costeroid treatment for polymyalgia rheumatica (p.1510) and in whom withdrawal is difficult.

Psoriatic arthritis. Azathioprine may be useful for severe or progressive cases of psoriatic arthritis (see under Spondyloarthropathies, p.13) when the arthritis is not controlled by physical therapy and NSAIDs.

Rheumatoid arthritis. Although azathioprine may be beneficial in rheumatoid arthritis (p.11) in the short-term, its toxicity is significantly more severe than other disease-modifying antirheumatic drugs (DMARDs).[1] It may, however, be useful in patients with severe disease unresponsive to other DMARDs especially in those with extra-articular manifestations such as vasculitis.[2]

1. Suarez-Almazor ME, *et al.* Azathioprine for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 15/01/08).
2. Heurkens AHM, *et al.* Prednisone plus azathioprine treatment in patients with rheumatoid arthritis complicated by vasculitis. *Arch Intern Med* 1991; **151:** 2249–54.

Sarcoidosis. Cytotoxic immunosuppressants such as azathioprine have been tried in patients with sarcoidosis (p.1512) who do not respond to or cannot tolerate corticosteroids.

Skin disorders. Like other immunosuppressants, azathioprine has been tried in various refractory skin disorders, notably in pemphigus and pemphigoid[1,2] (see below). Other conditions in which it has been tried include atopic eczema,[3-8] nodular prurigo,[9] chronic actinic dermatitis,[3,6] pyoderma gangrenosum,[4] erythema multiforme,[4,10] pompholyx, and plaque psoriasis,[6] as well as in the skin manifestations of systemic disorders such as dermatomyositis and lupus erythematosus.[2] Guidelines for the use of azathioprine in dermatology have been developed.[1] The recommended dose for azathioprine in dermatological disorders is 1 to 3 mg/kg daily, adjusted according to response. Treatment should be withdrawn if no response is seen within 3 months. Azathioprine should not be used in dermatology patients with very low or absent thiopurine methyltransferase (TPMT) activity (see Therapeutic Drug Monitoring, above), due to the danger of prolonged and severe myelosuppression (see Effects on the Blood, above). If azathioprine is given to patients with low TPMT activity, doses of 0.5 to 1 mg/kg daily should be used, with monitoring for myelosuppression. Patients with normal to high TPMT activity should be started on doses at the higher end of the range of 1 to 3 mg/kg daily; in those who do not respond, and have not experienced adverse effects, doses above this range may be considered for a trial period.

1. Anstey AV, *et al.* British Association of Dermatologists Therapy, Guidelines and Audit Subcommittee. Guidelines for prescribing azathioprine in dermatology. *Br J Dermatol* 2004; **151:** 1123–32. Also available at: http://www.bad.org.uk/healthcare/guidelines/Azathioprine.pdf (accessed 15/01/08)
2. Patel AA, *et al.* Azathioprine in dermatology: the past, the present, and the future. *J Am Acad Dermatol* 2006; **55:** 369–89.
3. Younger IR, *et al.* Azathioprine in dermatology. *J Am Acad Dermatol* 1991; **25:** 281–6.
4. Tan BB, *et al.* Azathioprine in dermatology: a survey of current practice in the UK. *Br J Dermatol* 1997; **136:** 351–5.
5. Lear JT, *et al.* A retrospective review of the use of azathioprine in severe atopic dermatitis. *Br J Dermatol* 1996; **135** (suppl 47): 38.
6. Scerri L. Azathioprine in dermatological practice: an overview with special emphasis on its use in non-bullous inflammatory dermatoses. *Adv Exp Med Biol* 1999; **455:** 343–8.
7. Murphy L-A, Atherton D. A retrospective evaluation of azathioprine in severe childhood atopic eczema, using thiopurine methyltransferase levels to exclude patients at high risk of myelosuppression. *Br J Dermatol* 2002; **147:** 308–15.
8. Meggitt SJ, *et al.* Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. *Lancet* 2006; **367:** 839–46.
9. Lear JT, *et al.* Nodular prurigo responsive to azathioprine. *Br J Dermatol* 1996; **134:** 1151.
10. Schofield JK, *et al.* Recurrent erythema multiforme: clinical features and treatment in a large series of patients. *Br J Dermatol* 1993; **128:** 542–5.

