inducers or competitive inhibitors of P-glycoprotein, or hepatic enzymes, particularly cytochrome P450 isoenzyme CYP3A4. Use with live vaccines should be avoided.

◊ References.

1. Kovarik JM, *et al.* Everolimus drug interactions: application of a classification system for clinical decision making. *Biopharm Drug Dispos* 2006; **27:** 421–6.

Immunosuppressants. The bioavailability of everolimus was significantly increased when given with *ciclosporin*,[1] and dose adjustment of everolimus may be necessary if the ciclosporin dose is altered (see Administration, below).

In contrast, results from a small study implied that *tacrolimus* appeared to have a minimal effect on everolimus blood concentrations, and the dose of everolimus, when used with tacrolimus, may need to be higher than that given with ciclosporin in order to achieve therapeutic everolimus blood concentrations.[2]

1. Kovarik JM, *et al.* Differential influence of two cyclosporine formulations on everolimus pharmacokinetics: a clinically relevant pharmacokinetic interaction. *J Clin Pharmacol* 2002; **42:** 95–9.
2. Kovarik JM, *et al.* Differential pharmacokinetic interaction of tacrolimus and cyclosporine on everolimus. *Transplant Proc* 2006; **38:** 3456–8.

Ketoconazole. In a pharmacokinetic study in 12 healthy subjects,[1] ketoconazole increased the maximum concentration of everolimus by an average of 3.9-fold; area under the concentration-time curve was also increased by about 15-fold. The half-life of everolimus was significantly prolonged, and its clearance reduced. Since ketoconazole inhibits both cytochrome P450 isoenzyme CYP3A4 and P-glycoprotein, the authors supposed that both pathways might have contributed to this interaction. The interaction was deemed to be clinically relevant and they advised against use of these 2 drugs together.

1. Kovarik JM, *et al.* Blood concentrations of everolimus are markedly increased by ketoconazole. *J Clin Pharmacol* 2005; **45:** 514–18.

Rifampicin. In a pharmacokinetic study,[1] rifampicin increased the clearance of everolimus, decreasing exposure to everolimus by about 63%. Licensed product information recommends against the combined use of these drugs.

1. Kovarik JM, *et al.* Effect of rifampin on apparent clearance of everolimus. *Ann Pharmacother* 2002; **36:** 981–5.

Verapamil. Verapamil increased the bioavailability of everolimus; the half-life of everolimus was essentially unchanged. The dose of everolimus should be reduced when these two drugs are given together, but the amount should be determined by blood concentrations and clinical monitoring. Verapamil concentrations may also be affected by everolimus, but the mechanism is unclear; any dose adjustment of verapamil should be guided by blood pressure monitoring.[1]

1. Kovarik JM, *et al.* Pharmacokinetic interaction between verapamil and everolimus in healthy subjects. *Br J Clin Pharmacol* 2005; **60:** 434–7.

Pharmacokinetics

Peak plasma concentrations of everolimus occur about 1 to 2 hours after an oral dose. Plasma protein binding is about 74%. Everolimus is metabolised in the liver and to some extent in the gastrointestinal wall; most metabolites are excreted in the faeces with small amounts found in urine.

◊ References.

1. Kovarik JM, *et al.* Clinical development of an everolimus pediatric formulation: relative bioavailability, food effect, and steady-state pharmacokinetics. *J Clin Pharmacol* 2003; **43:** 141–7.
2. Kirchner GI, *et al.* Clinical pharmacokinetics of everolimus. *Clin Pharmacokinet* 2004; **43:** 83–95.

Therapeutic drug monitoring. Licensed product information recommends routine monitoring of whole blood everolimus concentrations. Patients with trough levels of 3 nanograms/mL or greater have been found to have a lower incidence of acute rejection in both renal and cardiac transplantation; an upper limit of 8 nanograms/mL is recommended. Monitoring is considered especially important in those with hepatic impairment (see under Uses, below) and if ciclosporin formulation or dosage is changed (see Administration, below).

Further references.

1. Kovarik JM, *et al.* Exposure-response relationships for everolimus in de novo kidney transplantation: defining a therapeutic range. *Transplantation* 2002; **73:** 920–5.
2. Kovarik JM, *et al.* Everolimus therapeutic concentration range defined from a prospective trial with reduced-exposure cyclosporine in de novo kidney transplantation. *Ther Drug Monit* 2004; **26:** 499–505.
3. Starling RC, *et al.* Therapeutic drug monitoring for everolimus in heart transplant recipients based on exposure-effect modeling. *Am J Transplant* 2004; **4:** 2126–31.
4. Lorber MI, *et al.* Therapeutic drug monitoring for everolimus in kidney transplantation using 12-month exposure, efficacy, and safety data. *Clin Transplant* 2005; **19:** 145–52.
5. Mabasa VH, Ensom MH. The role of therapeutic monitoring of everolimus in solid organ transplantation. *Ther Drug Monit* 2005; **27:** 666–76.
6. Kovarik JM, *et al.* Everolimus in pulmonary transplantation: pharmacokinetics and exposure-response relationships. *J Heart Lung Transplant* 2006; **25:** 440–6.

