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(71) Applicant *(for all designated States except US)*: JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ENGELEN, Marc Alois Celine Maria [BE/BE]; Janssen Animal Health BVBA, Turnhoutseweg 30, B-2340 Beerse (BE). HOEBEN, Dagmar Theo Coleta Maria Ghislain [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE).

(74) Common Representative: JANSSEN PHARMACEUTICA N.V.; Turnhoutseweg 30, B-2340 Beerse (BE).

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(54) Title: INTERMITTENT DOSING REGIMEN FOR OVERWEIGHT AND OBESE SUBJECTS

(57) Abstract: The present invention concerns an intermittent dosing regimen for the treatment of obesity or the reduction of body weight wherein a pharmaceutical composition containing an apoB secretion/MTP inhibitor is administered to a subject in need thereof for a period of time, then withheld for a period of time, and again administered for a period of time. The intermittent regimen may be repeated depending on the response in the subject that is being sought.

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INTERMITTENT DOSING REGIMEN FOR OVERWEIGHT AND OBESE SUBJECTS

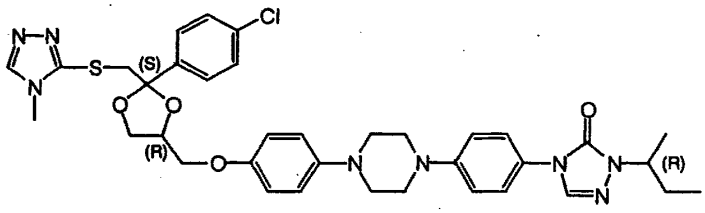
[0001] The present invention concerns an intermittent dosing regimen for the treatment of obesity or the reduction of body weight wherein a pharmaceutical composition containing an apoB secretion/MTP inhibitor is administered to a subject in need thereof for a period of time, then withheld for a period of time, and again administered for a period of time. The intermittent regimen may be repeated depending on the response in the subject that is being sought.

[0002] The microsomal triglyceride transfer protein (MTP) catalyses the transfer of lipids such as triglycerides, cholesteryl esters and phosphatidylcholine between phospholipid surfaces. MTP is found in the liver and intestine, both organs which produce lipoproteins. MTP is necessary for the production of apolipoprotein B (apoB) containing plasma lipoproteins, in particular apoB-100 within the liver, and apoB-48 within the intestine. ApoB-100 is the main protein component of VLDL (very low density lipoproteins). ApoB-48 is the main protein component of chylomicrons. Compounds that inhibit MTP reduce the secretion of apoB-containing lipoproteins and therefore have the potential to decrease VLDL and triglyceride plasmatic levels, and also intestinal lipid absorption. High VLDL plasmatic levels are a major risk factor for atherosclerosis and coronary artery diseases. Hence an intermittent dosing regimen of the present invention using apoB secretion/MTP inhibitors may be useful in the prevention, management and treatment of obesity, diabetes mellitus, non-insulin dependent diabetes mellitus, coronary heart disease, pancreatitis, mixed dyslipidemia, hyperlipemia, post-prandial hyperlipemia, hypercholesterolemia, hypertriglyceridemia, osteoarthritis and atherosclerosis.

[0003] A variety of apoB secretion/MTP inhibitors are known to one of ordinary skill in the art. Although any apoB secretion/MTP inhibitor may be used in the intermittent dosing regimens of the present invention, generally preferred apoB secretion/MTP inhibitors include those compounds that are disclosed in, for example, European patent applications EP-0,643,057, EP-0,719,763, EP-0,753,517, EP-0,764,647, EP-0,765,878, EP-0,779,276, EP-0,779,279, EP-0,799,828, EP-0,799,829, EP-0,802,186, EP-0,802,188, EP-0,802,192, and EP-0,802,197; international patent applications WO-96/13499, WO-96/33193, WO-96/40640, WO-97/26240, WO-97/43255, WO-97/43257, WO-98/16526, WO-98/23593, WO-00/32582,

WO-02/081460, WO-02/42271 and WO-02/20501; and U.S. patents US-5,595,872; US-5, 646,162; US-5,684,014; US-5,712,279; US-5,739,135 and US-5,789,197.

[0004] A particular apoB secretion/MTP inhibitor is mitratapide which is the INN (International Non Proprietary Name) for the compound (-)-[2S-[2α,4α(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl)-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]-phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one having the following structure.



[0005] Mitratapide has been described in WO-96/13499 as compound (40) having apolipoprotein B (apoB) secretion and microsomal triglyceride transfer protein (MTP) inhibiting properties and therefore being useful as a lipid lowering agent.

[0006] Warm-blooded animals such as humans and companion animals, in particular dogs and cats, with an excessive accumulation of body fat to the point of being 20% or more over ideal body weight are considered obese. Already an overweight of 10% over ideal body weight is considered a health risk. Obesity is known to cause liver disease, hypertension, constipation, heat intolerance, and increased risk under anaesthesia. Obese warm-blooded animals may have trouble breathing and may suffer from serious discomfort and body dysfunction and have life expectancies less as usual. Although obesity in warm-blooded animals is usually caused by too little exercise and intake of too many calories, a number of warm-blooded animals become obese due to genetic predisposition or hormonal disorders.