PEMPHIGUS AND PEMPHIGOID. Corticosteroids are the main treatment for blistering in pemphigus and pemphigoid (p.1582). Other immunosuppressants may be added to maintain disease control and allow a reduction in corticosteroid dosage, and azathioprine is commonly used in this way in pemphigus vulgaris.[1] There is limited evidence to suggest that azathioprine may also be effective as monotherapy to induce remission in mild pemphigus.[1] Azathioprine has been used similarly in bullous pemphigoid, but there is some disagreement about its efficacy,[2] and guidelines suggest that it should only be considered if the corticosteroid cannot be reduced to an acceptable dose.[3]

1. Harman KE, *et al.* British Association of Dermatologists. Guidelines for the management of pemphigus vulgaris. *Br J Dermatol* 2003; **149:** 926–37. Also available at: http://www.bad.org.uk/healthcare/guidelines/Pemphigus_Vulgaris.pdf (accessed 15/01/08)
2. Walsh SRA, *et al.* Bullous pemphigoid: from bench to bedside. *Drugs* 2005; **65:** 905–26.
3. Wojnarowska F, *et al.* British Association of Dermatologists. Guidelines for the management of bullous pemphigoid. *Br J Dermatol* 2002; **147:** 214–21. Also available at: http://www.bad.org.uk/healthcare/guidelines/Bullous_Pemphigoid.pdf (accessed 15/01/08)

Vasculitic syndromes. Azathioprine has been tried in vasculitic syndromes, including giant cell arteritis (p.1503), microscopic polyangiitis (p.1510), Churg-Strauss syndrome (p.1501), Takayasu's arteritis (p.1514), and Wegener's granulomatosis (p.1515). In general it is most useful in maintenance for its corticosteroid-sparing effect. Cyclophosphamide tends to be preferred where a more aggressive regimen is required, as in some combinations for induction of remission.

Preparations

BP 2008: Azathioprine Tablets;
USP 31: Azathioprine Oral Suspension; Azathioprine Sodium for Injection; Azathioprine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Imuran; ***Austral.:*** Azahexal; Azamun; Azapin; Imuran; Thioprine; ***Austria:*** Azaallen; Azaglax; Azarek†; Glaxoprin; Imurek; ***Belg.:*** Imuran; ***Braz.:*** Aseroprin†; Imunen; Imuran; ***Canad.:*** Imuran; ***Chile:*** Azafalk†; Imuran; ***Cz.:*** Azaprine; Immunoprin; Imuran; ***Denm.:*** Imurel; ***Fin.:*** Azamun; Imuprin†; Imurel; ***Fr.:*** Imurel; ***Ger.:*** Aza-Q; Azafalk; Azathiodura; Colinsan; Imurek; Zytrim; ***Gr.:*** Imuran†; ***Hong Kong:*** Azamun†; Imuran; ***Hung.:*** Imuran; ***India:*** Azoran; Imuran; Transimune; ***Indon.:*** Imuran; ***Irl.:*** Imuger; Imuran; ***Israel:*** Azopi; Imuran; ***Malaysia:*** Imuran; ***Mex.:*** Azatrilem; Imuran; Satedon†; ***Neth.:*** Imuran; ***Norw.:*** Imurel; ***NZ:*** Azamun; Imuran; Thioprine; ***Philipp.:*** Imuran; ***Pol.:*** Imuran; ***Port.:*** Imuran; ***Rus.:*** Imuran (Имуран)†; ***S.Afr.:*** Azamun; Azapress; Imuran; Zaprine; ***Singapore:*** Imuran; ***Spain:*** Imurel; ***Swed.:*** Imurel; ***Switz.:*** Azarek; Imurek; ***Thai.:*** Imuran; ***Turk.:*** Imuran; ***UK:*** Immunoprin†; Imuran; ***USA:*** Azasan; Imuran; ***Venez.:*** Azaprin.

