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With amended claims.

(54) Title: USE OF KETOCONAZOLE AND RELATED SUBSTANCES IN MEDICAMENTS FOR TREATMENT OF TYPE II DIABETES

(57) Abstract

The use of ketoconazole or molecules resembling ketoconazole but with some side-chains, not affecting the biological activity compared to ketoconazole, changed, for the manufacture of drugs for medical treatment of diabetes mellitus type II as well as for counteracting the other risk factors being part of the Metabolic Syndrome (also known as "the deadly quartet" or "Syndrome X" or the "Insulin Resistance Syndrome").

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Use of ketoconazole and related substances in medicaments for treatment of type II diabetes

The present invention relates to the use of ketoconazole or molecules resembling ketoconazole but with some side-chains, not affecting the biological activity compared to ketoconazole, changed for manufacturing drugs for treatment of diabetes mellitus type II.

The drug ketoconazole (Trade name Fungoral™) is a well-documented drug for treatment of fungal infections. The process of making ketoconazole is well known and described. In this invention Fungoral™ capsules aimed at oral administration should be used. This means that Fungoral™ should be administered the same way (oral) and in the same composition that is already well-known on the market for treatment of fungal infections the oral route. Therefor it is not considered necessary to further describe the process of making Fungoral™. For the same reason it is not considered necessary to give a full, clear, concise and exact term of this drug, since it is already well-known for persons skilled in the art of medicine.

The drug comprising ketoconazole (Trade name Fungoral™) and chemically closely related substances, the mode of operation of which is to influence the normal cortisol synthesis in the adrenal glands in such a way that the production of biologically perfectly acting cortisol is partly inhibited, is intended to be used for medical treatment of diabetes mellitus type II in men and women as well as for counteracting the risk factors which are parts of the Metabolic Syndrome (also known as "the deadly quartet" or "Syndrome X" or the "Insulin Resistance Syndrome"), which is characterised by an accumulation of risk factors for cardiovascular disease, stroke and diabetes mellitus type II, i.e. insulin resistance, hyperinsulinemia, abdominal obesity, (caused by an accumulation of intra-abdominal fat), elevated serum lipids, and raised blood pressure, as well as reducing the risk of development of these diseases.

In this new invention ketoconazole shall be administered the oral route in doses of 100 - 800 mg daily. The drug can be administered once or several times daily. At present a dose of 400 mg administered in the evening has been proven to be the best mode. However, we also claim that administration at other points of time, and in other doses (100 - 800 mg) can be equally effective.

Since ketoconazole is also inhibiting the normal production of testosterone in men, it is possible that this sex needs a certain amount of testosterone supplementation when treated with ketoconazole, to have an optimal effect of the treatment.

We have investigated a group of people with diabetes mellitus type II. They have been treated with ketoconazole during 2 and 6 weeks, respectively. Investigations before and after treatment have shown a decrease in blood glucose measured either in the fasting state or at 2 hours after an intravaneus glucose infusion, and most important, a remarkable improvement of insulin sensitivity. More exact data from these studies are given in the tests described below.

Since a decreased insulin sensitivity is a central part of "The metabolic syndrome", also known as "The deadly quartet", "Syndrome X" or the "Insulin Resistance Syndrome" we also claim that fungoral treatment to people with risk factors according to this syndrome should be expected to be effective also for treatment of these specific risk factors (abdominal obesity, hypertension, elevated blood lipids) as well as for decreasing the risk for diseases caused by these risk factors (Cardiovascular disease such as coronary artery disease, other arteriosclerotic manifestations including stroke).

The mechanism of the action of ketoconazole is that the substance influence the cortisol synthesis of the adrenal glands in such a way that a sub-fraction of a biologically non-perfect substance similar to cortisol, so called

"crippled cortisol", is formed instead of the normal cortisol molecule.

The cortisol antagonistic effect of the drug is considered to have a central importance for the positive effects on the risk factors mentioned above, decreasing the metabolic activity of fat inside the abdominal cavity, which in turn leads to a decreased fat infiltration of the liver, improving the glucose homeostasis over the liver and peripherally in the tissues in turn leading to improvement of diabetes mellitus type II (decreasing blood glucose and increasing insulin sensitivity), reducing the serum lipids through improvement of the regulating mechanisms in the liver and also inhibiting cholesterol synthesis by a direct effect on the adrenal glands. A positive effect on the blood pressure can also be expected via the cortisol-antagonistic effect.

The scientific basis for these effects can be explained by an inhibition of the physiologically increased cortisol secretion rate that is known to be present under the conditions described above. (The metabolic syndrome and its synonyms described above). This increased cortisol secretion can per se explain all the parts of the syndrome described including the development of diabetes mellitus type II. The scientific explanation for the beneficial effects of ketoconazole on the treatment of diabetes mellitus type II is its effects of decreasing the secretion of biologically active cortisol.

