

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US2005/043044

International filing date: 28 November 2005 (28.11.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/631,483
Filing date: 29 November 2004 (29.11.2004)

Date of receipt at the International Bureau: 02 February 2006 (02.02.2006)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

January 30, 2006

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: 60/631,483

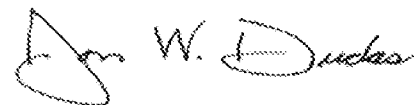
FILING DATE: November 29, 2004

RELATED PCT APPLICATION NUMBER: PCT/US05/43044

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



Certified by



Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

112904



20427 U.S. PTO

Docket Number TX/4-34053P1

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EV483667524US
Express Mail Label NumberNovember 29, 2004
Date of Deposit00746 U.S. PTO
60/631483

112904

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450**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		

CORRESPONDENCE ADDRESS

Direct all correspondence to the address associated with Customer No. 001095, which is currently:

Novartis
Corporate Intellectual Property
One Health Plaza, Building 104
East Hanover, NJ 07936-1080

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

The Commissioner is hereby authorized to charge filing fee and any additional fees required to Deposit Account Number: 19-0134 in the name of Novartis.

PROVISIONAL FILING FEE AMOUNT: \$ 160

- U.S. Government agency and contract number: (if the invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.)

Respectfully submitted,

Thomas R. Savitsky
Attorney for Applicant
Reg. No. 31,661
Tel. No. (862) 778-7909

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 G α -GTP and G $\beta\gamma$ -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 immunomodulating 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

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.