Adverse effects reported with gusperimus include bone-marrow depression, numbness of face and extremities, headache, gastrointestinal disturbances, alterations in liver enzyme values, and facial flushing. Rapid injection should be avoided as an acute increase in plasma concentration may produce respiratory depression.

◊ References.


1. Ramos EL, *et al.* Deoxyspergualin: mechanism of action and pharmacokinetics. *Transplant Proc* 1996; **28:** 873–5.
2. Tanabe K, *et al.* Effect of deoxyspergualin on the long-term outcome of renal transplantation. *Transplant Proc* 2000; **32:** 1745–6.
3. Amada N, *et al.* Prophylactic use of deoxyspergualin improves long-term graft survival in living related renal transplant recipients transfused with donor-specific blood. *Transplant Proc* 2001; **33:** 2256–7.
4. Birck R, *et al.* 15-Deoxyspergualin in patients with refractory ANCA-associated systemic vasculitis: a six-month open-label trial to evaluate safety and efficacy. *J Am Soc Nephrol* 2003; **14:** 440–7.
5. Schmitt WH, *et al.* Prolonged treatment of refractory Wegener's granulomatosis with 15-deoxyspergualin: an open study in seven patients. *Nephrol Dial Transplant* 2005; **20:** 1083–92.
6. Amada N, *et al.* Deoxyspergualin prophylaxis with tacrolimus further improves long-term graft survival in living-related renal-transplant recipients transfused with donor-specific blood. *Transplant Proc* 2005; **37:** 927–9.
7. Nojima M, *et al.* Combined therapy of deoxyspergualin and plasmapheresis: a useful treatment for antibody-mediated acute rejection after kidney transplantation. *Transplant Proc* 2005; **37:** 930–3.
8. Kawagishi N, *et al.* Usage of deoxyspergualin on steroid-resistant acute rejection in living donor liver transplantation. *Tohoku J Exp Med* 2006; **208:** 225–33.


### Preparations

**Proprietary Preparations** (details are given in Part 3)
***Cz.:*** Spanidin; ***Jpn:*** Spanidin.

## Inolimomab *(rINN)*

BT-563; Inolimomabum. Immunoglobulin G1, anti-(human interleukin 2 receptor α-chain) (mouse monoclonal B-B10 γ1-chain), disulfide with mouse monoclonal B-B10 κ-chain, dimer.

Инолимомаб

*CAS — 152981-31-2.*

### Profile

Inolimomab is a murine/human monoclonal antibody similar to daclizumab (p.1833) that acts as an interleukin-2 receptor antagonist at the alpha chain (CD25) of the interleukin-2 receptor on the surface of activated T-lymphocytes. It is under investigation for the treatment of graft-versus-host disease after organ transplantation (p.1810).

◊ References.


1. Winkler M. Inolimomab (OPi). *Curr Opin Investig Drugs* 2002; **3:** 1464–7.
2. Wabbijn M, *et al.* Ten-year follow-up of recipients of a kidney or heart transplant who received induction therapy with a monoclonal antibody against the interleukin-2 receptor. *Exp Clin Transplant* 2004; **2:** 201–7.
3. Bay JO, *et al.* Inolimomab in steroid-refractory acute graft-versus-host disease following allogeneic hematopoietic stem cell transplantation: retrospective analysis and comparison with other interleukin-2 receptor antibodies. *Transplantation* 2005; **80:** 782–8.

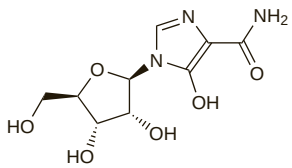

## Mizoribine *(rINN)*

HE-69; Mizoribina; Mizoribinum. 5-Hydroxy-1-β-D-ribofuranosylimidazole-4-carboxamide.

Мизорибин

$C_9H_{13}N_3O_6$ = 259.2.

*CAS — 50924-49-7.*




### Profile

Mizoribine is an oral immunosuppressant that is used for the management of rejection in kidney transplantation, for nephrotic syndrome associated with primary glomerular disease, for lupus nephritis, and for rheumatoid arthritis.

Adverse effects include myelosuppression, hyperuricaemia, gastrointestinal disturbances, and hypersensitivity reactions. Stevens-Johnson syndrome has also been reported.

◊ Although oral doses of mizoribine of 1 to 3 mg/kg daily have been recommended in renal transplantation, higher doses (above 5 mg/kg daily) have been widely used. Similarly, an oral dose of 50 mg three times daily has been recommended for patients with nephrotic syndrome associated with primary glomerular disease or lupus nephritis, and in rheumatoid arthritis, but high-dose regimens have been investigated.