Multi-ingredient: ***Ger.:*** Azamedac.

Basiliximab *(BAN, USAN, rINN)*

Basiliksimab; Basiliksimabi; Basiliximabum; chRFT5; SDZ-CHI-621. Immunoglobulin G1, anti-(human interleukin 2 receptor) (human-mouse monoclonal CHI621 γ1-chain), disulfide with human-mouse monoclonal CHI621 light chain, dimer.

Базиликсимаб
CAS — 179045-86-4.
ATC — L04AC02.
ATC Vet — QL04AC02.

Adverse Effects and Precautions

Severe acute hypersensitivity reactions have occurred rarely with basiliximab. These have included anaphylactoid-type reactions such as rash, urticaria, pruritus, sneezing, hypotension, tachycardia, cardiac failure, wheezing, dyspnoea, bronchospasm, pulmonary oedema, and respiratory failure. Capillary leak syndrome and cytokine release syndrome have been reported. Reactions have been seen both on initial exposure and with subsequent therapy. Patients in whom other immunosuppression was prematurely stopped, after initial therapy with basiliximab, appear to be at increased risk of hypersensitivity reactions. Therapy should be permanently stopped if a severe reaction occurs.

Giving basiliximab as a bolus may cause nausea, vomiting, and local reactions, including pain.

Pharmacokinetics

Basiliximab has a terminal half-life of about 7 days in adults and about 9 days in children.

Uses and Administration

Basiliximab is a chimeric murine/human monoclonal antibody similar to daclizumab (p.1833) that functions as an interleukin-2 receptor antagonist by binding to the alpha chain (CD25 antigen) of the interleukin-2 receptor on the surface of activated T-lymphocytes. It is used in the prevention of acute graft rejection episodes in patients undergoing renal transplantation, and is given as part of an immunosuppressive regimen that includes ciclosporin and corticosteroids; azathioprine or mycophenolate mofetil may also be added to the regimen. Doses are given either as an intravenous bolus, or diluted to a usual concentration of 400 micrograms/mL in sodium chloride 0.9% or glucose 5%, for infusion over 20 to 30 minutes. The recommended dose for adults is 20 mg, given within 2 hours before transplant surgery and repeated once after 4 days. (For children's doses, see Administration in Children, below). The second dose should be withheld if graft loss or a severe hypersensitivity reaction occurs.

Administration in children. Licensed product information recommends the following intravenous doses of basiliximab in children over 1 year of age, for prophylaxis of acute rejection in allogeneic renal transplantation, as part of an immunosuppressive regimen containing ciclosporin and corticosteroids:

- body-weight under 35 kg: 10 mg within 2 hours before transplantation surgery; 10 mg 4 days after surgery
- body-weight 35 kg or more: 20 mg within 2 hours before transplantation surgery; 20 mg 4 days after surgery (same as adults, see Uses and Administration, above)

Doses may be given either as an intravenous bolus, or diluted to a usual concentration of 400 micrograms/mL in sodium chloride 0.9% or glucose 5%, for infusion over 20 to 30 minutes.

