Use of gastrointestinal lipase inhibitors

Diabetes mellitus is a condition characterized by an abnormality of glucose utilization and associated with elevation of blood glucose concentration. The most common form of diabetes mellitus is non-insulin dependent diabetes mellitus (NIDDM: Type II). Over 10 million people in the United States alone are affected with type II diabetes mellitus. The initial approach in treating obese patients affected with type II diabetes mellitus is weight reduction. Other types of treatment include oral hypoglycemics and insulin. See, Gregerman, MD, Section 10, Metabolic and Endocrinological Problems, Chapter 72, Diabetes Mellitus, pages 977-989.

The invention relates to the use of a gastrointestinal lipase inhibitor for the manufacture of oral medicaments for treating or preventing type II diabetes mellitus. In another aspect the invention relates to an oral medicament for treating or preventing type II diabetes mellitus characterized in that it contains a gastrointestinal lipase inhibitor. The gastrointestinal lipase inhibitor is preferably tetrahydrolipstatin.

Tetrahydrolipstatin, also known as orlistat, is a known compound useful for the control or prevention of obesity and hyperlipidemia. See, U.S. Patent No. 4,598,089, issued July 1, 1986, which also discloses processes for making tetrahydrolipstatin.

It has now surprisingly been found that a gastrointestinal lipase inhibitor, preferably tetrahydrolipstatin, when administered orally is useful in the treatment and prevention of type II diabetes mellitus. Preferably, from 60 to 720 mg per day of the gastrointestinal lipase inhibitor are orally administered in divided doses two to three times per day.

Preferred is wherein from 180 to 360 mg, most preferably 360 mg per day of a gastrointestinal lipase inhibitor is administered to a subject, preferably in divided

doses two or, particularly, three times per day. The subject is preferably an obese or overweight human, i.e. a human with a body mass index of 25 or greater. Generally, it is preferred that the gastrointestinal lipase inhibitor be administered within about one or two hours of ingestion of a meal containing fat. Generally, for preventing type II diabetes mellitus it is preferred that treatment be administered to 1) a human who has a strong family history of type II diabetes mellitus and has obtained a body mass index of 25 or greater; or 2) a human with impaired glucose tolerance who has obtained a body mass index of 25 or greater. As used herein, the term „strong family history" means a human with at least one first degree relative who has type II diabetes mellitus. Generally, impaired glucose tolerance would be diagnosed by an oral glucose tolerance test.

Tetrahydrolipstatin can be administered to humans in conventional oral compositions, such as, tablets, coated tablets, hard and soft gelatin capsules, emulsions or suspensions. Examples of carriers which can be used for tablets, coated tablets, dragées and hard gelatin capsules are lactose, maize starch or derivatives thereof, talc, stearic acid or its salts and the like. Suitable carriers for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Moreover, the pharmaceutical preparations can contain preserving agents, solubilizers, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, coloring agents, flavoring agents, salts for varying the osmotic pressure, buffers, coating agents or antioxidants. They can also contain still other therapeutically valuable substances. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods known in the pharmaceutical art.

Preferably, tetrahydrolipstatin is administered according to the formulation of Example 1.

EXAMPLE 1

Ingredient	Quantity mg/Capsule
Tetrahydrolipstatin	120.00
Microcrystalline Cellulose (AVICEL PH-101)	93.60
Sodium Starch Glycolate (PRIMOJEL)	7.20
Sodium Lauryl Sulfate	7.20
Polyvinylpyrrolidone (Povidone (K-30))	12.00
Purified Water*	
Talc	0.24
Total	240.24 mg

*Removed during processing

Procedure:

1. Blend tetrahydrolipstatin, microcrystalline cellulose, and sodium starch glycolate in a suitable mixer.
2. Granulate with a solution of polyvinylpyrrolidone and sodium lauryl sulfate in purified water.
3. Pass the granulation through an extruder and pass the extrudate through a spheronizer to form pellets.
4. Dry the pellets at 30°C.
5. Add talc and mix.
6. Fill into hard gelatin capsules.

EXAMPLE 2

Ingredient	Quantity mg/Capsule
Tetrahydrolipstatin	60
Microcrystalline Cellulose	46.8
Sodium Starch Glycolate	3.6
Sodium Lauryl Sulfate	3.6
Polyvinylpyrrolidone	6.0
Purified Water*	
Talc	0.12
Total	120.12 mg

*Removed during processing.