Further references.


1. Tanabe K, *et al.* Long-term results in mizoribine-treated renal transplant recipients: a prospective, randomized trial of mizoribine and azathioprine under cyclosporine-based immunosuppression. *Transplant Proc* 1999; **31:** 2877–9.
2. Yoshioka K, *et al.* A multicenter trial of mizoribine compared with placebo in children with frequently relapsing nephrotic syndrome. *Kidney Int* 2000; **58:** 317–24.
3. Yokota S. Mizoribine: mode of action and effects in clinical use. *Pediatr Int* 2002; **44:** 196–8.
4. Takei S. Mizoribine in the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. *Pediatr Int* 2002; **44:** 205–9.
5. Honda M. Nephrotic syndrome and mizoribine in children. *Pediatr Int* 2002; **44:** 210–6.
6. Nagaoka R, *et al.* Mizoribine treatment for childhood IgA nephropathy. *Pediatr Int* 2002; **44:** 217–23.
7. Tsuzuki K. Role of mizoribine in renal transplantation. *Pediatr Int* 2002; **44:** 224–31.
8. Shibasaki T, *et al.* A randomized open-label comparative study of conventional therapy versus mizoribine onlay therapy in patients with steroid-resistant nephrotic syndrome (postmarketing survey). *Clin Exp Nephrol* 2004; **8:** 117–26.
9. Akiyama T, *et al.* Mizoribine in combination therapy with tacrolimus for living donor renal transplantation: analysis of a nationwide study in Japan. *Transplant Proc* 2005; **37:** 843–5.
10. Tanaka H, *et al.* Long-term mizoribine intermittent pulse therapy for young patients with flare of lupus nephritis. *Pediatr Nephrol* 2006; **21:** 962–6.
11. Tanaka E, *et al.* Acceptability and usefulness of mizoribine in the management of rheumatoid arthritis in methotrexate-refractory patients and elderly patients, based on analysis of data from a large-scale observational cohort study. *Mod Rheumatol* 2006; **16:** 214–19.
12. Sugitani A, *et al.* Revival of effective and safe high-dose mizoribine for the kidney transplantation. *Clin Transplant* 2006; **20:** 590–5.
13. Kawasaki Y, *et al.* Efficacy of single dose of oral mizoribine pulse therapy two times per week for frequently relapsing nephrotic syndrome. *J Nephrol* 2007; **20:** 52–6.


### Preparations

**Proprietary Preparations** (details are given in Part 3)
***Jpn:*** Bredinin.

# Muromonab-CD3 *(USAN, rINN)*

Muromonabum-CD3; OKT3.

Муромонаб-CD3

*ATC — L04AA02.*

*ATC Vet — QL04AA02.*

**Description.** A murine monoclonal antibody comprising a purified $IgG_{2a}$ immunoglobulin with a heavy chain having a molecular weight of about 50 000 daltons and a light chain with a molecular weight of about 25 000 daltons.

**Pharmacopoeias.** In *Chin.*

### Adverse Effects, Treatment, and Precautions

An acute cytokine release syndrome occurs in most patients, typically 30 to 60 minutes after the first few doses of muromonab-CD3 (although it may occur later). Frequency and severity tend to decrease with successive doses, while prophylactic corticosteroids may reduce initial adverse reactions (see Uses and Administration, below). The syndrome ranges from a more frequently reported, mild, self-limiting, flu-like illness to a less common, severe, and life-threatening, shock-like reaction, which may include serious cardiovascular and CNS manifestations. Typical clinical manifestations of the cytokine release syndrome include high fever, chills or rigors, headache, tremor, gastrointestinal disturbances, myalgia, and generalised weakness. Rash and pruritus may also occur. Cardiorespiratory findings may include apnoea, dyspnoea, bronchospasm or wheezing, tachypnoea, respiratory arrest or failure, acute respiratory distress syndrome, angina, myocardial infarction, chest pain or tightness, tachycardia, hypertension, hypotension, cardiac failure, pulmonary oedema, hypoxaemia, and arrhythmias. Reversible impairment of renal function may also be associated with the syndrome.

Other reported effects of muromonab-CD3 include encephalopathy, cerebral oedema, and a syndrome resembling aseptic meningitis, with headache, fever, stiff neck, and photophobia; seizures have also occurred. Hypersensitivity reactions, including fatal anaphylaxis, have been reported and may be difficult to distinguish from the cytokine release syndrome.

