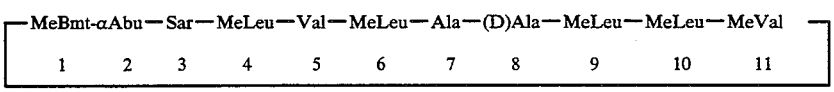
PHARMACEUTICAL COMPOSITIONS COMPRISING CYCLOSPORINS

This is a continuation of application Ser. No. 07/680,211, filed Apr. 4, 1991 now abandoned which in turn is a continuation of application Ser. No. 07/406,656, filed Sep. 13, 1989, now abandoned.

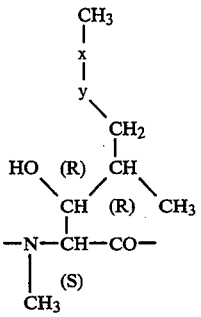
The present invention relates to novel galenic formulations comprising a cyclosporin as active ingredient.

The cyclosporins comprise a class of structurally distinctive, cyclic, poly-N-methylated endecapeptides, commonly possessing pharmacological, in particular immunosuppressive, anti-inflammatory and/or anti-parasitic activity. The first of the cyclosporins to be isolated was the naturally occurring fungal metabolite Ciclosporin or Cyclosporine, also known as cyclosporin A and commercially available under the Registered Trade Mark SANDIMMUN® or SANDIMMUNE®. Ciclosporin is the cyclosporin of formula A.



(A)

wherein -MeBmt- represents the N-methyl-(4R)-4-but-2E-en-1-yl-4-methyl-(L) threonyl residue of formula B



(B)

in which -x-y- is —CH=CH— (trans).

As the parent of the class Ciclosporin has so far received the most attention. The primary area of clinical investigation for Ciclosporin has been as an immunosuppressive agent, in particular in relation to its application to recipients of organ transplants, e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, bone-marrow, skin and corneal transplants and, in particular, allogenic organ transplants. in this field Ciclosporin has achieved a remarkable success and reputation.

At the same time, applicability of Ciclosporin to various autoimmune diseases and to inflammatory conditions, in particular inflammatory conditions with an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases, has been intensive and reports and results in vitro, in animal models and in clinical trials are wide-spread in the literature. Specific auto-immune diseases for which Ciclosporin therapy has been proposed or applied include, autoimmune hematological disorder (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopaenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease) endocrine opthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary billiary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy).

Further areas of investigation have been potential applicability as an anti-parasitic, in particular anti-protozoal agent, with possible uses suggested including treatment of malaria, coccidiomycosis and schistosomiasis and, yet more recently, use as an agent for reversing or abrogating anti-neoplastic agent resistance in tumours and the like.

Since the original discovery of ciclosporin, a wide variety of naturally occurring cyclosporins have been isolated and identified and many further non-natural cyclosporins have been prepared by total- or semi-synthetic means or by the application of modified culture techniques. The class comprised by the cyclosporins is thus now substantial and includes, for example, the naturally occurring cyclosporins A through Z [c.f. Traber et al. 1, Helv. Chim. Acta. 60, 1247–1255 (1977); Traber et al. 2, Helv. Chim. Acta. 65 no. 162, 1655–1667 (1982); Kobel et al., Europ. J. Applied Microbiology and Biotechnology 14, 273–240 (1982); and von Wartburg et al., Progress in Allergy, 38, 28–45 (1986)], as well as various non-natural cyclosporin derivatives and artificial or synthetic cyclosporins including the so called dihydro-cyclosporins (in which the moiety -x-y- of the -MeBmt- residue (Formula B above) is saturated to give -x-y-=—CH_2—CH_2—; derivatised cyclosporins (e.g. in which a further substituent is introduced at the α-carbon atom of the sarcosyl residue at the 3-position of the cyclosporin molecule); cyclosporins in which the -MeBmt- residue is present in isomeric form (e.g. in which the configuration across positions 6′ and 7′ of the -MeBmt- residue is cis rather than trans); and cyclosporins wherein variant amino acids are incorporated at specific positions within the peptide sequence, employing e.g. the total synthetic method for the production of cyclosporins developed by R. Wenger-see e.g. Traber 1, Traber 2 and Kobel loc. cit.; U.S. Pat. Nos. 4,108,985, 4,210,581 and 4,220,641; European Patent Publication Nos. 0 034 567 and 0 056 782; International Patent Publication No. WO 86/02080; Wenger 1, Transp. Proc. 15, Suppl. 1:2230 (1983); Wenger 2, Angew. Chem. Int. Ed., 24, 77 (1985); and Wenger 3, Progress in the Chemistry of Organic Natural Products 50, 123 (1986).

The class comprised by the cyclosporins is thus now very large indeed and includes, for example, $[Thr]^2$-, $[Val]^2$-, $[Nva]^2$- and $[Nva]^2$-$[Nva]^5$-Ciclosporin (also known as cyclosporins C,D, G and M respectively), $[3\text{-}0\text{-acyl-MeBmt}]^1$-Ciclosporin (also known as cyclosporin A acetate), $[\text{Dihydro-MeBmt}]^1$-$[Val]^2$-Ciclosporin (also known as dihydrocyclosporin D), $[(D)\text{Fluoromethyl-Sar}]^3$-Ciclosporin, $[(D)Ser]^8$-Ciclos-