(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 July 2003 (10.07.2003)

PCT

(10) International Publication Number
WO 03/055485 A1

(51) International Patent Classification[7]: A61K 31/4402, 31/42

(21) International Application Number: PCT/US02/40699

(22) International Filing Date:
18 December 2002 (18.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/345,153 21 December 2001 (21.12.2001) US

(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM CORPORATION** [US/US]; One Franklin Park, Philadelphia, PA 19101 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BROWN, Kathleen, Keating** [US/US]; GlaxoSmithKline, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US). **BAER, Philip, G.** [US/US]; 377 Potluck Farm Road, Rougmont, NC 27572 (US).

(74) Agents: **LEVY, David, J.** et al.; GlaxoSmithKline, Corporate Intellectual Property Department, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709 (US).

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

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

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 03/055485 A1

(54) Title: DOSING REGIMEN FOR PPAR-GAMMA ACTIVATORS

(57) Abstract: The present invention provides a method of treating a disease or condition, for example diabetes, with a PPAR-gamma activator comprising administration of the PPAR-gamma activator according to a dosing schedule which comprises a period of less than daily administration of the activator, for example alternate day administration.

Dosing Regimen For PPAR-gamma Activators

Field of the Invention

This invention relates to methods for treating diseases or conditions with PPAR-gamma activators. In particular, this invention relates to dosing regimens for PPAR-gamma activators.

Background

Peroxisome Proliferator Activated Receptors (PPARs) are orphan receptors belonging to the steroid/retinoid receptor superfamily of ligand-activated transcription factors. See, for example, Willson, T. M. and Wahli, W., Curr. Opin. Chem. Biol., (1997), Vol. 1, pp 235-241. Three mammalian PPARs have been identified which are termed PPAR-alpha, PPAR-gamma, and PPAR-delta. PPARs regulate expression of target genes by binding to DNA response elements as heterodimers with the retinoid X receptor. These DNA response elements have been identified in the regulatory regions of a number of genes encoding proteins involved in glucose and lipid metabolism as well as energy balance. The biological role of the PPARs in the regulation of lipid metabolism and storage has been recently reviewed. See, for example, Spiegelman, B. M., Diabetes, (1998), Vol. 47, pp 507-514, Schoonjans, K., Martin, G., Staels, B., and Auwerx, J., Curr. Opin. Lipidol. (1997), Vol. 8, pp 159-166, and Brun, R. P., Kim, J. B., Hu, E., and Spiegelman, B. M., Curr. Opin. Lipidol. (1997), Vol. 8, pp 212-218, Way J.M., Harrington W. W., Brown K. K., Gottschalk W. K., Sundseth S. S., Mansfield T. A., Ramachandran R. K., Willson T. M. and Kliewer S. A., Endocrinology (2001), Vol. 142, pp1269-1277, Desvergne, B. Wahli, W Endocrinology Reviews (1999) 20(5): 649-688).

PPAR-gamma activators are typically used to treat type 2 diabetes. PPAR-gamma activators enhance sensitivity to insulin-stimulated glucose uptake and utilization, and thus reduce plasma glucose levels in human diabetics and in rodent models of diabetes. This sustained plasma glucose lowering effect, reflected clinically as a decrease in HbA1c, is referred to as "glycemic control", and represents the desired anti-diabetic efficacy of this compound class. Additional benefits of PPAR-gamma activator treatment in diabetic patients are reduction in serum triglyceride and free fatty acid levels, decrease in LDL cholesterol and an increase in HDL cholesterol.

However, the benefits of treatment with PPAR-gamma activators can be accompanied by undesired side effects. A significant dose-limiting side effect of the currently marketed PPAR-gamma activators, observed in diabetic patients, is weight gain due to fluid retention. This fluid retention may lead to edema and, particularly in patients with pre-existing heart

failure, the development of congestive symptoms,. The incidence of edema may be increased if the PPAR-gamma activator) is used in combination either with agents that stimulate insulin secretion, for example sulfonylureas, or exogenously administered insulin. See, for example, ACTOS, Physicians Desk Reference, (2001) 55th edition, pp. 3171-3175 or AVANDIA Physicians Desk Reference, (2001) 55th edition, pp. 3871-3875.