Organ and tissue transplantation. Basiliximab is used as induction therapy to reduce the incidence of acute rejection episodes after kidney transplantation (p.1813), including paediatric renal transplant recipients;[1-6] it is usually given as part of an immunosuppressive regimen that includes ciclosporin and corticosteroids. A small study found that basiliximab significantly reduced the occurrence of rejection episodes in those treated with dual therapy (calcineurin inhibitor and corticosteroids) but not in those given triple therapy (including mycophenolate).[7] In a study of paediatric renal transplant recipients, addition of basiliximab to a tacrolimus-based regimen was safe, but did not result in a lower incidence of rejection episodes.[8] There is some suggestion that antilymphocyte immunoglobulins may be more effective than basiliximab in reduction of acute rejection in adult renal transplant patients,[9,10] although some consider basiliximab to offer improved clinical efficacy over antilymphocyte immunoglobulin induction in paediatric patients,[11] and others have commented[12] that graft survival at 12 months has been similar with each drug. Two reviews[13,14] concluded that the use of basiliximab in renal transplantation was safe and effective, with reduced rates of acute rejection, but no long-term benefit in terms of graft survival; basiliximab appears to allow the safe withdrawal of corticosteroids or the use of corticosteroid-free immunosuppressive regimens.

There is a short report suggesting that the use of a single dose is as effective as the standard 2-dose regimen in renal transplantation in terms of the incidence of acute rejection.[15]

Basiliximab has also been investigated in liver transplantation (p.1815). Given with dual therapy to adult patients, it was found to reduce the incidence of acute rejection episodes in the first year when compared with placebo, including patients positive for hepatitis C.[16] Basiliximab with dual therapy also reduced the incidence of acute graft rejection in small paediatric studies.[17,18] In paediatric liver transplantation, corticosteroid-free immunosuppressive regimens using basiliximab and tacrolimus have been associated with significantly lower rejection rates at 1 year than corticosteroid-based regimens.[19,20]

Basiliximab has been investigated for the prevention of rejection in heart,[21,22] lung,[23,24] and pancreatic transplantation (see p.1812). It has been reported to be effective[25] in the treatment of corticosteroid-refractory acute graft-versus-host disease (GVHD; see Haematopoietic Stem Cell Transplantation, p.1811).

1. Nashan B, *et al.* Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. *Lancet* 1997; **350:** 1193–8. Correction. *ibid.*; 1484.
2. Kahan BD, *et al.* Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody. *Transplantation* 1999; **67:** 276–84.
3. Thistlethwaite JR, *et al.* Reduced acute rejection and superior 1-year renal allograft survival with basiliximab in patients with diabetes mellitus. *Transplantation* 2000; **70:** 784–90.
4. Ponticelli C, *et al.* A randomized, double-blind trial of basiliximab immunoprophylaxis plus triple therapy in kidney transplant recipients. *Transplantation* 2001; **72:** 1261–7.
5. Swiatecka-Urban A, *et al.* Basiliximab induction improves the outcome of renal transplants in children and adolescents. *Pediatr Nephrol* 2001; **16:** 693–6.
6. Pape L, *et al.* Single centre experience with basiliximab in paediatric renal transplantation. *Nephrol Dial Transplant* 2002; **17:** 276–80.
7. Lee BM, *et al.* Effect of basiliximab on renal allograft rejection within 1 year after transplantation. *Transplant Proc* 2006; **38:** 2025–8.
8. Grenda R, *et al.* A prospective, randomized, multicenter trial of tacrolimus-based therapy with or without basiliximab in pediatric renal transplantation. *Am J Transplant* 2006; **6:** 1666–72.
9. Heilman RL, *et al.* Acute rejection risk in kidney transplant recipients on steroid-avoidance immunosuppression receiving induction with either antithymocyte globulin or basiliximab. *Transplant Proc* 2006; **38:** 1307–13.
10. Brennan DC, *et al.* Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med* 2006; **355:** 1967–77.
11. Clark G, *et al.* Improved efficacy of basiliximab over antilymphocyte globulin induction therapy in paediatric renal transplantation. *Nephrol Dial Transplant* 2002; **17:** 1304–9.
12. Josephson MA. Rabbit antithymocyte globulin or basiliximab for induction therapy? *N Engl J Med* 2006; **355:** 2033–5.
13. Chapman TM, Keating GM. Basiliximab: a review of its use as induction therapy in renal transplantation. *Drugs* 2003; **63:** 2803–35.
14. Boggi U, *et al.* A benefit-risk assessment of basiliximab in renal transplantation. *Drug Safety* 2004; **27:** 91–106.
15. Baquero A, *et al.* Basiliximab: a comparative study between the use of the recommended two doses versus a single dose in living donor kidney transplantation. *Transplant Proc* 2006; **38:** 909–10.
16. Neuhaus P, *et al.* Improved treatment response with basiliximab immunoprophylaxis after liver transplantation: results from a double-blind randomized placebo-controlled trial. *Liver Transpl* 2002; **8:** 132–42.
17. Ganschow R, *et al.* First experience with basiliximab in pediatric liver graft recipients. *Pediatr Transplant* 2001; **5:** 353–8.
18. Ganschow R, *et al.* Long-term results of basiliximab induction immunosuppression in pediatric liver transplant recipients. *Pediatr Transplant* 2005; **9:** 741–5.
19. Reding R, *et al.* Steroid-free liver transplantation in children. *Lancet* 2003; **362:** 2068–70.