Uses and Administration

Everolimus is a derivative of sirolimus (p.1841). It is used as a proliferation signal inhibitor in the prevention of graft rejection episodes in patients undergoing renal or cardiac transplantation as part of an immunosuppressive regimen that includes ciclosporin (microemulsifying) and corticosteroids. The recommended adult oral dose is 750 micrograms twice daily, begun as soon as possible after transplantation, and given at the same time as ciclosporin (see Administration, below). Doses of everolimus should be reduced in patients with hepatic impairment, see below.

Everolimus is also under investigation for the treatment of renal cell carcinoma.

Everolimus-releasing stents have been developed to reduce restenosis after coronary artery stent placement.

Administration. Everolimus is given with ciclosporin and corticosteroids. Ciclosporin exposure reduction is recommended 1 month after transplantation. Because ciclosporin interacts with everolimus, and the dose adjustments of ciclosporin will affect exposure to everolimus, licensed product information for everolimus recommends that levels of both drugs be monitored to minimise the risk of graft rejection. Before dose reduction of ciclosporin, everolimus whole blood concentrations should be at least 3 nanograms/mL (see Therapeutic Drug Monitoring, above, and under Ciclosporin, p.1829).

In renal transplantation, ciclosporin doses should be adjusted to the following target ciclosporin concentration ranges, as measured 2 hours after the dose of ciclosporin:

- weeks 0-4: 1000 to 1400 nanograms/mL
- weeks 5-8: 700 to 900 nanograms/mL
- weeks 9-12: 550 to 650 nanograms/mL
- weeks 13-52: 350 to 450 nanograms/mL

In cardiac transplantation, ciclosporin levels are adjusted according to ciclosporin blood trough levels.

Administration in hepatic impairment. The clearance of everolimus was significantly reduced in patients with moderate hepatic impairment.[1] Product information states that the dose should be reduced by 50% in mild to moderate hepatic impairment (Child-Pugh class A or B) with further titration of the dose based on therapeutic drug monitoring (see under Pharmacokinetics, above). Everolimus has not been studied in severe hepatic impairment.

1. Kovarik JM, *et al.* Influence of hepatic impairment on everolimus pharmacokinetics: implications for dose adjustment. *Clin Pharmacol Ther* 2001; **70:** 425–30.

Organ and tissue transplantation. References.

1. Eisen HJ, *et al.* Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *N Engl J Med* 2003; **349:** 847–58.
2. Vitko S, *et al.* Everolimus with optimized cyclosporine dosing in renal transplant recipients: 6-month safety and efficacy results of two randomized studies. *Am J Transplant* 2004; **4:** 626–35.
3. Nashan B, *et al.* Everolimus and reduced-exposure cyclosporine in de novo renal-transplant recipients: a three-year phase II, randomized, multicenter, open-label study. *Transplantation* 2004; **78:** 1332–40.
4. Lorber MI, *et al.* Everolimus versus mycophenolate mofetil in the prevention of rejection in de novo renal transplant recipients: a 3-year randomized, multicenter, phase III study. *Transplantation* 2005; **80:** 244–52.
5. Vitko S, *et al.* Three-year efficacy and safety results from a study of everolimus versus mycophenolate mofetil in de novo renal transplant patients. *Am J Transplant* 2005; **5:** 2521–30. Correction. *ibid.* 2006; **6:** 243.
6. Snell GI, *et al.* Everolimus versus azathioprine in maintenance lung transplant recipients: an international, randomized, double-blind clinical trial. *Am J Transplant* 2006; **6:** 169–77.
7. Pascual J. Everolimus in clinical practice—renal transplantation. *Nephrol Dial Transplant* 2006; **21** (suppl 3): iii18–iii23.
8. Webster AC, *et al.* Target of rapamycin inhibitors (TOR-I; sirolimus and everolimus) for primary immunosuppression in kidney transplant recipients. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 18/02/08).
9. Dunn C, Croom KF. Everolimus: a review of its use in renal and cardiac transplantation. *Drugs* 2006; **66:** 547–70.
10. Snell GI, *et al.* Everolimus versus azathioprine in maintenance lung transplant recipients: an international, randomized, double-blind clinical trial. *Am J Transplant* 2006; **6:** 169–77.
11. Levy G, *et al.* Safety, tolerability, and efficacy of everolimus in de novo liver transplant recipients: 12- and 36-month results. *Liver Transpl* 2006; **12:** 1640–8.
12. Chapman JR, *et al.* Proliferation signal inhibitors in transplantation: questions at the cutting edge of everolimus therapy. *Transplant Proc* 2007; **39:** 2937–50.