Drug dosing regimens are typically designed to be convenient for the patient, to promote compliance, to produce maximal benefit, and to minimize undesired side effects. For the vast majority of drugs, this is best achieved through constant drug exposure at the lowest level that produces efficacy, and thus the optimal regimen is in most cases daily drug administration. For drugs given daily, efficacy and side effects are generally separable by total drug dosage, with side effects occurring at drug dosages that are higher by some multiple than the dosage producing the desired efficacy. Currently, PPAR-gamma activators are administered once or twice daily. See, for example ACTOS, (Physicians Desk Reference, (2001) 55th edition, p 3175 or AVANDIA, Physicians Desk Reference, (2001) 55th edition, p 3875.

In addition to daily drug dosing, there are examples of drugs that use dosing regimens in which the interval between drug doses is more than a single day. While the interval may be two days (i.e. alternate-day dosing), or one week (i.e. once weekly dosing), or an extended period of no dosing following a period of daily dosing, the underlying principles are the same. In this discussion, any regimen intentionally comprising an inter-dose interval greater than one day is referred to as less than daily dosing.

Less than daily dosing is discussed extensively in therapeutic areas in which glucocorticoid therapy is a mainstay. See, for example, Axelrod L., Glucocorticoids, Textbook of Rheumatology, 4th edition, vol 1, pp 779-ff, (1986); Physicians Desk Reference, 48th edition, section on DELTASONE, pp 2408-2409, (1994); Holland and Taylor, Glucocorticoids in clinical practice, J Family Prac 32: 512-519, (1991); and Hodson EM, Knight JR, Willis NS, and Craig JC, Corticosteroid therapy for nephrotic syndrome in children (Cochrane Review), The Cochrane Library, Issue 4, (2001).

For hormone replacement therapy, for treatment of menopausal disorders, estrogen has been administered by a variety of dosing regimens, often given daily for several weeks, followed by one week of no dosage. This is intended to minimize stimulation of proliferation in estrogen-sensitive tissues, such as uterus, by partly mimicking the normal endocrine physiology. See, for example The Pharmacological Basis of Therapeutics, (1996) 9th edition, pp. 1422-1423.

Alendronate, used for prevention and treatment of osteoporosis, was originally developed for daily dosing. Subsequently, for various reasons, including minimization of

esophagitis seen as a side effect, the drug was approved for once-a-week dosing. In this case, knowledge of pharmacokinetics, specifically that the drug distributes only into bone, was used to predict that infrequent dosing would be fully efficacious, since bone is the target tissue for the drug. See, for example Schnitzer, TJ, Update on Alendronate: Once-Weekly dosing. Expert Opin Pharmacother 2: 1461-1472, (2001).

In addition to minimization of side effects, minimization of drug cost is sometimes part of the rationale for alternate-day dosing. For treatment of hypercholesterolemia, it was recently reported that lovastatin given as less than daily dosing was equally as efficacious as when given daily, and thus was a cost-effective method of treatment. See, for example Dennis, VC, Britton ML, Sirmans SM, Letassy NA, Freeman DA, The use of alternate-day lovastatin in hypercholesterolemic men, Ann Pharmacother 31: 708-711, (1997).

Brief Description of the Invention

Briefly, in one aspect, the present invention provides a method of treating a disease or condition, for example diabetes, with a PPAR-gamma activator comprising administration of the PPAR-gamma activator according to a dosing schedule that comprises at least one period of less than daily dosing of the activator, for example alternate day dosing. The dosing regimen of this invention, as compared to dosing regimens comprising daily or twice daily administration of PPAR-gamma activator, may result in no significant decrease in efficacy, for example glycemic control, but with a significant decrease in undesired effects, for example fluid retention which can lead to weight gain, hemodilution, and edema. The dosing regimen of this invention may be used in conjunction with other treatments. For example, the PPAR-gamma activator dosing regimen of this invention can be used in combination with either exogenous insulin or drugs that increase the secretion of endogenous insulin.

Detailed Description of the Invention

PPAR-gamma activators includes PPAR-gamma agonists. As used herein, a "PPAR-gamma activator" includes any compound that activates human PPAR-gamma by any accepted assay, or any compound generally recognized as a PPAR-gamma activator or agonist. Such PPAR-gamma activators may be activators of more than one PPAR subtype. Preferred PPAR-gamma activators include the thiazolidinediones (TZDs) known to be useful for treating diabetes and also non-thiazolidinedione (non-TZDs) PPAR-gamma activators such as those disclosed in US Patent 6,294,580. Particularly preferred TZDs include those currently marketed, such as rosiglitzone and pioglitazone. Particularly preferred non-TZDs include compounds in development such as the GlaxoSmithKline compound GI262570 (farglitazar).

