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.

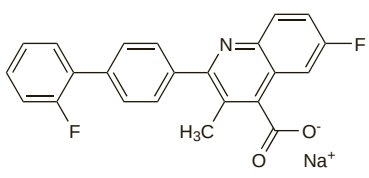
Brequinar Sodium *(USAN, rINNM)*

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)-}.

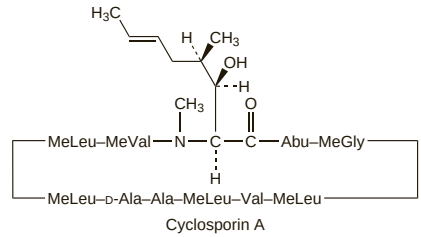
Циклоспорин

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

1. Penn I. Cancers following cyclosporine therapy. *Transplantation* 1987; **43:** 32–5.
2. Beveridge T, *et al.* Lymphomas and lymphoproliferative lesions developing under cyclosporin therapy. *Lancet* 1984; **i:** 788.
3. Malatack JJ, *et al.* Orthotopic liver transplantation, Epstein-Barr virus, cyclosporine, and lymphoproliferative disease: a growing concern. *J Pediatr* 1991; **118:** 667–75.