

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
1 June 2006 (01.06.2006)

PCT

(10) International Publication Number  
**WO 2006/058316 A1**

- (51) International Patent Classification:  
A61K 31/135 (2006.01) A61P 37/06 (2006.01)
- (21) International Application Number:  
PCT/US2005/043044
- (22) International Filing Date:  
28 November 2005 (28.11.2005)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
60/631,483 29 November 2004 (29.11.2004) US

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(71) Applicant (for all designated States except US): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (for AT only): **NOVARTIS PHARMA GmbH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

**Declaration under Rule 4.17:**  
— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **KOVARIK, John, M.** [US/CH]; Kraftstrasse 10, CH-4056 Basel (CH). **APPEL-DINGEMANSE, Silke** [DE/CH]; Luetzelbachweg 28, CH-4123 Allschwil (CH).

**Published:**  
— with international search report  
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(74) Agent: **SAVITSKY, Thomas, R.**; NOVARTIS, Corporate Intellectual Property Department, One Health Plaza, Bldg 104, East Hanover, NJ 07936-1080 (US).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 2006/058316 A1

(54) Title: DOSAGE REGIMEN OF AN S1P RECEPTOR AGONIST

(57) Abstract: S1P receptor modulators or agonists are administered following a dosage regimen whereby during the initial 3 to 6 days of treatment the daily dosage is raised so that in total the R-fold (R being the accumulation factor) standard daily dosage is administered and thereafter continued at the standard daily dosage or at a daily dosage lower than the standard daily dosage.

### Dosage Regimen of an S1P Receptor Agonist

The present invention relates to a dosage regimen of an S1P receptor modulator or agonist particularly in the course of the treatment of transplant patients or patients suffering from autoimmune diseases or disorders.

S1P receptor modulators or 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 $\alpha$ -GTP and G $\beta\gamma$ -GTP, and/or increased phosphorylation of the agonist-occupied receptor and activation of downstream signaling pathways/kinases.

S1P receptor modulators or agonists are valuable compounds for the manufacture of medication for the treatment of various conditions in mammals, especially in human beings. For example, efficacy in transplantation has been demonstrated in rats (skin, heart, liver, small bowel), dogs (kidney), and monkeys (kidney) models. Combination experiments with cyclosporin A showed synergy in skin and heart transplantation models in rats and in monkey renal transplantation. S1P receptor agonists or modulators combined with everolimus prolong survival of cardiac (rat) and renal (monkey) allografts. Due to their immune-modulating potency, S1P receptor modulators or 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.

The binding affinity of S1P receptor agonists or modulators to individual human S1P receptors may be determined in following assay:

S1P receptor agonist or modulator activities of compounds are tested on the human S1P receptors S1P<sub>1</sub>, S1P<sub>2</sub>, S1P<sub>3</sub>, S1P<sub>4</sub> and S1P<sub>5</sub>. Functional receptor activation is assessed by quantifying compound induced GTP [ $\gamma$ -<sup>35</sup>S] binding to membrane protein prepared from transfected CHO or RH7777 cells stably expressing the appropriate human S1P receptor. The assay technology used is SPA (scintillation proximity based assay). Briefly, DMSO dissolved compounds are serially diluted and added to SPA- bead (Amersham-Pharmacia) immobilised S1P receptor expressing membrane protein (10-20 $\mu$ g/well) in the presence of 50 mM Hepes, 100 mM NaCl, 10 mM MgCl<sub>2</sub>, 10  $\mu$ M GDP, 0.1% fat free BSA and 0.2 nM GTP [ $\gamma$ -<sup>35</sup>S] (1200 Ci/mmol). After incubation in 96 well microtiterplates at RT for 120 min, unbound GTP [ $\gamma$ -<sup>35</sup>S] is separated by a centrifugation step. Luminescence of SPA beads triggered by membrane bound GTP [ $\gamma$ -<sup>35</sup>S] is quantified with a TOPcount plate reader (Packard). EC<sub>50</sub>s are calculated using standard curve fitting software. In this assay, the S1P receptor modulators or agonists preferably have a binding affinity to S1P receptor <50 nM.