As used herein "less than daily dosing" will be used to indicate any intentional dosing regimen that comprises at least one period in which the frequency of dosing is less than daily, for example every other day, or which comprises at least one gap of at more than 1 day where there is no administration of the PPAR-gamma activator. In the case of dosing regimens that comprise a gap or day without administration, as used herein such gaps or days without administration of the PPAR-gamma activator must be preceded and followed by administration of activator. This is meant to include any dosing regimen comprising gaps in dosing of more than one day. For example, the dosing regimens of this invention include regimens comprising 5 days with and 2 days without administration of the activator, or 12 with and 2 without, or 19 with and 2 without, or 26 with and 2 without, or 11 with and 3 without, or 18 with and 3 without, or 25 with and 3 without, or 10 with and 4 without, or 17 with and 4 without, or 24 on and 4 without, etc. This is true regardless of the average number of doses per day. For example, twice daily administration every other day would be less than daily dosing. The dosing regimen of this invention can include several days or weeks of daily or twice daily dosing followed by a period of less than daily dosing. As used herein a day with dosing or a day with administration of activator includes once, twice, or any number of doses on that particular day.

Preferred dosing regimens are those that comprise periods of every other day or every third day or twice weekly dosing, or that comprise one or two or three consecutive days without administration. When the PPAR-gamma activator dosing regimen of this invention is used in combination with administration of either exogenous insulin or drugs that increase the secretion of endogenous insulin, the insulin or additional drug can be administered with a dosing regimen that is the same as or different from the PPAR-gamma activator regimen. As used herein "dosing" and "administration" are intended to be identical.

Experimental

Four animal studies were carried out regarding the effects of PPAR-gamma activator treatment. The PPAR-gamma activator used in these experiments was GI262570 (farglitazar), which may be prepared as described in US Patent 6,294,580. These four studies are described in detail below. As used herein "bid" means twice daily.

Study 1: Rat Model of PPAR-gamma Activator Induced Fluid Retention/Edema

Normal Han Wistar female adult rats were housed in metabolic cages and orally dosed (8 mg/kg, bid) with PPAR-gamma activator or vehicle (PEG400, 1 ml/kg) for 21 days. Electrolyte and water balance, plasma volume, hematocrit, and interstitial fluid volume were

measured. Compared with vehicle treated control rats, rats treated with PPAR-gamma activator showed a sustained increase in electrolyte and water retention, ultimately resulting in a 6% increase in plasma volume and a 6% decrease in hematocrit. In addition, there was a 50% increase in interstitial fluid volume, correlating to an edematous state.

These results indicate that daily treatment with a PPAR-gamma activator caused sustained fluid retention and development of edema. As noted in the background section above, this PPAR-gamma activator effect has also been observed in human clinical studies.

Study 2: Rat Model of PPAR-gamma Activator Induced Cardiovascular Changes Leading to Fluid Retention and Edema

Normal Han Wistar female adult rats were chronically instrumented for measurement of cardiac output, blood pressure and total peripheral resistance and orally dosed (8 mg/kg, bid) with PPAR-gamma activator or vehicle (PEG400, 1 ml/kg) for 10 days. Data were collected for 7 days prior to the start of dosing, for 10 days of dosing, and for 7 days after discontinuation of dosing. In rats treated with the PPAR-gamma activator, total peripheral resistance decreased, and cardiac output increased, beginning within six hours after the initial dose, and reached steady state by treatment day four. When dosing was discontinued, total peripheral resistance and cardiac output began to return toward control values within 24 hours, with full recovery after four days. The decrease in total peripheral resistance is believed to be the initial pharmacodynamic effect of PPAR-gamma activators leading to fluid retention and edema.

