

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
23 December 2004 (23.12.2004)

PCT

(10) International Publication Number
WO 2004/110368 A2

- (51) International Patent Classification⁷: A61K
- (74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (21) International Application Number: PCT/US2004/017090
- (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, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 2 June 2004 (02.06.2004)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/476,390 6 June 2003 (06.06.2003) US
- (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, IT, LU, 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 all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): FONG, Tung, M. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). ERONDU, Ngozi, E [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). MACNEIL, Douglas, J. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). MCINTYRE, James, H. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). VAN DER PLOEG, Leonardus, H. T. [NL/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

Published:

— without international search report and to be republished upon receipt of that 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 2004/110368 A2

(54) Title: COMBINATION THERAPY FOR THE TREATMENT OF HYPERTENSION

(57) Abstract: The present invention relates to compositions comprising an anti-obesity agent and an anti-hypertensive agent useful for the treatment of hypertension, hypertension associated with obesity, and hypertension-related disorders. The present invention further relates to methods of treating or preventing obesity, and obesity-related disorders, in a subject in need thereof by administering a composition of the present invention. The present invention further provides for pharmaceutical compositions, medicaments, and kits useful in carrying out these methods.

TITLE OF THE INVENTION

COMBINATION THERAPY FOR THE TREATMENT OF HYPERTENSION

BACKGROUND OF THE INVENTION

5 Hypertension, or high blood pressure, is a generally symptomless condition characterized by abnormally high pressure in the arteries. Untreated high blood pressure increases the risk of stroke, aneurysm, heart disease, heart failure, heart attack, and kidney damage. Hypertension may also result in changes in the heart, such as enlargement of the heart (cardiac hypertrophy and left ventricular hypertrophy) due to the increased work required to pump blood. For an otherwise healthy individual,
10 high blood pressure is defined as a systolic pressure (pressure when the heart contracts) that averages 140 mm Hg or more, a diastolic pressure (pressure when the heart relaxes) that averages 90 mm Hg or more, or both.

 The pressure in arteries can be increased in various ways. For one, the heart can pump with more force, putting out more fluid each second. Another possibility is that the large arteries can lose
15 their normal flexibility and become stiff, so that they can't expand when the heart pumps blood through them. Thus, the blood through each heartbeat is forced through less space than normal, and the pressure increases. This occurs when arterial walls become thickened and stiff due to arteriosclerosis. Blood pressure is similarly increased in vasoconstriction - when the tiny arteries (arterioles) are temporarily constricted as a result of stimulation by nerves or by hormones in the blood. A third way in which the
20 pressure in the arteries can be increased is for more fluid to be added to the system. This happens when the kidneys malfunction and aren't able to remove enough salt and water from the body. The volume of blood in the body increases, so the blood pressure increases.

 Cardiac hypertrophy, including left ventricular hypertrophy, is due to the response of the heart to chronic pressure or volume overload. Left ventricular hypertrophy (LVH) is characterized by thickening
25 of the left ventricular wall, including increased left ventricular mass and increased left ventricular wall thickness, and is defined as a left ventricular mass index exceeding 131 g/m^2 of the body surface area in men, and 100 g/m^2 in women (Savage et al., The Framingham Study, *Circulation*, 75 (1 Pt 2): 26-33 (1987)).

 Left ventricular hypertrophy is independently associated with increased incidence of
30 cardiovascular disease, such as congestive heart failure, ischaemic heart disease, cardiovascular and all-cause mortality, sudden death, and stroke. Regression of left ventricular hypertrophy has been associated with a reduction in cardiovascular risk. It has also been found that the incidence of morbid events in patients with progression of left ventricular hypertrophy is greater than in patients with regression of left ventricular hypertrophy.

35 Dyslipidemia and a serum cholesterol ester fatty acid composition indicating a high dietary intake of saturated and monounsaturated fats, as well as, obesity and hypertension, at age 50 have been

shown to be predictive of the prevalence of LVH at age 70 for men (Sundstroem, J. et al., *Circulation*, February, 836-840 (2001).

Associations have also been found between left ventricular hypertrophy and metabolic syndrome (Lind, L. et al., *J Hypertens*. 13:433-38 (1995).

