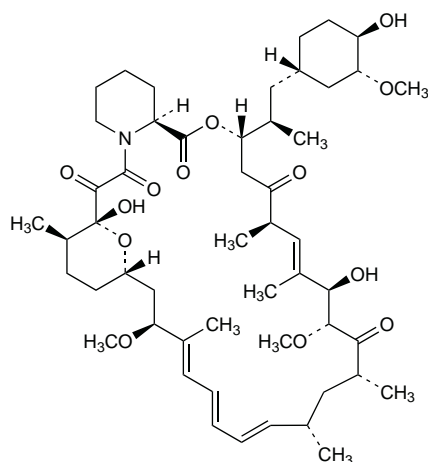
Сиролимус

$C_{51}H_{79}NO_{13}$ = 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/m², 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. 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.

The symbol † denotes a preparation no longer actively marketed