20. Spada M, *et al.* Randomized trial of basiliximab induction versus steroid therapy in pediatric liver allograft recipients under tacrolimus immunosuppression. *Am J Transplant* 2006; **6:** 1913–21.
21. Segovia J, *et al.* A randomized multicenter comparison of basiliximab and muromonab (OKT3) in heart transplantation: SIMCOR study. *Transplantation* 2006; **81:** 1542–8.
22. Mattei MF, *et al.* Lower risk of infectious deaths in cardiac transplant patients receiving basiliximab versus anti-thymocyte globulin as induction therapy. *J Heart Lung Transplant* 2007; **26:** 693–9.
23. Hachem RR, *et al.* A comparison of basiliximab and anti-thymocyte globulin as induction agents after lung transplantation. *J Heart Lung Transplant* 2005; **24:** 1320–6.
24. Borro JM, *et al.* Comparative study of basiliximab treatment in lung transplantation. *Transplant Proc* 2005; **37:** 3996–8.
25. Funke VAM, *et al.* Therapy for severe refractory acute graft-versus-host disease with basiliximab, a selective interleukin-2 receptor antagonist. *Bone Marrow Transplant* 2006; **37:** 961–5.

Skin disorders. There are a few case reports of successful treatment with basiliximab in psoriasis[1-4] (p.1583), chronic atopic dermatitis[5] (see Eczema, p.1579), lichen planus,[6] and epidermolysis bullosa acquisita[7] (p.1579).

1. Salim A, *et al.* Successful treatment of severe generalized pustular psoriasis with basiliximab (interleukin-2 receptor blocker). *Br J Dermatol* 2000; **143:** 1121–2.
2. Mrowietz U, *et al.* Treatment of severe psoriasis with anti-CD25 monoclonal antibodies. *Arch Dermatol* 2000; **136:** 675–6.
3. Owen CM, Harrison PV. Successful treatment of severe psoriasis with basiliximab, an interleukin-2 receptor monoclonal antibody. *Clin Exp Dermatol* 2000; **25:** 195–7.
4. Bell HK, Parslew RAG. Use of basiliximab as a cyclosporin-sparing agent in palmoplantar pustular psoriasis with myalgia as an adverse effect. *Br J Dermatol* 2002; **147:** 606–7.
5. Kägi MK, Heyer G. Efficacy of basiliximab, a chimeric anti-interleukin-2 receptor monoclonal antibody, in a patient with severe chronic atopic dermatitis. *Br J Dermatol* 2001; **145:** 350–1.
6. Rebora A, *et al.* Basiliximab is effective for erosive lichen planus. *Arch Dermatol* 2002; **138:** 1100–1.
7. Haufs MG, Haneke E. Epidermolysis bullosa acquisita treated with basiliximab, an interleukin-2 receptor antibody. *Acta Derm Venereol (Stockh)* 2001; **81:** 72.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Simulect; ***Austral.:*** Simulect; ***Belg.:*** Simulect; ***Braz.:*** Simulect; ***Canad.:*** Simulect; ***Chile:*** Simulect; ***Cz.:*** Simulect; ***Denm.:*** Simulect; ***Fin.:*** Simulect; ***Fr.:*** Simulect; ***Ger.:*** Simulect; ***Gr.:*** Simulect; ***Hong Kong:*** Simulect; ***Hung.:*** Simulect; ***Irl.:*** Simulect; ***Israel:*** Simulect; ***Ital.:*** Simulect; ***Malaysia:*** Simulect; ***Mex.:*** Simulect; ***Neth.:*** Simulect; ***Norw.:*** Simulect; ***NZ:*** Simulect; ***Philipp.:*** Simulect; ***Pol.:*** Simulect; ***Port.:*** Simulect; ***Rus.:*** Simulect (Симулект); ***S.Afr.:*** Simulect; ***Spain:*** Simulect; ***Swed.:*** Simulect; ***Switz.:*** Simulect; ***Thai.:*** Simulect; ***Turk.:*** Simulect; ***UK:*** Simulect; ***USA:*** Simulect; ***Venez.:*** Simultec.

