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

(57) Abstract: The present invention relates to compositions comprising an anti-obesity agent and an anti-dyslipidemic agent useful for the treatment of dyslipidemia, dyslipidemia associated with obesity and dyslipidemia-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 DYSLIPIDEMIA

## BACKGROUND OF THE INVENTION

Disorders of lipid metabolism, or dyslipidemias, include various conditions characterized by abnormal concentrations of one or more lipids (i.e. cholesterol and triglycerides), and/or apolipoproteins (i.e., apolipoproteins A, B, C and E), and/or lipoproteins (i.e., the macromolecular complexes formed by the lipid and the apolipoprotein that allow lipids to circulate in blood, such as LDL, VLDL and IDL). Hyperlipidemia is associated with abnormally high levels of lipids, LDL and VLDL cholesterol, and/or triglycerides. Cholesterol is mostly carried in Low Density Lipoproteins (LDL), and this component is commonly known as the "bad" cholesterol because it has been shown that elevations in LDL-cholesterol correlate closely to the risk of coronary heart disease. A smaller component of cholesterol is carried in the High Density Lipoproteins and is commonly known as the "good" cholesterol. In fact, it is known that the primary function of HDL is to accept cholesterol deposited in the arterial wall and to transport it back to the liver for disposal through the intestine. Although it is desirable to lower elevated levels of LDL cholesterol, it is also desirable to increase levels of HDL cholesterol. Generally, it has been found that increased levels of HDL are associated with lower risk for coronary heart disease (CHD). See, for example, Gordon, et al., Am. J. Med., *62*, 707-714 (1977); Stampfer, et al., N. England J. Med., *325*, 373-381 (1991); and Kannel, et al., Ann. Internal Med., *90*, 85-91 (1979). An example of an HDL raising agent is nicotinic acid, a drug with limited utility because doses that achieve HDL raising are associated with undesirable effects, such as flushing.

Dyslipidemias were originally classified by Fredrickson according to the combination of alterations mentioned above. The Fredrickson classification includes 6 phenotypes (i.e., I, IIa, IIb, III, IV and V) with the most common being the isolated hypercholesterolemia (or type IIa) which is usually accompained by elevated concentrations of total and LDL cholesterol. The initial treatment for hypercholesterolemia is often aimed at avoiding risk factors such as obesity, and at modifying the diet to one low in fat and cholesterol, coupled with appropriate physical exercise, followed by drug therapy when LDL-lowering goals are not met by diet and exercise alone.

A second common form of dyslipidemia is the mixed or combined hyperlipidemia or type IIb and III of the Fredrickson classification. This dyslipidemia is often prevalent in patients with type 2 diabetes, obesity and metabolic syndrome. In this dyslipidemia there are modest elevations of LDL-cholesterol, accompanied by more pronounced elevations of small dense LDL-cholesterol particles, VLDL and/or IDL (i.e., triglyceride rich lipoproteins), and total triglycerides. In addition, concentrations of HDL are often low.

The risk of atherosclerosis and coronary artery or carotid artery disease, and therefore the risk of having a heart attack or stroke, increases as the total cholesterol level increases. Atherosclerosis refers to

a disease in which the wall of an artery becomes thicker and less elastic. In atherosclerosis, fatty material accumulates under the inner lining of the arterial wall. Atherosclerosis can affect the arteries of the brain, heart, kidneys, other vital organs, and the arms and legs. When atherosclerosis develops in the arteries that supply the brain (carotid arteries), a stroke may occur; when it develops in the arteries that supply the heart (coronary arteries), a heart attack may occur. Arteries affected with atherosclerosis lose their elasticity, an as the atheromas (patchy thickening in the inner lining of the artery) grow, the arteries narrow. With time, the atheromas collect calcium deposits, may become brittle, and may rupture. Blood may then enter a ruptured atheroma, making it larger, so that it narrows the artery even more. A ruptured atheroma also may spill its fatty contents and trigger the formation of a blood clot (thrombus). The clot may further narrow or even occlude the artery, or it may detach and float downstream where it causes an occlusion (embolism).