Procedure:

1. Blend tetrahydrolipstatin, microcrystalline cellulose, and sodium starch glycolate in a suitable mixer.
2. Granulate with solution of polyvinyl pyrrolidone and sodium lauryl sulfate in purified water.
3. Pass the granulation through an extruder and pass the extrudate through a spheronizer to form pellets.
4. Dry the pellets at 30°C.
5. Add talc and mix.
6. Fill into hard gelatin capsules.

EXAMPLE 3

Ingredient	Quantity mg/Capsule	
Tetrahydrolipstatin	60	120
Lactose	40	80
Microcrystalline Cellulose	60	120
Sodium Lauryl Sulfate	5.7	11.4
Sodium Starch Glycolate	20	40
Polyvinylpyrrolidone	10	20
Purified Water*		
Talc	0.2	0.4
Total	195.9 mg	391.8 mg

*Removed during processing.

Procedure:

1. Blend tetrahydrolipstatin, lactose, microcrystalline cellulose and sodium starch glycolate in a suitable mixer.
2. Granulate with a solution of polyvinylpyrollidone and sodium lauryl sulfate in purified water.
3. Pass the granulation through an extruder, and pass the extrudate through a spheronizer to form pellets.
4. Dry the pellets at 30°C.
5. Add talc and mix.
6. Fill into hard gelatin capsules.

EXAMPLE 4

Study of Patients with Non-insulin Dependent Diabetes Mellitus:

A one-year double-blind, placebo-controlled study in 321 non-insulin dependent diabetics stabilized on sulfonylureas, was conducted. The results indicate

that 30% of patients treated with tetrahydrolipstatin (120 mg, three-times a day) achieved at least a 5% reduction in baseline body weight compared to 13% of the placebo patients ($p<0.001$). Tetrahydrolipstatin also improved glycemic control in these patients as evidenced by statistically significant reductions in hemoglobin Alc levels (0.5% improvement versus placebo, $p<0.001$) and in doses of sulfonylureas. In this study, 43% of the patients treated with tetrahydrolipstatin were able to reduce or discontinue their oral hypoglycemic medications compared to 29% of the patients receiving placebo, $p<0.01$. Mean levels of fasting glucose remained essentially unchanged compared to baseline in the tetrahydrolipstatin group (-0.02 mmol/L) while there was an increase (+0.54 mmol/L) in the placebo group, $p<0.05$. There were statistically significant improvements in total cholesterol, LDL-cholesterol, LDL/HDL ratio and triglycerides in the group treated with tetrahydrolipstatin compared to placebo.

EXAMPLE 5

Glucose Tolerance in Obese Patients:

Two-year studies that included oral glucose tolerance tests were conducted in obese patients whose baseline oral glucose tolerance test (OGTT) status was either normal, impaired or diabetic. The progression from a normal OGTT as baseline to a diabetic or impaired OGTT following two years of treatment with tetrahydrolipstatin (n=242) (120 mg administered orally three-times a day) or placebo (n=201) were compared. Following treatment with tetrahydrolipstatin, 0.0% and 6.2% of the patients progressed from normal to diabetic and impaired respectively, compared to 1.5% and 12.4% of the placebo treatment group respectively, $p<0.01$. In patients found to have an impaired OGTT at baseline, the percent of patients improving to normal or deteriorating to diabetic status following one and two years of treatment with tetrahydrolipstatin compared to placebo are presented below and the difference between treatment groups was significant:

Baseline OGTT Status Intent-to-treat population		Patients Normal Post-Treatment	Patients Diabetic Post-Treatment
Impaired		one year of treatment	one year of treatment
Placebo	n=48	45.8%	10.4%
tetrahydrolipstatin*	n=115	72.2%	2.6%
Impaired		2 years of treatment	2 years of treatment
Placebo	n=40	47.5%	7.5%
tetrahydrolipstatin**	n=60	71.7%	1.7%

* $p<0.01$ and ** $p\leq0.05$, Fisher's Exact Test

* C L M S *

Claims

1. Use of a gastrointestinal lipase inhibitor for the manufacture of oral medicaments for treating or preventing type II diabetes mellitus.

2. The use according to claim 1 wherein the gastrointestinal lipase inhibitor is tetrahydrolipstatin.

3. An oral medicament for treating or preventing type II diabetes mellitus characterized in that it contains an effective amount of a gastrointestinal lipase inhibitor.

4. An oral medicament as in claim 3, wherein the gastrointestinal lipase inhibitor is tetrahydrolipstatin.

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