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**THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS** *US60/631,483*

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# PATENT COVER SHEET FOR PROVISIONAL APPLICATION

Transmitted herewith for filing under 37 CFR §1.53(c) is the PROVISIONAL APPLICATION for patent of

| INVENTOR(S) | | |
|---|---|---|
| Given Name (first and middle [if any]) | Family Name or Surname | Residence (City and either State or Foreign Country) |
| John M | Kovarik | Basel, Switzerland |

TITLE OF THE INVENTION (280 characters max)

ORGANIC COMPOUNDS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

- ☒ Specification (Including Any Claims and Abstract) - 20 pages
- ☐ Drawings - sheets
- ☒ Other (specify): Application Data Sheet

METHOD OF PAYMENT

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Respectfully submitted,

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Date: November 29, 2004

Organic Compounds

The present invention relates to a dosage regimen of an S1P receptor agonist particularly in the course of the treatment of transplant patients.

S1P receptor agonists are compounds which signal as agonists at one or more sphingosine-1 phosphate receptors, e.g. S1P1 to S1P8. Agonist binding to a S1P receptor may e.g. result in dissociation of intracellular heterotrimeric G-proteins into Gα-GTP and Gβγ-GTP, and/or increased phosphorylation of the agonist-occupied receptor and activation of downstream signaling pathways/kinases.

S1P receptor agonists are valuable compounds for the manufacture of medication for the treatment of various conditions in mammals, especially in human beings. For example, S1P receptor agonists have successfully been used in the treatment of transplant patients, particularly prolonging allograft survival with great potency and efficacy and demonstrating excellent synergy with several immunosuppressants. This has been documented in rats (skin, heart, liver, small bowel), dogs (kidney), and monkeys (kidney). Combination experiments with cyclosporin A showed synergy in skin and heart transplantation models in rats and in monkey renal transplantation. S1P receptor agonists combined with everolimus prolong survival of cardiac (rat) and renal (monkey) allografts. Due to their immune-modulating potency, S1P receptor agonists are also useful for the treatment of inflammatory and autoimmune diseases. Further characteristics of S1P receptor agonists can be found in the following publications:

Brinkmann V, Chen S, Feng L, et al (2001) FTY720 alters lymphocyte homing and protects allografts without inducing general immunosuppression. Transplant Proc; 33:530-531.

Brinkmann V, Pinschewer D, Feng L, et al (2001) FTY720: altered lymphocyte traffic results in allograft protection (review). Transplantation; 72:764-769.

Pinschewer DD, Ochsenbein AF, Odermatt B, et al (2000) FTY720 immunosuppression impairs effector T-cell peripheral homing without affecting induction, expansion, and memory. J Immunol; 164:5761.

Yanagawa Y, Sugahara K, Kataoka H, et al (1998) FTY720, a novel immunosuppressant, induces sequestration of circulating mature lymphocytes by acceleration of lymphocyte homing in rats. II. FTY720 prolongs skin allograft survival by decreasing T cell infiltration into grafts but not cytokine production in vivo. J Immunol.; 160(11):5493-9.

It has now surprisingly been found that a specific dosage regimen, e.g. a loading dose, will provide further unexpected benefits. In particular, the otherwise observed moderate and

transient decrease in heart rate associated with the up-take of S1P receptor agonists by the body is suppressed or no longer observed after at most one week of treatment. Also the specific dosage regimen allows for re-initiation of the treatment after a hiatus avoiding said decrease in heart rate.

Accordingly it is provided the use of an S1P receptor agonist in the manufacture of a medication, whereby said medication is administered in such a way that during the initial 3 to 6 days, preferably 4 or 5 days, most preferred 4 days, of treatment the dosage of said S1P receptor agonist is raised so that in total the R-fold (R being the accumulation factor) standard daily dosage of said S1P receptor agonist is administered and thereafter the treatment is continued with the standard daily dosage of said S1P receptor agonist.

Preferred medications comprise medication for transplant patients providing prolonged survival rates, in particular prolonged allograft survival rates especially for renal or liver transplants, or for patients suffering from autoimmune diseases, e.g. multiple sclerosis.

In view of the normally prolonged taking of the medication, the standard daily dosage refers to the dosage of an S1P receptor agonist necessary for a steady-state trough blood level of the medication or its active metabolite(s) providing effective treatment. Said dosage is dependent on the accumulation factor (R). Steady-state trough blood levels may be assessed, for example, by averaging data collected at months 2, 3, and 6 of a treatment with a constant daily dosage, thereby allowing calculation of R. Preferably R is approximately from 3 to 12, preferably about 10.

Preferably, the dosage of said S1P receptor agonist during the initial 3 to 6 days of treatment is increased stepwise. A particularly preferred dosage of the preferred S1P receptor agonist FTY720 is 5, 10, 15 and 20 mg, respectively, during the initial period of 4 days. Thereafter the treatment is continued with the maintenance therapy, e.g. a daily dosage of 5 mg.

Preferably, the dosage of said S1P receptor agonist during the initial 3 to 6 days, preferably 4 or 5 days, most preferred 4 days, of treatment is increased incrementally up to 3- to 6-fold, particularly preferred up to 4-fold, the standard daily dosage of said S1P receptor agonist.

S1 P receptor agonists are typically sphingosine analogues, such as 2-substituted 2-amino-propane-1,3-diol or 2-amino-propanol derivatives, e. g. a compound comprising a group of formula X

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