Psoriasis. A patient with psoriasis and a poor response to conventional therapy was treated with everolimus and ciclosporin. All manifestations improved after 4 weeks of therapy, but treatment had to be stopped after the patient developed leucopenia.[1]

1. Frigerio E, *et al.* Severe psoriasis treated with a new macrolide: everolimus. *Br J Dermatol* 2007; **156:** 372–4.

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

1. Grube E, *et al.* Six- and twelve-month results from first human experience using everolimus-eluting stents with bioabsorbable polymer. *Circulation* 2004; **109:** 2168–71.
2. Grube E, Buellesfeld L. Everolimus for stent-based intracoronary applications. *Rev Cardiovasc Med* 2004; **5** (suppl): S3–S8.
3. Tsuchiya Y, *et al.* Effect of everolimus-eluting stents in different vessel sizes (from the pooled FUTURE I and II trials). *Am J Cardiol* 2006; **98:** 464–9.
4. Ormiston JA, *et al.* First-in-human implantation of a fully bioabsorbable drug-eluting stent: the BVS poly-L-lactic acid everolimus-eluting coronary stent. *Catheter Cardiovasc Interv* 2007; **69:** 128–31.
5. Beijk MA, Piek JJ. XIENCE V everolimus-eluting coronary stent system: a novel second generation drug-eluting stent. *Expert Rev Med Devices* 2007; **4:** 11–21.
6. Stone GW, *et al.* SPIRIT III Investigators. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. *JAMA* 2008; **299:** 1903–13.
7. Biondi-Zoccai G, *et al.* Percutaneous coronary intervention with everolimus-eluting stents (Xience V): systematic review and direct-indirect comparison meta-analyses with paclitaxel-eluting stents (Taxus) and sirolimus-eluting stents (Cypher). *Minerva Cardioangiol* 2008; **56:** 55–65.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Certican; ***Austral.:*** Certican; ***Austria:*** Certican; ***Belg.:*** Certican; ***Braz.:*** Certican; ***Chile:*** Certican; ***Cz.:*** Certican; ***Denm.:*** Certican; ***Fin.:*** Certican; ***Fr.:*** Certican; ***Ger.:*** Certican; ***Gr.:*** Certican; ***Hung.:*** Certican; ***Israel:*** Certican; ***Ital.:*** Certican; ***Mex.:*** Certican; ***Neth.:*** Certican; ***Norw.:*** Certican; ***Pol.:*** Certican; ***Port.:*** Certican; ***S.Afr.:*** Certican; ***Spain:*** Certican; ***Swed.:*** Certican; ***Switz.:*** Certican; ***Thai.:*** Certican; ***Venez.:*** Certican.

Gavilimomab *(rINN)*

Gavilimomabum. Immunoglobulin M, anti-(human antigen CD147)(mouse monoclonal ABX-CBL μ-chain), disulfide with mouse monoclonal ABX-CBL light chain, pentamer.

Гавилимомаб

CAS — 244096-20-6.

Profile

Gavilimomab is an anti-CD147 monoclonal antibody of murine origin that has been investigated for the treatment of acute graft-versus-host disease.

◊ References.

1. Deeg HJ, *et al.* Treatment of steroid-refractory acute graft-versus-host disease with anti-CD147 monoclonal antibody ABX-CBL. *Blood* 2001; **98:** 2052–8.
2. Macmillan ML, *et al.* A phase 2/3 multicenter randomized clinical trial of ABX-CBL versus ATG as secondary therapy for steroid-resistant acute graft-versus-host disease. *Blood* 2007; **109:** 2657–62.

Gusperimus Hydrochloride *(rINNM)*

BMS-181173; BMY-42215-1; Deoxyspergualin Hydrochloride; 15-Deoxyspergualin Hydrochloride; Guspérimus, Chlorhydrate de; Gusperimus Trihydrochloride *(USAN)*; Gusperimusi Hydrochloridum; Hidrocloruro de gusperimús; NKT-01; NSC-356894. (±)-*N*-[({4-[(3-Aminopropyl)amino]butyl}carbamoyl)hydroxymethyl]-7-guanidinoheptanamide trihydrochloride.

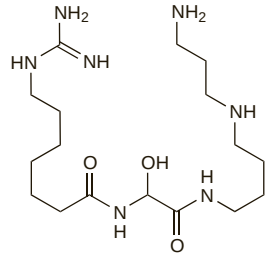
Гусперимуса Гидрохлорид

$C_{17}H_{37}N_7O_3,3HCl$ = 496.9.

CAS — 104317-84-2 (gusperimus); 89149-10-0 (gusperimus); 85468-01-5 (gusperimus hydrochloride).

ATC — L04AA19.

ATC Vet — QL04AA19.



(gusperimus)

Profile

Gusperimus is a guanidine derivative that inhibits both cell-mediated and antibody-mediated immunity. It is used in the treatment of renal graft rejection, and has been investigated in the management of graft-versus-host disease and Wegener's granulomatosis. For mention of its role in reversing acute graft rejection in kidney transplantation, see p.1813.

Gusperimus is used as the hydrochloride. A dose of 3 to 5 mg/kg of gusperimus hydrochloride given daily for 7 days, by intravenous infusion over 3 hours, has been suggested in the treatment of acute renal graft rejection. Treatment may be continued for a further 3 days if required.