Preferred S1P receptor agonists or modulators are e.g. compounds which in addition to their S1P binding properties also have accelerating lymphocyte homing properties, e.g. compounds which elicit a lymphopenia resulting from a re-distribution, preferably reversible, of lymphocytes from circulation to secondary lymphatic tissue, without evoking a generalized immunosuppression. Naïve cells are sequestered; CD4 and CD8 T-cells and B-cells from the blood are stimulated to migrate into lymph nodes (LN) and Peyer's patches (PP).

The lymphocyte homing property may be measured in following Blood Lymphocyte Depletion assay:

A S1P receptor agonist or modulator or the vehicle is administered orally by gavage to rats. Tail blood for hematological monitoring is obtained on day -1 to give the baseline individual values, and at 2, 6, 24, 48 and 72 hours after application. In this assay, the S1P receptor agonist or modulator depletes peripheral blood lymphocytes, e.g. by 50%, when administered at a dose of e.g. < 20 mg/kg.

S1 P receptor modulators or 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



carbonylamino, acyloxy, (C<sub>1-4</sub>alkyl)carbamoyl, nitro, halogen, amino, hydroxyimino, hydroxy or carboxy; or

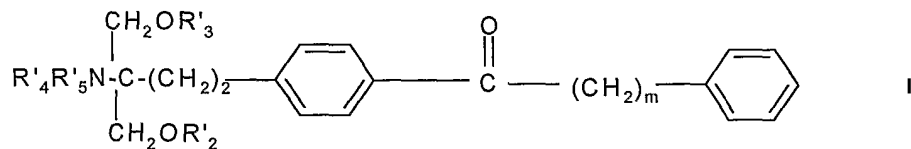
R<sub>1</sub> is

- a phenylalkyl wherein alkyl is a straight- or branched (C<sub>6-20</sub>)carbon chain; or
- a phenylalkyl wherein alkyl is a straight- or branched (C<sub>1-30</sub>)carbon chain wherein said phenylalkyl is substituted by
  - a straight- or branched (C<sub>6-20</sub>)carbon chain optionally substituted by halogen,
  - a straight- or branched (C<sub>6-20</sub>)alkoxy chain optionally substituted by halogen,
  - a straight- or branched (C<sub>6-20</sub>)alkenyloxy,
  - phenyl-C<sub>1-14</sub>alkoxy, halophenyl-C<sub>1-4</sub>alkoxy, phenyl-C<sub>1-14</sub>alkoxy-C<sub>1-14</sub>alkyl, phenoxy-C<sub>1-4</sub>alkoxy or phenoxy-C<sub>1-4</sub>alkyl,
  - cycloalkylalkyl substituted by C<sub>6-20</sub>alkyl,
  - heteroarylalkyl substituted by C<sub>6-20</sub>alkyl,
  - heterocyclic C<sub>6-20</sub>alkyl or
  - heterocyclic alkyl substituted by C<sub>2-20</sub>alkyl,

and wherein

the alkyl moiety may have

- in the carbon chain, a bond or a heteroatom selected from a double bond, a triple bond, O, S, sulfinyl, sulfonyl, or NR<sub>6</sub>, wherein R<sub>6</sub> is as defined above, and
  - as a substituent C<sub>1-4</sub>alkoxy, C<sub>2-4</sub>alkenyloxy, C<sub>2-4</sub>alkynyloxy, arylC<sub>1-4</sub>alkyloxy, acyl, C<sub>1-4</sub>alkyl-amino, C<sub>1-4</sub>alkylthio, acylamino, (C<sub>1-4</sub>alkoxy)carbonyl, (C<sub>1-4</sub>alkoxy)carbonylamino, acyloxy, (C<sub>1-4</sub>alkyl)carbamoyl, nitro, halogen, amino, hydroxy or carboxy, and
- each of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub>, independently, is H, C<sub>1-4</sub> alkyl or acyl or a pharmaceutically acceptable salt or hydrate thereof;
- Compounds as disclosed in EP 1002792A1, e.g. a compound of formula II



wherein m is 1 to 9 and each of R'<sub>2</sub>, R'<sub>3</sub>, R'<sub>4</sub> and R'<sub>5</sub>, independently, is H, C<sub>1-6</sub>alkyl or acyl, or a pharmaceutically acceptable salt or hydrate thereof;

- Compounds as disclosed in EP0778263 A1, e.g. a compound of formula III

# 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.