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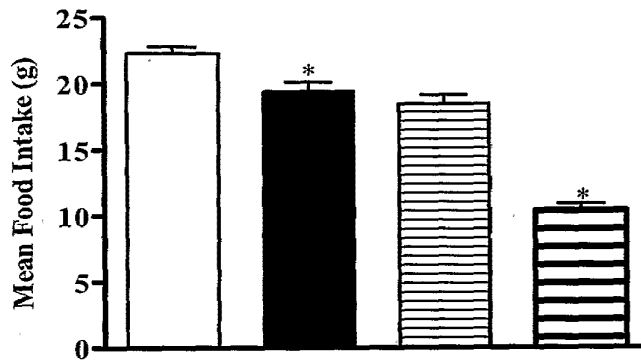
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(54) Title: METHOD OF TREATMENT OF OBESITY WITH AN MTP INHIBITOR IN CONJUNCTION WITH AN INCREASED-FAT DIET



Mean ( $\pm$  SEM) daily food intake of rats on a high or low fat diet during the 3 day treatment period. Empty bar = low fat vehicle placebo, solid black bar = low fat dirlotapide, small horizontal slashes = high fat vehicle, thick horizontal slashes = high fat dirlotapide. \* Significantly different from appropriate diet vehicle.

(57) Abstract: A method of treating a subject suffering from obesity or related eating disorders and/or reducing food consumption, the method comprising administering to the subject a therapeutically effective amount of an MTP inhibitor in conjunction with an increased-fat diet.

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- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

METHOD OF TREATMENT OF OBESITY WITH AN MTP INHIBITOR IN CONJUNCTION WITH AN INCREASED-FAT DIET

**Field of the Invention**

The present invention generally relates to therapy for obesity or related eating disorders and/or reducing food consumption using MTP inhibitors in conjunction with an increased-fat diet.

**Background of the Invention**

Obesity is a major public health concern because of its increasing prevalence and associated health risks. Moreover, obesity may affect a person's or animal's quality of life through limited mobility and decreased physical endurance as well as through social, academic and job discrimination.

Inhibitors of microsomal triglyceride transfer protein (MTP) and/or Apo B secretion are useful in reducing food intake in mammals (European patent application publication No. 1 099 438 A2), reducing intestinal fat absorption (European patent application publication No. 1 099 439 A2) and for treating obesity and associated diseases. See, for example, PCT patent application publication Nos. WO 03/002533, WO 2005/046644 and WO 2005/080373, and US 6,066, 653.

However, it has been reported in WO 2005/087234 that use of inhibitors of MTP can cause side effects such as hepatotoxicities.

The instant inventors have also found that the MTP inhibitor dirlotapide (disclosed in WO 03/002533) may cause emesis when administered according to conventional treatment regimens.

Thus, there is a need to develop more effective methods for treating obesity or related eating disorders and/or reducing food consumption using MTP inhibitors.

**Summary of the Invention**

The invention provides a method of treating a subject suffering from obesity or related eating disorders and/or reducing food consumption, the method comprising administering to the subject a therapeutically effective amount of an MTP inhibitor in conjunction with an increased-fat diet.

The invention also provides the use of an MTP inhibitor in the manufacture of a medicament for treating a subject suffering from obesity or related eating disorders and/or reducing food consumption, wherein a therapeutically effective amount of an MTP inhibitor is administered in conjunction with an increased-fat diet.

5 The invention also provides a method of treating a subject suffering from obesity or related eating disorders and/or reducing food consumption, the method comprising administering to the subject a therapeutically effective amount of an MTP inhibitor in conjunction with an increased-fat diet optionally followed by administration of at least one step-wise, escalating dosage of the MTP inhibitor and, optionally, followed by a  
10 weight maintenance/management or retraining phase.

The invention also provides the use of an MTP inhibitor in the manufacture of a medicament for treating a subject suffering from obesity or related eating disorders and/or reducing food consumption, wherein a therapeutically effective amount of an MTP inhibitor is administered in conjunction with an increased-fat diet optionally  
15 followed by administration of at least one step-wise, escalating dosage of the MTP inhibitor and, optionally, followed by a weight maintenance/management or retraining phase.

The invention also provides a method of treating a subject suffering from obesity or related eating disorders and/or reducing food consumption, the method comprising  
20 administering to the subject an MTP inhibitor in conjunction with an increased-fat diet such that the amount of said MTP inhibitor required to be therapeutically effective is reduced compared with conventional treatment regimens.

The invention also provides a method of increasing the rate of weight loss in a subject suffering from obesity or related eating disorders, the method comprising  
25 administering to the subject a therapeutically effective amount of an MTP inhibitor in conjunction with an increased-fat diet.

The invention also provides a method of treating a subject suffering from obesity or related eating disorders and/or reducing food consumption, the method comprising administering to the subject an initial amount of an MTP inhibitor effective to ameliorate  
30 the obesity or disorder yet low enough to reduce the side effects associated with administration of the MTP inhibitor in conjunction with an increased-fat diet, optionally

followed by administration of at least one step-wise, escalating dosage of the MTP inhibitor and, optionally, followed by a weight maintenance/management or retraining phase.

5 The invention also provides a method of treating a subject suffering from obesity or related eating disorders and/or reducing food consumption, the method comprising administering to the subject an initial amount of an MTP inhibitor in the range of 0.025 to 0.30 mg/kg/day in conjunction with an increased-fat diet, optionally followed by administration of at least one step-wise, escalating dosage of the MTP inhibitor and, optionally, followed by a weight maintenance/management or retraining phase.

10 The invention further provides a method for inhibiting MTP in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an MTP inhibitor in conjunction with an increased-fat diet.

15 The invention further provides a method of treating a subject suffering from obesity or related eating disorders and/or reducing food consumption, or a method for inhibiting MTP in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an MTP inhibitor in conjunction with an increased-fat diet, and wherein said administration is in combination with at least one additional pharmaceutical agent, such as another anti-obesity agent.

20 Also provided is a method of weight control in a subject the method comprising administering to the subject an effective weight-controlling amount of an MTP inhibitor in conjunction with an increased-fat diet. The MTP inhibitor may be used alone or in combination with at least one additional pharmaceutical agent, preferably an anti-obesity agent.

25 In some embodiments the MTP inhibitor is dirilotapide ((S)-N-{2-[benzyl(methyl)amino]-2-oxo-1-phenylethyl}-1-methyl-5-[4'-trifluoromethyl][1,1'-biphenyl]-2-carboxamido]-1H-indole-2-carboxamide).

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