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.

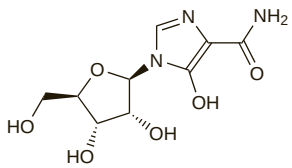
Mizoribine *(rINN)*

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.