Belatacept *(USAN, rINN)*

Bélatacept; Belataceptum; BMS-224818; LEA-29Y.

Белатацепт

CAS — 706808-37-9.

Profile

Belatacept is a derivative of abatacept (p.14). It is a fusion protein and co-stimulation blocker that prevents T-cell activation. Belatacept is under investigation for the management of solid organ transplant rejection.

◊ References.

1. Vincenti F, *et al.* Costimulation blockade with belatacept in renal transplantation. *N Engl J Med* 2005; **353:** 770–81.

Biolimus A9

42-*O*-(2-Ethoxyethyl) rapamycin.

$C_{55}H_{87}NO_{14}$ = 986.3.

CAS — 851536-75-9.

Profile

Biolimus A9 is an analogue of sirolimus (p.1841). A biolimus A9-releasing stent has been developed to reduce restenosis after coronary artery stent placement.

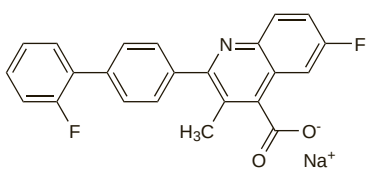
Brequinar Sodium *(USAN, rINNM)*

Brequinar sódico; Bréquinar Sodique; DuP-785; Natrii Brequinarum; NSC-368390. Sodium 6-fluoro-2-(2′-fluoro-4-biphenyl)-3-methyl-4-quinolinecarboxylate.

Натрий Брехинар

$C_{23}H_{14}F_2NO_2Na$ = 397.3.

CAS — 96187-53-0 (brequinar); 96201-88-6 (brequinar sodium).



Profile

Brequinar sodium is an inhibitor of pyrimidine metabolism with potent immunosuppressant properties that has been investigated for the prevention and treatment of rejection episodes after organ and tissue transplantation and for treating various cancers.

Ciclosporin *(BAN, rINN)*

27-400; Ciclosporina; Ciclosporina A; Ciclosporine; Ciclosporinum; Ciklosporin; Ciklosporinas; Cyclosporin; Cyclosporin A; Cyclosporine *(USAN)*; Cyklosporin; OL-27-400; Siklosporiini; Siklosporin. Cyclo{-[4-(*E*)-but-2-enyl-*N*,4-dimethyl-L-threonyl]-L-homoalanyl-(*N*-methylglycyl)-(*N*-methyl-L-leucyl)-L-valyl-(*N*-methyl-L-leucyl)-L-alanyl-D-alanyl-(*N*-methyl-L-leucyl)-(*N*-methyl-L-leucyl)-(*N*-methyl-L-valyl)-}.