As with other potent immunosuppressants, treatment with muromonab-CD3 may increase the risk of serious infections and the development of certain malignancies. 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.

Muromonab-CD3 should not be given to patients with uncontrolled hypertension, or in patients hypersensitive to products of murine origin. It should be avoided in patients with a history of seizures. Because fluid overload is associated with an increased risk of pulmonary oedema due to the cytokine release syndrome, muromonab-CD3 is contra-indicated in patients who have undergone a more than 3% weight gain in the week preceding therapy, or who have radiographic evidence of fluid overloading. Repeated courses of muromonab-CD3 may be less effective because of the development of antibodies to the drug. Paediatric patients may be at increased risk of serious adverse effects following muromonab-CD3 therapy.

**Effects on the blood.** ***THROMBOEMBOLISM.*** Intragraft thromboses developed in 9 of 93 consecutive kidney transplant recipients given high-dose muromonab-CD3 (10 mg daily) as part of their immunosuppressive regimen.[1] In one patient the thrombosis was in the renal artery, and in 3 in the renal vein; the remainder had thromboses in the glomerular capillaries and thrombotic microangiopathy similar to that of haemolytic-uraemic syndrome. The authors suggested that muromonab-CD3 has procoagulant effects, perhaps mediated by released tumour necrosis factor; these effects had also been seen in 3 patients receiving muromonab-CD3 at conventional doses (5 mg daily). Another group[2] has also reported an apparently increased incidence of acute vascular thrombosis in patients given muromonab-CD3 at conventional doses, but in the experience of others,[3] despite evidence of activation of coagulation by the drug, treatment of acute rejection with 5 mg daily was not associated with thromboembolic complications. US licensed product information states that the relationship to dose remains unclear, but that the relative risk appears to be greater with doses above the recommended dose.


1. Abramowicz D, *et al.* Induction of thromboses within renal grafts by high-dose prophylactic OKT3. *Lancet* 1992; **339:** 777–8.
2. Gomez E, *et al.* Main graft vessels thromboses due to conventional-dose OKT3 in renal transplantation. *Lancet* 1992; **339:** 1612–13.
3. Raasveld MHM, *et al.* Thromboembolic complications and dose of monoclonal OKT3 antibody. *Lancet* 1992; **339:** 1363–4.


**Effects on the ears.** Bilateral sensorineural hearing loss has occurred after muromonab-CD3 therapy. In one case series, 5 out of 7 patients were affected, showing a mean hearing loss of 18 decibels.[1] Tinnitus may also occur.[1,2] Although symptoms are generally reversible,[1,2] one patient still showed a deficit in hearing after 6 months.[3]


1. Hartnick CJ, *et al.* Reversible sensorineural hearing loss following administration of muromonab-CD3 (OKT3) for cadaveric renal transplant immunosuppression. *Ann Otol Rhinol Laryngol* 2000; **109:** 45–7.
2. Hartnick CJ, *et al.* Reversible sensorineural hearing loss after renal transplant immunosuppression with OKT3 (muromonab-CD3). *Ann Otol Rhinol Laryngol* 1997; **106:** 640–2.
3. Michals M, *et al.* Hearing loss associated with muromonab-CD3 therapy. *Clin Pharm* 1988; **7:** 867–8.


**Effects on the nervous system.** Generalised seizures were reported in 2 uraemic kidney-graft recipients given muromonab-CD3.[1] Delayed graft function may result in the accumulation of uraemic toxins which combine with cytokines released by the immunosuppressant to produce the effects on the CNS. Seizures and encephalopathy were reported in siblings given muromonab-CD3 after renal transplantation, and appeared to predispose one of them to develop ciclosporin neurotoxicity.[2] A neurological syndrome characterised by akinetic mutism, blepharospasm, anomic aphasia, and delirium, occurred in a heart transplant patient given muromonab-CD3; symptoms resolved after stopping therapy.[3]

The manufacturers have warned that children treated with muromonab-CD3 may be at increased risk of nervous system complications, notably cerebral oedema that may result in fatal cerebral herniation. Since 1986, and as of May 2004, 9 cases of cerebral oedema had been reported worldwide in children, resulting in 6 deaths. Cerebral herniation had occurred within a few hours to 1 day after injection. Signs include the sudden appearance of severe headache, seizures, impaired mental function, drowsiness and lethargy, and coma.[4]


1. Seifeldin RA, *et al.* Generalized seizures associated with the use of muromonab-CD3 in two patients after kidney transplantation. *Ann Pharmacother* 1997; **31:** 586–9.