Study 3: Model of PPAR-gamma Activator Induced Efficacy/Glycemic Control

Two glucose-matched groups (n=6/group) of Zucker Diabetic Fatty (ZDF) rats, 7-8 weeks of age, were treated with vehicle (n-methylglucamine, 0.05M, 1 ml/kg, p.o.) or PPAR-gamma activator (5 mg/kg, bid). After four weeks of treatment, all rats treated with PPAR-gamma activator were volume expanded and two were overtly edematous, and PPAR-gamma activator dosing was discontinued. At the time dosing was discontinued, the average non-fasted plasma glucose was 154 mg/dl in PPAR-gamma agonist treated rats compared to 464 mg/dl in the vehicle-treated controls. This level of glycemic control was maintained despite discontinuation of PPAR-gamma activator treatment for 10 days, at which time the average plasma glucose in the rats previously treated with PPAR-gamma activator was 175 mg/dl, compared to 462 mg/dl in vehicle-treated controls. In contrast to the sustained glycemic control, the fluid volume expansion was not sustained, as evidenced by the finding that the hematocrit returned from and end-of-treatment value of 47% to a control value or 52% within 3 days.

Taking the hematocrit response as indicative of the expanded plasma volume resulting from increased fluid and electrolyte retention, these data suggested that the beneficial pharmacodynamic effect of PPAR-gamma activators (glycemic control) was of longer duration than the pharmacodynamic effects leading to salt and water retention. In other words, the results above show that the time course for the cardiovascular changes that lead to the reversal of the fluid retention and edema was shorter than the duration of glycemic control after discontinuation of dosing. This time-differential finding suggests that it may be possible to achieve glucose control without fluid retention during PPAR-gamma activator therapy by decreasing the frequency of dosing from daily to some form of less than daily dosing. The results also show that the mechanism of PPAR-gamma induced fluid retention, namely the fall in total peripheral resistance, begins within six hours of the first dose, a vascular effect that will stimulate salt and water retention. Knowledge of the on and off rate of the primary vascular and secondary renal effects suggests an appropriate dosing regimen. This was tested in Study 4 below.

Study 4: Less Than Daily Dosing with PPAR-gamma Activator

Three groups of 8 plasma glucose-matched ZDF rats with non-fasted glucose values greater than 250 mg/dl were dosed with PPAR-gamma activator. During the study plasma glucose and serum albumin were measured weekly, HbA1c was measured every other week, and heart weights and body weights were measured terminally. Reduction of plasma glucose and HbA1c are markers for anti-diabetic efficacy (glycemic control). Decreased plasma albumin concentration is a marker for plasma volume expansion or hemodilution. The heart weight-to-body weight ratio is a marker for increased cardiac output secondary to volume expansion.

All three groups were initially dosed with PPAR-gamma activator for one week at 5 mg/kg twice daily, in order to achieve glycemic control as shown by plasma glucose less than 250 mg/dl, and volume expansion as shown by reduced serum albumin.

After the initial week of dosing, the mean non-fasted plasma glucose for all rats was 138 mg/dl (compared to pre-treatment values of 321 mg/dl) and the serum albumin concentration was 3.5 gm/dl (compared to pre-treatment value of 3.8 gm/dl). Following the first week one group (Group BID) was continued on the daily dosing regimen while the other two were moved to less than daily dosing. Group BID continued to be dosed at 5 mg/kg twice daily, Group MWF was dosed at 10 mg/kg per day three times weekly (Monday/Wednesday/Friday), and Group MF was dosed at 10 mg/kg per day twice weekly (Monday/Friday). These three dosing regimens were continued for five weeks.

Because this study was designed to determine whether fluid retention could be eliminated while glycemic control was maintained, only animals demonstrating continued glycemic control (non-fasted plasma glucose less than 250 mg/dl) were evaluated. All 8 rats in the BID group met this criterion, as did 6 in the MWF group and 5 in the MF group. The data is summarized in Tables 1, 2, and 3, and only includes the 19 rats that exhibited glycemic control.

The data summarized in Figure 1 show that during the last two weeks of study, plasma glucose (in the 11 responding rats) was slightly higher in the MWF and MF dose groups, but still well below pre-dosing levels, thus demonstrating that all three dosing regimens resulted in glycemic control in these animals.

As further evidence of this, HbA_{1c} values, which indicate average plasma glucose integrated over time, were below 6% for all 19 animals. The data summarized in Figure 2 show that serum albumin concentration was similarly decreased in all rats after the first week of dosing, indicating that plasma volume was increased. By day 14 of reduced frequency dosing, the MWF and MF group values returned to and remained at pre-treatment baseline values, while the BID group value remained below the pre-treatment baseline value throughout dosing.