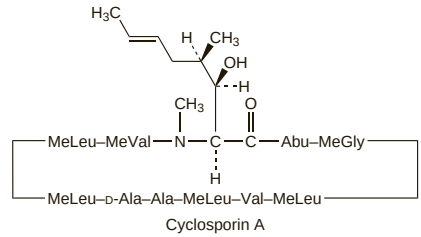
Циклоспорин

$C_{62}H_{111}N_{11}O_{12}$ = 1202.6.

CAS — 59865-13-3.

ATC — L04AD01.

ATC Vet — QL04AD01; QS01XA90.



Cyclosporin A

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 6.2 (Ciclosporin). A substance produced by *Beauveria nivea* (=*Tolypocladium inflatum* Gams) or obtained by any other means. A white or almost white powder; practically insoluble in water; freely soluble in dehydrated alcohol and in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Cyclosporine). A white to almost white powder. Practically insoluble in water; soluble in alcohol, in acetone, in chloroform, in dichloromethane, in ether, and in methyl alcohol; slightly soluble in saturated hydrocarbons. Store in airtight containers. Protect from light.

Incompatibility. The plasticiser diethylhexyl phthalate, which is a possible carcinogen, was leached from PVC containers by ciclosporin preparations containing polyoxyl castor oil.[1] Such preparations should not be given through PVC tubing nor stored in PVC containers. Polysorbate 80, which is an excipient in other ciclosporin preparations, also leached plasticiser from PVC,[1] and similar precautions would apply to preparations so formulated. UK licensed product information further recommends that containers and stoppers be free of silicone oil and fatty substances.

For reported incompatibility between ciclosporin and mycophenolate, see Incompatibility, under Mycophenolate, p.1836.

1. Pearson SD, Trissel LA. Leaching of diethylhexyl phthalate from polyvinyl chloride containers by selected drugs and formulation components. *Am J Hosp Pharm* 1993; **50:** 1405–9.

Stability. Ciclosporin was stable over 72 hours after dilution in glucose 5% or glucose/amino-acid solutions and storage at room temperature in the dark; similar stability was seen after dilution in lipid emulsion, but dilutions in sodium chloride 0.9% were considered to be stable only for 8 hours.[1] In all cases miscibility in the diluent was poor and vigorous shaking was required after addition to produce even distribution of ciclosporin. An extemporaneously compounded paste produced from ciclosporin oral solution (*Sandimmun*) in an oral gel base was found to be stable[2] for at least 31 days in aluminium-lined ointment tubes stored at 2° to 37°.

1. McLeod HL, *et al.* Stability of cyclosporin in dextrose 5%, NaCl 0.9%, dextrose/amino acid solution, and lipid emulsion. *Ann Pharmacother* 1992; **26:** 172–5.
2. Ghnassia LT, *et al.* Stability of cyclosporine in an extemporaneously compounded paste. *Am J Health-Syst Pharm* 1995; **52:** 2204–7.

Adverse Effects and Treatment

Nephrotoxicity, manifesting as raised serum creatinine and urea, is the major adverse effect of ciclosporin. It is related to drug-plasma concentrations and is usually reversible on reduction of the dose. In renal graft recipients episodes of nephrotoxicity may be difficult to distinguish from graft rejection. Interstitial fibrosis may develop during long-term therapy.

Other frequent adverse effects include hypertension, gastrointestinal disturbances, fatigue, hepatotoxicity, hypertrichosis, gum hyperplasia, tremor, headaches, hyperlipidaemias, hyperkalaemia, hypomagnesaemia, hyperuricaemia, paraesthesia, and muscle cramps and myalgia. Less commonly, anaemia, thrombocytopenia, rashes, weight increase, oedema, pancreatitis, myopathy, neuropathy, and hyperglycaemia have been reported. Glomerular capillary thrombosis has occurred, and may progress to graft failure. Encephalopathy, manifest as convulsions, confusion, visual disturbances including blindness, movement disorders, or psychiatric disturbances, has been reported. Optic disc oedema, including papilloedema with possible visual impairment secondary to benign intracranial hypertension, has occurred rarely.