2. Thaisetthawatkul P, *et al*. Muromonab-CD3-induced neurotoxicity: report of two siblings, one of whom had subsequent cyclosporin-induced neurotoxicity. *J Child Neurol* 2001; **16:** 825–31.
3. Pittock SJ, *et al*. OKT3 neurotoxicity presenting as akinetic mutism. *Transplantation* 2003; **75:** 1058–60.
4. Janssen-Ortho, Canada. Important new safety information on Orthoclone OKT*3 (muromonab-CD3) (issued 17 May 2004). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/orthoclone_okt3_pa-ap-eng.pdf (accessed 18/02/08)

### Pharmacokinetics

**Therapeutic drug monitoring.** US licensed product information states that serum concentrations of muromonab-CD3 are measurable using an enzyme-linked immunosorbent assay (ELISA). Studies in organ transplant recipients found that patients less than 10 years of age had higher concentrations than patients aged 10 to 50 years. Subsequent clinical experience has shown that serum concentrations of muromonab-CD3 greater than or equal to 800 nanograms/mL block the function of T-cells. Reduced T-cell clearance or low plasma concentrations of muromonab-CD3 provide a basis for adjusting muromonab dosage or stopping therapy.

In adults, periodic monitoring to ensure plasma muromonab-CD3 concentrations of 800 nanograms/mL or greater, or CD3-positive cells less than 25 cells/mm$^3$ is recommended. Paediatric patients are known to have higher CD3 lymphocyte counts than adults, and often require increased doses of muromonab-CD3 to achieve similar depletion of CD3-positive cells and therapeutic serum concentrations; both T-cell clearance and plasma muromonab-CD3 should be monitored daily in children.

### Uses and Administration

Muromonab-CD3 is a murine monoclonal antibody to the T3 (CD3) antigen of human T-lymphocytes, which is essential to antigen recognition and response; the antibody thus specifically blocks T-cell generation and function, to exert an immunosuppressant effect without affecting the bone marrow.

It is used in the treatment of acute allograft rejection in organ transplant recipients, in doses of 5 mg daily by intravenous injection for 10 to 14 days. For children's doses, see Administration in Children, below. The dose of any other immunosuppressant therapy may need to be reduced. Patients should be monitored closely after the first few doses of muromonab-CD3 because of the risk of cytokine release syndrome and hypersensitivity reactions. The first dose may be preceded by intravenous methylprednisolone sodium succinate, in a dose of 8 mg/kg, 1 to 4 hours before muromonab-CD3. Paracetamol and antihistamines may also be given with muromonab-CD3 to reduce early reactions.

Muromonab-CD3 has also been given experimentally as part of regimens for the prophylaxis of graft rejection. For further details of the use of muromonab-CD3 in the treatment and prophylaxis of graft rejection see Organ and Tissue Transplantation, p.1810, *et seq*.

◊ References.

1. ten Berge IJM, *et al*. Guidelines for optimal use of muromonab CD3 in transplantation. *BioDrugs* 1999; **11:** 277–84.
2. Flechner SM. A randomized prospective trial of low-dose OKT3 induction therapy to prevent rejection and minimize side effects in recipients of kidney transplants. *Transplantation* 2000; **69:** 2374–81.
3. Henry ML, *et al*. A randomized prospective trial of OKT3 induction in the current immunosuppression era. *Clin Transplant* 2001; **15:** 410–14.
4. Benfield MR, *et al*. A randomized multicenter trial of OKT3 mAbs induction compared with intravenous cyclosporine in pediatric renal transplantation. *Pediatr Transplant* 2005; **9:** 282–92.
5. Knop S, *et al*. OKT3 muromonab as second-line and subsequent treatment in recipients of stem cell allografts with steroid-resistant acute graft-versus-host disease. *Bone Marrow Transplant* 2005; **36:** 831–7.
6. Sevmis S, *et al*. OKT3 treatment for steroid-resistant acute rejection in kidney transplantation. *Transplant Proc* 2005; **37:** 3016–18.
7. Wilmot I, *et al*. OKT3 treatment in refractory pediatric heart transplant rejection. *J Heart Lung Transplant* 2005; **24:** 1793–7.