The data summarized in Figure 3 show that the terminal heart weight to body weight ratio for the BID group was increased by 13% compared to the MWF and MF dose groups. Heart weight/body weight ratio values from the literature for normal rats of the same body weight average 0.23 with a range of 0.19-0.25 as the 95% confidence limits. Thus, both the MWF and MF dose group heart weight/body weight ratios were within normal ranges, while that for the BID dose group was increased beyond the normal range. This indicates that the alternate day dosing regimens prevented the fluid retention that occurs with daily dosing, and thus prevented the increase in cardiac output that leads to increased heart weight.

The results of the studies described above demonstrate that, with alternate day dosing regimens, it is possible to achieve the desired glycemic control with PPAR-gamma activators, without producing undesired fluid retention and edema.

What is claimed is:

1. Method of treating a disease or condition with a PPAR-gamma activator comprising administration of the PPAR-gamma activator according to a dosing schedule which comprises a period of less than daily dosing.

2. The method of Claim 1 wherein the dosing schedule comprises at least one day in which there is no administration of the PPAR-gamma activator.

3. The method of Claim 1 wherein the dosing schedule comprises 2 consecutive days in which there is no administration of the PPAR-gamma activator.

4. The method of Claim 1 wherein the dosing schedule comprises a period selected from the group consisting of administration of the activator on alternate days, administration of the activator on only two days per week, and administration of the activator every third day.

5. The method of Claim 1 wherein the PPAR-gamma activator is rosiglitazone or farglitazar.

6. The method of Claim 1 wherein the disease or condition is selected from the group consisting of hyperglycaemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, anorexia nervosa, and cardiovascular disease, including ischemia-reperfusion injury and atherosclerosis, cancer, Alzheimer's disease or other cognitive disorders.