Causes of high cholesterol levels include a diet high in saturated fats and cholesterol; cirrhosis, poorly controlled diabetes, underactive thyroid gland, overactive pituitary gland, kidney failure, porphyria, and heredity. Causes of high triglyceride levels include excess calories in diet, severe uncontrolled diabetes, kidney failure, acute alcohol abuse, certain drugs, and heredity.

Obesity is one of the factors contributing to high levels of certain lipids, such as VLDL and LDL, as a result, the initial treatment for overweight patients with high cholesterol or triglyceride levels is to lose weight. Levels of fatty material such as cholesterol and triglycerides may also be controlled with a variety of drugs. Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors block the synthesis of cholesterol and enhance the removal of low density lipoproteins from the bloodstream. HMG-CoA synthase inhibitors inhibit the biosynthesis of hydroxymethylglutaryl-coenzyme A from acetyl-coenzyme A. Lipoprotein synthesis inhibitors reduce the rate of very low density lipoprotein production. Bile acid sequestrants, or absorbers, bind bile acids in the intestine and enhance low density lipoprotein removal from the bloodstream. Renin angiotensin system inhibitors may also decrease the formation of atherosclerotic plaques. Cholesterol absorption inhibitors inhibit intestinal cholesterol absorption by blocking the movement of cholesterol from the intestinal lumen into enterocytes of the small intestinal wall. Cholesteryl ester transfer protein (CETP) inhibitors inhibit the CETP mediated transport of various cholesteryl esters and triglycerides from HDL to LDL and VLDL. Other compounds reduce serum cholesterol levels primarily by mechanisms of action such as squalene synthetase inhibition, acyl coenzyme A - cholesterol acyl transferase (ACAT) inhibition, triglyceride synthesis inhibition, MTP inhibition, bile acid sequestration, and transcription modulation, such as agonists or antagonists of nuclear hormones.

Additionally, three sub-types of peroxisome proliferator activated receptor (PPAR) have been discovered and described; they are peroxisome proliferator activated receptor alpha (PPARα), peroxisome proliferator activated receptor gamma (PPARγ), and peroxisome proliferator activated receptor delta (PPARδ). Fibric acid derivatives such as clofibrate, fenofibrate, benzafibrate, ciprofibrate,

beclofibrate and etofibrate, as well as gemfibrozil, each of which are PPARα ligands and/or activators, produce a substantial reduction in plasma triglycerides as well as some increase in HDL. The effects on LDL cholesterol are inconsistent and might depend upon the compound and/or the dyslipidemic phenotype. For these reasons, this class of compounds has been primarily used to treat hypertriglyceridemia (i.e, Fredrickson Type IV and V) and/or mixed hyperlipidemia.

It has been disclosed in WO97/28149 that agonists of PPARδ are useful in raising HDL plasma levels. WO97/27857, 97/28115, 97/28137 and 97/27847 disclose compounds that are useful as antidiabetic, antiobesity, anti-atherosclerosis and antihyperlipidemic agents, and which may exert their effect through activation of PPARs. PPARα agonists should improve the lipid profile and alleviate dyslipidemias by reducing elevated LDL levels and elevated triglyceride levels and/or increasing HDL levels.

Left ventricular hypertrophy (LVH), which is characterized by thickening of the left ventricular wall, is due to the response of the heart to chronic pressure or volume overload. Left ventricular hypertrophy 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 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.

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). The impact of obesity, dyslipidemia, and the evidence of high dietary intake of saturated fats on left ventricular hypertrophy was found to be independent of the history of ischemic heart disease, valvular disease, and the use of antihypertensive medication. Associations have also been found between left ventricular hypertrophy and metabolic syndrome (Lind, L. et al., J Hypertens. 13:433-38 (1995).

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.

Obesity, which can be defined as a body weight more than 20% above the ideal body weight, is a 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 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, metabolic syndrome, endometrial, breast, prostate, kidney, and colon cancer, osteoarthritis, respiratory complications, such as obstructive sleep apnea, gallstones, arterioscelerosis, heart disease, abnormal heart rhythms, and heart arrythmias (Kopelman, P.G., Nature 404, 635-643 (2000)).

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 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.

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 and can lead to improvement of obesity-related disorders such as diabetes, 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-

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