**Administration in children.** The initial recommended doses in children given muromonab-CD3 for acute allograft rejection are as follows:

- those weighing 30 kg or less: 2.5 mg daily
- those weighing more than 30 kg: 5 mg daily

Doses are given by intravenous injection for 10 to 14 days.

Paediatric patients are known to have higher CD3 lymphocyte counts than adults, and often require doses to be titrated upwards. The initial dose may be subsequently adjusted in 2.5 mg increments to achieve T-cell clearance (CD3-positive cells less than 25 cells/mm$^3$) and ensure therapeutic serum concentrations of muromonab-CD3 (of 800 nanograms/mL or greater, see Therapeutic Drug Monitoring, above).

### Preparations

**Proprietary Preparations** (details are given in Part 3)
***Austral.:*** Orthoclone OKT3; ***Belg.:*** Orthoclone OKT3; ***Braz.:*** Orthoclone OKT3; ***Canad.:*** Orthoclone OKT3; ***Chile:*** Ior T3†; ***Cz.:*** Cedetrin-T†; Orthoclone OKT3†; ***Fin.:*** Orthoclone OKT3; ***Fr.:*** Orthoclone OKT3; ***Ger.:*** Orthoclone OKT3; ***Gr.:*** Orthoclone; ***Hong Kong:*** Orthoclone OKT3†; ***Israel:*** Orthoclone OKT3; ***Ital.:*** Orthoclone OKT3; ***Malaysia:*** Orthoclone OKT3†; ***Mex.:*** Ior-T3; Orthoclone OKT3; ***Neth.:*** Orthoclone OKT3; ***Norw.:*** Orthoclone OKT3; ***NZ:*** Orthoclone OKT3; ***S.Afr.:*** Orthoclone; ***Swed.:*** Orthoclone OKT3; ***Switz.:*** Orthoclone OKT3; ***Thai.:*** Orthoclone OKT3†; ***Turk.:*** Orthoclone OKT3; ***USA:*** Orthoclone OKT3.

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## Mycophenolate

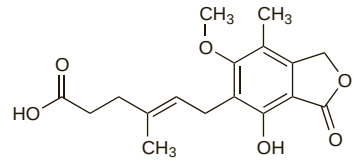
*ATC — L04AA06.*
*ATC Vet — QL04AA06.*

### Mycophenolic Acid *(BAN, USAN, rINN)*

Acide Mycophénolique; Ácido micofenólico; Acidum Mycophenolicum; Lilly-68618; MPA; NSC-129185. (*E*)-6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-5-phthalanyl)-4-methyl-4-hexenoic acid.

Микофеноловая Кислота

$C_{17}H_{20}O_6$ = 320.3.
*CAS — 24280-93-1.*
*ATC — L04AA06.*
*ATC Vet — QL04AA06.*



### Mycophenolate Mofetil *(BANM, USAN, rINNM)*

Micofenolato de mofetilo; Mikofenolat Mofetil; Mikofenolato mofetilis; Mofetilis Mycophenolas; Mofetil-mykofenolát; Mycophenolas Mofetil; Mycophenolas Mofetilum; Mycophenolasmofetil; Mycophénolate mofétil; Mycophénolate, Mofétil de; Mycophenolate Morpholinoethyl; Mykofenolaattimofetiili; Mykofenolatmofetil; RS-61443. 2-Morpholinoethyl (*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-5-phthalanyl)-4-methyl-4-hexenoate.

Микофеноловая Мофетил

$C_{23}H_{31}NO_7$ = 433.5.
*CAS — 115007-34-6.*
*ATC — L04AA06.*
*ATC Vet — QL04AA06.*

**Pharmacopoeias.** In *Eur.* (see p.vii) and *US*.
**Ph. Eur. 6.2** (Mycophenolate Mofetil). A white or almost white, crystalline powder. M.p. about 96°. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in acetone. Protect from light.
**USP 31** (Mycophenolate Mofetil). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol; soluble in methyl alcohol; freely soluble in acetone. Store in airtight containers.

### Mycophenolate Mofetil Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro del micofenolato de mofetilo; Mycophénolate, Mofétil Chlorhydrate de; Mycophenolati Mofetili Hydrochloridum; RS-61443-190. 2-Morpholinoethyl (*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-5-phthalanyl)-4-methyl-4-hexenoate hydrochloride.