5 Metabolic syndrome, also known as syndrome X, is characterized by insulin resistance, along with abdominal obesity, hyperinsulinemia, high blood pressure, low HDL and high VLDL. Although the causal relationship between the various components of metabolic syndrome remains to be confirmed, insulin resistance appears to play an important role (Requen, G.M., et al., *N. Eng. J. Med.* 334:374-381 (1996); Despres, J-P., et al., *N. Engl. J. Med.* 334:952-957 (1996); Wajchenberg, B. L., et al., *Diabetes /Metabolism Rev.* 10:19-29 (1994)). Metabolic syndrome patients are at increased risk of developing the cardiovascular complications listed above.

High blood pressure is treated with a variety of therapeutic agents including diuretics, adrenergic blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, or angiotensin blockers, calcium channel blockers or calcium channel antagonists, direct vasodilators, 15 neutral endopeptidase inhibitors, and endothelin antagonists. Diuretics cause the reduction of water and sodium, or block sodium transport, resulting in a reduction in blood pressure. Adrenergic blockers consist of a group of drugs, including alpha-blockers, beta-blockers, and the alpha/beta blocker, labetalol, that block the effects of the sympathetic nervous system, which responds to stress by raising blood pressure. Angiotensin converting enzyme (ACE) inhibitors lower blood pressure by dilating arteries by 20 blockin the effects of the angiotensin-renin-aldosterone system. Angiotensin II receptor antagonists, or angiotensin blockers, lower blood pressure by a mechanism similar to, but more direct than, ACE inhibitors. Calcium channel blockers, or calcium channel antagonists, and direct vasodilators reduce blood pressure by causing blood vessel dilation. Neutral endopeptidase inhibitors produce higher levels of atrial natriuretic peptide, which opens blood vessels.

25 Obesity, a sedentary lifestyle, stress, and excessive amounts of salt or alcohol can play a role in the development of high blood pressure in people who have an inherited sensitivity. Overweight people with high blood pressure are advised to reduce their weight to ideal levels. Changes in diet for those with diabetes, obesity, or high blood cholesterol levels are also important for overall cardiovascular health.

Obesity, which can be defined as a body weight more than 20% above the ideal body weight, is a 30 major health concern in Western societies. It is estimated that about 97 million adults in the United States are overweight or obese. Obesity is the result of a positive energy balance, as a consequence of increased ratio of caloric intake to energy expenditure. The molecular factors regulating food intake and body weight balance are incompletely understood. [B. Staels et al., *J. Biol. Chem.* 270(27), 15958 (1995); F. Lonnquist et al., *Nature Medicine* 1(9), 950 (1995)]. Although the genetic and/or 35 environmental factors leading to obesity are poorly understood, several genetic factors have been identified.

Epidemiological studies have shown that increasing degrees of overweight and obesity are important predictors of decreased life expectancy. Obesity causes or exacerbates many health problems, both independently and in association with other diseases. The medical problems associated with obesity, which can be serious and life-threatening, include type 2 diabetes mellitus, hypertension, elevated plasma insulin concentrations, insulin resistance, dyslipidemias, hyperlipidemia, endometrial, breast, prostate, kidney and colon cancer, osteoarthritis, respiratory complications, such as obstructive sleep apnea, gallstones, arteriosclerosis, heart disease, abnormal heart rhythms, and heart arrhythmias (Kopelman, P.G., *Nature* 404, 635-643 (2000)). Obesity is also associated with metabolic syndrome, cardiac hypertrophy, in particular left ventricular hypertrophy, premature death, and with a significant increase in mortality and morbidity from stroke, myocardial infarction, congestive heart failure, coronary heart disease, and sudden death.

Abdominal obesity has been linked with a much higher risk of coronary artery disease, and with three of its major risk factors: high blood pressure, diabetes that starts in adulthood, and high levels of fats (lipids) in the blood. Losing weight dramatically reduces these risks. Abdominal obesity is further closely associated with glucose intolerance, hyperinsulinemia, hypertriglyceridemia, and other disorders associated with metabolic syndrome (syndrome X), such as raised high blood pressure, decreased levels of high density lipoproteins (HDL) and increased levels of very low density lipoproteins (VLDL) (Montague et al., *Diabetes*, 2000, 49: 883-888).