The basic substance is ketoconazole in the chemical form which is known and well documented in the literature. This substance can be further chemically modified while maintaining the same biological effects by exchange of different molecular side chains. These substances similar to ketoconazole can then be expected to have similar and/or better effects on the cortisol inhibiting mechanism, which is described above.

A positive effect on the treatment of patients with diabetes mellitus type II with ketoconazole has been shown in that

after the administration of ketoconazole a reduction of the insulin insensitivity (resistance), which is often associated with this disease, has been measured. This has been measured as an improved (i.e. reduced) insulin resistance measured with a so called euglychemic glucose clamp method. Thus, the examined patients have improved with regard to their diabetes, measured in the above described way, which in parallell also have resulted in lower blood glucose after treatment compared to before treatment.

The category of patients, that would have an especially good use of ketoconazole are patients with diabetes mellitus type II with insulin insensitivity and despite treatment with usual anti-diabetic drugs and/or insulin still have remaining elevated glucose values in the blood in fasting condition as well as after a meal. The investigated patients had decreased insulin sensitivity compared to healthy persons, measured by euglychemic glucose clamp. Supply of ketoconazole to this category of patients has been shown to have a positive and specific effect on the insulin insensitivity in such a way that their diabetes mellitus type II was improved. This was measured as improved insulin sensitivity and lower blood glucose.

Other positive effects have also been detected among these patients: Reduced cholesterol levels in the plasma as well as decreasing blood pressure values.

<u>Results of Clinical tests of women with diabetes mellitus type II, treated with ketoconazole.</u>

Group 1 consists of 3 patients (mean age: 46 years) treated with ketoconazole for 2 weeks, administered orally 22.00 in the evening in the dose of 400 mg.

Group 2 consists of 5 patients (mean age: 51 years) treated with ketoconazole for 6 weeks, administered orally 22.00 in the evening in the dose of 400 mg.

Results are expressed as mean values within groups.

Variables studied	Group 1		Group 2	
	Before t.	After t.	Before t.	After t.
Fasting blood glucose (mmol/L)	10.20	8.77	7.20	7.10
Blood glucose (mmol/L) 2 hours after start of an i.v. glucose infusion	9.73	7.90	6.48	5.76
GIR (glucose infusion rate during euglycemic glucose clamp expressed as mg glucose per minute divided by lean body mass), indicating insulin sensitivity	0.9	1.85	2.97	4.32
Fasting serum total cholesterol (mmol/L)	5.80	5.67	4.80	4.10
Systolic blood pressure (mm Hg) measured after 5 min. in supine position. 2 measurements averaged	140	135	125	123
Diastolic blood pressure (mm Hg) measured after 5 min. in supine position. 2 measurements averaged	70	70	75	72
Serum-ASAT (μkat/L)	0.36	0.33	0.26	0.25
Serum-ALAT (μkat/L)	0.61	0.52	0.40	0.37

Claim

The use of ketoconazole or molecules resembling ketoconazole but with some side-chains, not affecting the biological activity compared to ketoconazole, changed, for the manufacture of drugs for medical treatment of diabetes mellitus type II as well as for counteracting the other risk factors being part of the Metabolic Syndrome (also known as "the deadly quartet" or "Syndrome X" or the "Insulin Resistance Syndrome").

AMENDED CLAIMS

[received by the International Bureau on 23 May 1995 (23.05.95);
original claim replaced by amended claims 1-4 (1 page)]

1.The use of inhibitors of cortisol synthesis for the manufacture of drugs for medical treatment of diabetes mellitus type II as well as for counteracting the other risk factors being part of the Metabolic Syndrome (also known as "the deadly quartet" or "syndrom X" or the "Insuline Resistance Syndrom").

2. The use according to claim 1, wherein the inhibitor is ketoconazole or derivatives thereof having a corresponding biological activity as compared to ketoconazole.

3. The use of a first composition comprising an inhibitor of cortisol synthesis accordning to claim 1 or 2 and a second composition comprising testosterone for the manufacture of a drug or drug system for medical treatment of diabetes mellitus type II as well as for counteracting the other risk factors being part of the Metabolic Syndrome (also known as "the deadly quartet" or "syndrom X" or the "Insuline Resistance Syndrom").

4. The use according to claim 1 or 2, wherein the daily dose of the inhibitor is between 100 and 800 mg.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00729

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/495
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, Volume 65, No 5, 1987, G. M. Pepper et al, "Ketoconazole Reverses Hyperandrogenism in a Patient with Insulin Resistance and Acanthosis Nigricans" page 1047 - page 1052 --	1
A	WO, A1, 9414462 (WALSER, MACKENZIE), 7 July 1994 (07.07.94) -- --------	1

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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17 March 1995	24 -03- 1995
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INTERNATIONAL SEARCH REPORT

Information on patent family members

09/02/95

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9414462	07/07/94	NONE	