Микофеноловой Мофетила Гидрохлорид

$C_{23}H_{31}NO_7$,HCl = 470.0.
*CAS — 116680-01-4.*
*ATC — L04AA06.*
*ATC Vet — QL04AA06.*

**Incompatibility.** Solutions of mycophenolate mofetil hydrochloride were found to be physically compatible and chemically stable with solutions containing clinically relevant concentrations of cefepime, dopamine, noradrenaline, tacrolimus, and vancomycin, for up to 4 hours of simulated Y-site administration. However, combining ciclosporin and mycophenolate resulted in effervescence and chemical instability.[1]

1. Cochran BG, *et al*. Physical compatibility and chemical stability of mycophenolate mofetil during simulated Y-site administration with commonly coadministered drugs. *Am J Health-Syst Pharm* 2007; **64:** 1410–14.

**Stability.** UK and US licensed product information states that, after reconstitution of *mycophenolate mofetil oral suspension*, it may be stored at room temperature (15° to 30°) or in a refrigerator (2° to 8°) for up to 60 days; it should not be frozen.

UK licensed product information for *mycophenolate mofetil hydrochloride solution for infusion* states that the infusion should be started within 3 hours of reconstitution and dilution; solutions may be kept at room temperature (15° to 30°). A study found that solutions of mycophenolate mofetil hydrochloride in concentrations equivalent to mycophenolate mofetil 1, 5, or 10 mg/mL were stable for 7 days when stored at 4° or 25° in PVC infusion bags.[1] However, it was noted that a progressive discoloration occurred in bags unprotected from light and stored at 25°; further study was required to determine the source of the discoloration.

1. Certain E, *et al*. Stability of i.v. mycophenolate mofetil in 5% dextrose injection in polyvinyl chloride infusion bags. *Am J Health-Syst Pharm* 2002; **59:** 2434–9.

### Mycophenolate Sodium *(BANM, USAN, rINNM)*

ERL-080; Micofenolato sódico; Mycophénolate de Sodium; Natrii Mycophenolas. Sodium 4(*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate.

Натрий Микофеноловая

$C_{17}H_{19}NaO_6$ = 342.3.
*CAS — 37415-62-6.*
*ATC — L04AA06.*
*ATC Vet — QL04AA06.*

### Adverse Effects, Treatment, and Precautions

Mycophenolate is associated with gastrointestinal disturbances, particularly diarrhoea and vomiting; gastrointestinal haemorrhage and perforation have occurred. Leucopenia may develop; as with other immunosuppressants there is an increased risk of infection and certain malignancies in patients receiving mycophenolate mofetil (see below). To minimise any risk of skin cancer, exposure to sunlight or ultraviolet light should be limited. Thrombocytopenia and anaemia are also common; there have been reports of aplastic anaemia and bone-marrow depression, sometimes fatal. Regular full blood counts are recommended during therapy, and treatment may need to be stopped if severe neutropenia develops. Other reported adverse effects include asthenia, fever, pain, headache, renal impairment, hypertension or hypotension, hyperglycaemia, disturbances of electrolytes and blood lipids, peripheral oedema, pleural effusion, dyspnoea, cough, acne, rash, alopecia, dizziness, insomnia or somnolence, paraesthesia, and tremor. Agitation, depression, anxiety, tachycardia, and arthralgia are also common. Abnormal hepatic function tests have also been reported. Hypersensitivity reactions, including angioedema and anaphylaxis, have occurred. Pancreatitis and hepatitis have been reported. There are rare reports of interstitial lung disorders, including fatal pulmonary fibrosis. Other less common adverse effects include renal tubular necrosis, haematuria, conjunctivitis, blurred vision, and impotence. Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have also been reported. Mycophenolate is teratogenic in *animals*; malformations, especially of the external ear, and other facial abnormalities, have been reported in infants after maternal exposure to mycophenolate (see below).

Mycophenolate should be given with care to patients with severe renal impairment or active disorders of the gastrointestinal tract. Intra-uterine devices should be used with caution in those given immunosuppressive treatment as there is an increased risk of infection. Live vaccines should be avoided in these patients for the same reason.

Mycophenolate mofetil and mycophenolate sodium should not be indiscriminately interchanged or substituted because of their differing pharmacokinetic profiles.

**Effects on the gastrointestinal tract.** The adverse effects of mycophenolate mofetil on the gastrointestinal tract appeared to be mostly of an irritative nature and included diarrhoea, abdominal pain, nausea and vomiting, anorexia, dyspepsia, and occasionally gastrointestinal haemorrhage or perforation.[1] Paediatric