Anaphylactoid reactions have occurred after intravenous use; it has been suggested that these represent a reaction to the polyoxyl castor oil vehicle of the intravenous preparation.

There is an increased incidence of certain malignancies and a predisposition to infection in patients receiving ciclosporin therapy.

Alopecia. Although ciclosporin is more often associated with reports of hypertrichosis, there have been cases of alopecia areata developing in patients given ciclosporin,[1] sometimes with complete hair loss (alopecia universalis).[2,3]

1. Davies MG, Bowers PW. Alopecia areata arising in patients receiving cyclosporin immunosuppression. *Br J Dermatol* 1995; **132:** 835–6.
2. Monti M, *et al.* Alopecia universalis in liver transplant patients treated with cyclosporin. *Br J Dermatol* 1995; **133:** 663–4.
3. Parodi A, *et al.* Alopecia universalis and cyclosporin A. *Br J Dermatol* 1996; **135:** 657.

Carcinogenicity. The use of ciclosporin in **organ transplant** recipients is associated with an increased incidence of malignancy, notably lymphoma,[1] and also skin cancer and Kaposi's sarcoma. The manufacturers have stated that of an estimated 5550 transplant patients who had been treated with ciclosporin by February 1984, lymphoproliferative disorders had been reported in 40; this represented an overall incidence of 0.7%, varying from 0.2 to 8% in different series.[2] In 1991, a report of 12 cases of lymphoproliferative disorders among 132 paediatric liver graft recipients estimated the incidence at about 2.8% per year for the first 6 years after transplantation, giving a cumulative risk of nearly 20% after 7 years.[3] There is evidence that the incidence of malignancy is related to dose,[2,4] and is greater when ciclosporin is used with other potent immunosuppressants.[2] In addition, the incidence of malignancy varies geographically, possibly reflecting environmental triggers and genetic susceptibility.[5]

It has been suggested that these lymphomas represent proliferation of B-cells under the influence of Epstein-Barr virus, a process normally prevented by the T-cells which are specifically inhibited by ciclosporin.[3] The resultant, usually polyclonal, lymphoproliferative tumours appear to regress on prompt excision of the affected tissue and reduction or withdrawal of the immunosuppressant regimen, in most cases without graft loss.[6] However, the need for vigilance and rapid response to these conditions has been stressed, since the responsive polyclonal disorder may evolve into a monoclonal, frankly malignant form; where the presentation is indistinguishable from a classic non-Hodgkins lymphoma the prognosis is much less good.[3] Interestingly, use of lower dose ciclosporin regimens appears to maintain normal elimination of Epstein-Barr virus-infected B-cells by specific T-cells,[7] and may lead to a reduced incidence of malignancy compared with earlier results.[4,7]

The risk of skin cancers in ciclosporin recipients is further increased by the exposure to sunlight.[8] Prophylactic retinoid therapy may prevent skin cancer in patients with renal transplants.[9]

There is no clear evidence that ciclosporin is associated with an increased incidence of malignancy compared with other immunosuppressants, although in one study dysplastic skin lesions were found in 14 of 64 transplant patients receiving ciclosporin compared with 3 of 33 previous similar patients who had received azathioprine.[10] However, such comparisons are difficult, not least because many transplant patients tend to have received multiple immunosuppressant agents. The safety of ciclosporin in **dermatology** patients has been reviewed.[11] Despite reports of lymphomas and other malignancies in dermatology patients treated with ciclosporin, a 5-year cohort study showed no increased risk of lymphoma or internal malignancies. While there was an increased risk of non-melanoma skin cancers, especially squamous cell carcinoma, many patients had been previously exposed to PUVA, methotrexate, or other immunosuppressants. Adjusting for these variables, more than 2 years of cumulative treatment with ciclosporin was estimated to increase the risk of non-melanoma skin cancer by a factor of 3.3 when compared with less than 2 years of cumulative treatment.

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