[0007] Subjects suffering from obesity or overweight can be treated by administering an apoB secretion/MTP inhibitor. A pharmaceutical composition comprising the apoB secretion/MTP inhibitor is typically administered once or several times a day during a period of several weeks or months until the weight of the subject is equal to or close to its ideal body weight.

[0008] It has been observed that the administration of an apoB secretion/MTP inhibitor during a continuous period of eight weeks resulted in an initial reduction of body weight which however levelled off after three weeks. Sustained administration of the apoB secretion/MTP inhibitor did not result in a further reduction of body weight.

[0009] It has now been found that an intermittent treatment schedule or dosing regimen with alternating periods of administration and non-administration of the apoB secretion/MTP inhibitor can overcome the problem of body weight reduction levelling off. This intermittent treatment schedule or dosing regimen comprises of a period of several weeks during which the subject is administered an apoB secretion/MTP inhibitor followed by a period of several weeks of non-administration of the apoB secretion/MTP inhibitor, again followed by a period of several weeks of administration of the apoB secretion/MTP inhibitor. In order to achieve a further reduction of body weight, it is possible to repeat this intermittent treatment schedule two, three or four times.

[0010] For the purposes of this invention, the term "subject" includes warm-blooded animals, preferably mammals, including humans and companion animals such as dogs, cats, rabbits, ferrets, guinea pigs and the like.

[0011] The term "overweight" as used in the present invention refers to a body weight that is above the ideal body weight of a subject. Ideal body weight for human subjects can be determined using the "Body Mass Index" (BMI). The BMI is defined as the body weight in kilograms divided by the square of the height in meters. A BMI ranging from 20 to 25 is generally considered as ideal and human subjects having a BMI higher than 25 are considered overweight. Another method to determine ideal body for human subjects is based on the Metropolitan Life tables created by the Metropolitan Life Insurance company. Ideal body weight for companion animals, in particular dogs, can be looked up in breed standards, providing breed-specific information on body weight and height at withers for male and female animals.

[0012] The term "therapeutically effective amount of an apoB secretion/MTP inhibitor" as used herein, means that amount of an apoB secretion/MTP inhibitor that elicits the biological or medicinal response in the subject that is being sought, which includes alleviation of the symptoms of the condition being treated. The therapeutically effective amount can be determined using routine optimization techniques and is dependent upon the particular condition to be treated, the condition

of the subject, the route of administration, the formulation, and the judgment of the practitioner and other factors evident to those skilled in the art. A therapeutically effective amount may be achieved by multiple dosing.

[0013] The regimen which is the basis of the present invention is an intermittent dosing regimen wherein a pharmaceutical composition containing an apoB secretion/MTP inhibitor is administered for a period of time, then withheld for a period of time, and again administered for a period of time. These three periods of time may be of the same or of different length. The length of each period can be expressed in days or in weeks and – dependent upon the specific apoB secretion/MTP inhibitor that is being used and the response of the subject - may range from 1 to 56 days or from 1 to 8 weeks. Said intermittent regimen may be repeated two, three, four or more times depending on the response in the subject that is being sought. The period of time between two intermittent dosing regimens is variable and in practice ranges from 2 to 6 months.

[0014] The intermittent dosing regimen consists of three terms which can be all of different length. Hence an infinite number of intermittent dosing regimens is possible by varying the length of each of the three terms. From a practical viewpoint it is preferable to express each term as a number of weeks so that one intermittent dosing regimen is defined as **Aw-Bw-Cw** wherein A represents the number of weeks during which an apoB secretion/MTP inhibitor is administered, B represents the number of weeks during which administration is withheld, and C represents the number of weeks during which an apoB secretion/MTP inhibitor is again administered. In practice, the first administration period ranges from 2 to 4 weeks, the period during which administration is withheld ranges from 2 to 4 weeks, and the second administration period ranges from 2 to 4 weeks. For instance, in a 4w-3w-4w dosing regimen, the pharmaceutical composition comprising the apoB secretion/MTP inhibitor is administered for 4 weeks, withheld for 3 weeks, and again administered for 4 weeks. Practical dosing regimens are 4w-4w-4w, 4w-3w-4w, 4w-2w-4w, 3w-3w-3w, 3w-2w-3w, and 2w-2w-2w. The three terms of the intermittent dosing regimen may also be expressed in number of days.

[0015] The three terms of the intermittent dosing regimen may also be defined alternatively with a starting date and a final date. Accordingly a 4w-3w-4w dosing regimen can be expressed as 1-28/29-49/50-77 which refers to administration of an apoB secretion/MTP inhibitor from day 1 to day 28, no administration from day 29 to

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