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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.

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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.

Mycophenolate

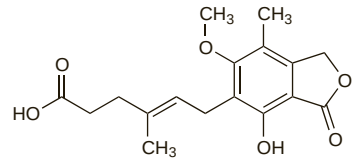
ATC — L04AA06.
ATC Vet — QL04AA06.

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