7. The method of Claim 6 wherein the disease or condition is diabetes.

8. The method of claim 7 further comprising administration of an agent that stimulates insulin secretion or insulin.

9. The method of Claim 8 wherein said agent is selected from the group consisting of sulfonyureas, metformin, glucophage

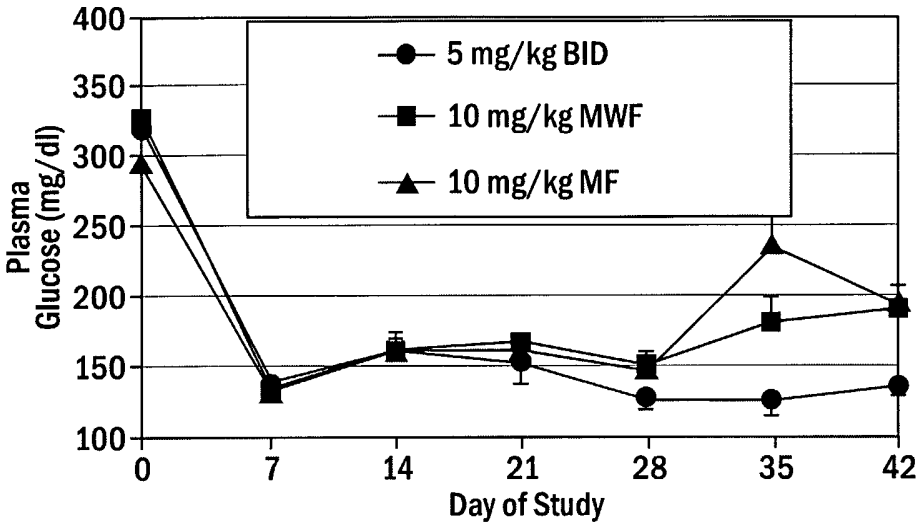


FIGURE 1

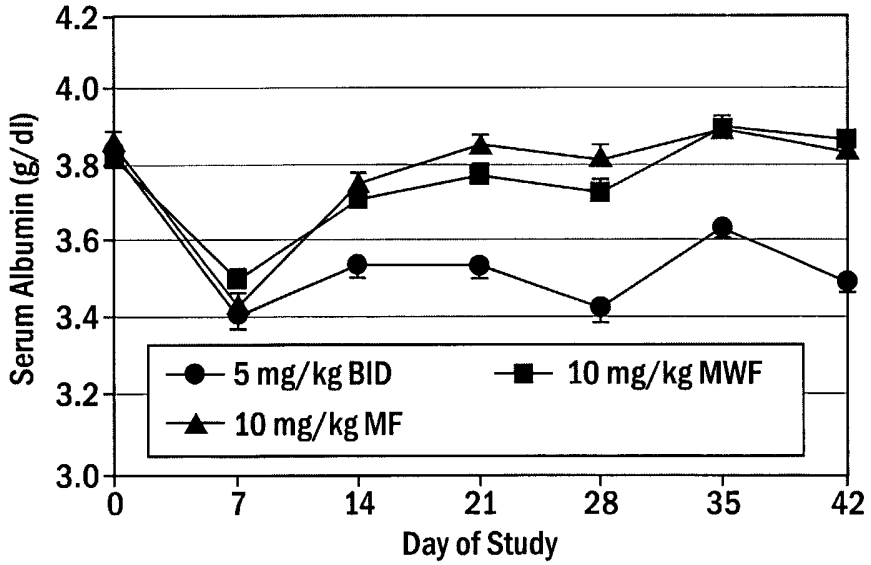


FIGURE 2

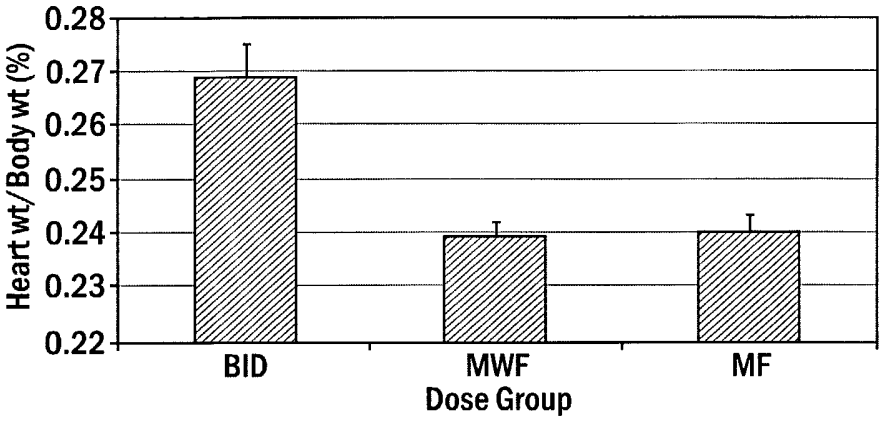

0.28
0.27
0.26
0.25
0.24
0.23
0.22
Heart wt/Body wt (%)
BID
MWF
MF
Dose Group

FIGURE 3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/40699

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4402 A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 294 580 B1 (O'CALLAGHAN JOHN MARK ET AL) 25 September 2001 (2001-09-25) column 1, line 6 - line 15 column 13, line 66 -column 14, line 12	1-9
A	WO 00 27341 A (SMITHKLINE BEECHAM CORP ;JUSKO WILLIAM (US); BENINCOSA LISA (US)) 18 May 2000 (2000-05-18) page 3, line 10 - line 21 page 3, line 22 - line 27 page 8, line 28 - line 29 page 8, line 34 - line 35	1-10
A	WO 00 28990 A (RE VINCENZO ;SKINNER JANET LOUISE (GB); SMITHKLINE BEECHAM PLC (GB) 25 May 2000 (2000-05-25) page 1, line 6 - line 27 page 1, line 29 - line 32	1-10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 March 2003	03/04/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Giacobbe, S

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 78333 A (JOHNSON WILLIAM T ;STRAMM LAWRENCE E (US); YAKUBU MADUS FATIMA EMI) 28 December 2000 (2000-12-28) page 10, line 20 - line 23 ---	1-10
A	US 6 288 095 B1 (CAWTHORNE MICHAEL ANTONY ET AL) 11 September 2001 (2001-09-11) column 1, line 23 - line 30 column 10, line 62 -column 11, line 2 -----	1-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/40699