Obesity and obesity-related disorders are often treated by encouraging patients to lose weight by reducing their food intake or by increasing their exercise level, thereby increasing their energy output. A sustained weight loss of 5% to 10% of body weight has been shown to improve the co-morbidities associated with obesity, such as diabetes, and can lead to improvement of obesity-related disorders such as metabolic syndrome, left ventricular hypertrophy, osteoarthritis, and pulmonary and cardiac dysfunction.

Weight loss drugs used for the treatment of obesity include orlistat (Davidson, M.H. et al. (1999) *JAMA* 281:235-42), dexfenfluramine (Guy Grand, B. et al. (1989) *Lancet* 2:1142-5), sibutramine (Bray, G. A. et al. (1999) *Obes. Res. &*:189-98) and phentermine (Douglas, A. et al. (1983) *Int. J. Obes.* 7:591-5). However, the side effects of these drugs and anti-obesity agents may limit their use. Dexfenfluramine was withdrawn from the market because of suspected heart valvulopathy; orlistat is limited by gastrointestinal side effects; and the use of sibutramine is limited by its cardiovascular side effects, which have led to reports of deaths and its withdrawal from the market in Italy.

In patients with hypertension, effective blood pressure control generally regarded as the most important intervention to reduce left ventricular hypertrophy. Blood pressure reduction and control in hypertensive patients is associated with a significant regression in left ventricular hypertrophy (Cesare, C. et al., *Ital Heart J* 3 (9):514-519 (2002)). However, the variation in 24-hour blood pressure explains only 25-30% of the variation in left ventricular mass (Majahalme, S. et al., *Am J Hypertens.* 9:1110-1118

(1996). Non-pharmacological interventions, such as weight reduction, sodium restriction, and aerobic physical exercise can also reduce left ventricular mass (Ghali, J.K. et al., American Journal of Geriatric Cardiology, 6:38-49 (1997). Weight reduction has also been shown to decrease left ventricular mass in overweight hypertensive patients even more than pharmacological anti-hypertensive treatment (MacMahon, S.W. et al., N Engl J Med., 314; 334-339 (1986).

There is a continuing need for new methods of treating hypertension, hypertension associated with obesity, and hypertension-related disorders, such as cardiac hypertrophy, left ventricular hypertrophy and metabolic syndrome.

The present invention addresses these problems by providing a combination therapy comprising of at least one anti-obesity agent and at least one anti-hypertensive agent for the treatment of obesity, hypertension, hypertension associated with obesity, and hypertension-related disorders. The combination of an anti-obesity agent and an anti-hypertensive agent, at their respective clinical doses, is expected to be more effective than treatment with either agent alone. Treatment with a combination of an anti-obesity agent and an anti-hypertensive agent at sub-clinical doses is expected to produce clinical efficacy with fewer side effects than treatment with either single agent at the monotherapy clinical dose. As a result, combination therapy is more likely to achieve the desired medical benefits without the trial and error involved in prescribing each agent individually during primary care.

The present invention further provides a method for synergistically treating and/or preventing metabolic syndrome comprised of administering the compositions of the present invention in combination with an anti-diabetic agent and/or an anti-dyslipidemic agent to a subject in need thereof. Metabolic syndrome is a multi-factorial disease characterized by obesity, diabetes, hypertension and dyslipidemia. Due to the polygenic nature of the metabolic syndrome etiology, it is predicted that the combination therapies of the present invention will be more effective than currently available monotherapies in treating or reducing the risk of metabolic syndrome. Combinations of different agents with different modes of action, eg. a combination of an anti-obesity agent, an anti-hypertensive agent, with an anti-diabetic agent and/or an anti-dyslipidemic agent, will achieve a better outcome relative to monotherapies using agents with only one mode of action. Additionally, combination therapy is more likely to achieve the desired medical benefits without the trial and error of prescribing each agent alone in primary care.

SUMMARY OF THE INVENTION

The present invention provides compositions comprising at least one anti-obesity agent and at least one anti-hypertensive agent useful in the treatment, control and/or prevention of hypertension, hypertension associated with obesity, and hypertension-related disorders. The present invention further provides compositions comprising at least one anti-obesity agent and at least one anti-hypertensive agent useful in the treatment, control and/or prevention of obesity, and obesity-related disorders.

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