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/40699

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6294580 B1	25-09-2001	AT 205485 T	15-09-2001
		AU 717699 B2	30-03-2000
		AU 2093597 A	16-09-1997
		BG 102792 A	31-08-1999
		BR 9707786 A	27-07-1999
		DE 69706658 D1	18-10-2001
		DE 69706658 T2	20-06-2002
		DK 888317 T3	21-01-2002
		EA 1403 B1	26-02-2001
		EE 9800288 A	15-02-1999
		EP 0888317 A1	07-01-1999
		HK 1015369 A1	15-02-2002
		HU 0004845 A2	28-05-2001
		IL 125796 A	14-06-2001
		JP 3255930 B2	12-02-2002
		JP 2000507216 T	13-06-2000
		NO 983940 A	27-10-1998
		NZ 331381 A	23-06-2000
		PL 328871 A1	01-03-1999
		SI 888317 T1	30-04-2002
		SK 116398 A3	13-04-1999
		AP 780 A	22-11-1999
		CA 2247443 A1	04-09-1997
		CN 1218460 A ,B	02-06-1999
		CZ 9802750 A3	13-01-1999
		WO 9731907 A1	04-09-1997
		ES 2163125 T3	16-01-2002
		HR 970110 A1	30-04-1998
		PT 888317 T	28-03-2002
		TR 9801707 T2	21-12-1998
		ZA 9701645 A	10-12-1997
WO 0027341 A	18-05-2000	AU 1719600 A	29-05-2000
		BG 105569 A	31-01-2002
		BR 9915284 A	13-02-2002
		CA 2350425 A1	18-05-2000
		CN 1354661 T	19-06-2002
		CZ 20011656 A3	12-06-2002
		EP 1135128 A2	26-09-2001
		HR 20010344 A1	30-06-2002
		HU 0104262 A2	28-08-2002
		NO 20012301 A	09-07-2001
		PL 349421 A1	29-07-2002
		SK 6422001 A3	03-12-2001
		TR 200101348 T2	21-02-2002
		WO 0027341 A2	18-05-2000
WO 0028990 A	25-05-2000	AU 1272900 A	05-06-2000
		BG 105570 A	28-02-2002
		BR 9915215 A	31-07-2001
		CA 2350659 A1	25-05-2000
		CN 1333683 T	30-01-2002
		CZ 20011628 A3	12-12-2001
		WO 0028990 A1	25-05-2000
		EP 1128827 A1	05-09-2001
		HR 20010342 A1	30-06-2002
		HU 0104307 A2	29-07-2002
		JP 2002529505 T	10-09-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat[redacted] Application No
PCT/US 02/40699

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0028990 A		NO	20012351 A	04-07-2001
		PL	348153 A1	06-05-2002
		SK	6432001 A3	03-12-2001
		TR	200101337 T2	21-11-2001
WO 0078333 A	28-12-2000	AU	5325200 A	09-01-2001
		CA	2349865 A1	28-12-2000
		EP	1133312 A2	19-09-2001
		WO	0078333 A2	28-12-2000
US 6288095 B1	11-09-2001	US	5232925 A	03-08-1993
		US	5646169 A	08-07-1997
		US	5521201 A	28-05-1996
		US	5756525 A	26-05-1998
		US	2002049240 A1	25-04-2002
		AT	186724 T	15-12-1999
		AU	2173888 A	09-03-1989
		BR	1100841 A3	20-06-2000
		CA	1328452 A1	12-04-1994
		CA	1339902 A1	09-06-1998
		CZ	9103916 A3	17-03-1993
		DE	3856378 D1	23-12-1999
		DE	3856378 T2	11-05-2000
		DK	490288 A	05-03-1989
		DK	200001556 A	18-10-2000
		EP	0306228 A1	08-03-1989
		EP	0842925 A1	20-05-1998
		ES	2137915 T3	01-01-2000
		GR	3031873 T3	29-02-2000
		HK	1011029 A1	03-11-2000
		JP	10194970 A	28-07-1998
		JP	10194971 A	28-07-1998
		JP	1131169 A	24-05-1989
		JP	2614497 B2	28-05-1997
		JP	2817840 B2	30-10-1998
		JP	9183771 A	15-07-1997
		JP	2837139 B2	14-12-1998
		JP	9183726 A	15-07-1997
		JP	9183772 A	15-07-1997
		KR	164207 B1	15-01-1999
		KR	164275 B1	15-01-1999
		KR	169463 B1	15-01-1999
		LU	90711 A9	05-03-2001
		NZ	226027 A	26-03-1992
		PT	88410 A ,B	31-07-1989
		SG	59988 A1	22-02-1999
		SK	391691 A3	11-12-2000
		US	5002953 A	26-03-1991
		US	5194443 A	16-03-1993
		US	5260445 A	09-11-1993
		ZA	8806536 A	26-07-1989