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(54) **Title:** DOSE REDUCTION OF A CANNABINOID CB_1 RECEPTOR ANTAGONIST IN THE TREATMENT OF OVERWEIGHT OR OBESITY

(57) **Abstract:** O-(3-Piperidino-2-hydroxy-1-propyl)-nicotinic amidoxime or a pharmaceutically acceptable acid addition salt thereof is administered to patients suffering from overweight or obesity and treated with a cannabinoid CB1 receptor antagonist such as rimonabant to reduce the unfavourable psychiatric side effect of the latter.

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Dose reduction of a cannabinoid CB_1 receptor antagonist in the treatment of overweight or obesity

Field of the invention

The invention refers to a dose reduction of a cannabinoid CB_1 receptor antagonist in the treatment of overweight or obesity. In particular, the invention refers to a synergistic increase of the effect of a cannabinoid CB_1 receptor antagonist, for example rimonabant, in the treatment of overweight or obesity and a reduction of the psychiatric side effect of said antagonist as well as pharmaceutical compositions comprising a cannabinoid CB_1 receptor antagonist and O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic amidoxime) as the active agents.

Background of the invention

Overweight and obesity represent the most prevalent nutritional problem in the developed countries. According to the estimations of World Health Organization, more than 300 million adults are obese worldwide. In case of adults, overweight is characterized by a body mass index of 25-30 kg/m^2, while a body mass index of above 30 kg/m^2 indicates obesity.

Overweight and obesity themselves are associated with hypertension and abnormal metabolic changes such as insulin resistance and dyslipidemia which are risk factors for diabetes. Obesity (particularly abdominal obesity), insulin resistance and dyslipidemia are major features of „pre-diabetes" (metabolic

syndrome) that leads to type 2 diabetes mellitus. Diabetes is accompanied by increased mortality due to a greater risk of cardiovascular diseases. Thus, it can be stated that obesity predisposes to diseases of high risk such as type 2 diabetes mellitus, cardiovascular diseases, osteoarthritis, formation of gall stones and various malignant diseases.

Cannabis binds to and expresses its effect through specific receptors named as cannabinoid receptors. Currently, there are two known subtypes of cannabinoid receptors: CB_1 and CB_2. The cannabinoid CB_1 receptors are believed to play a role in controlling food consumption, food intake, energy expenditure, the neuroendocrine response of the stress system, and the metabolic functions of crucial peripheral tissues such as the adipose tissue, the gastrointestinal tract, the liver, and the skeletal muscles. Cannabinoid receptor antagonists block or inhibit the activation of cannabinoid receptors.

Therefore, one of the approaches to reduce overweight and obesity consists in the administration of a cannabinoid CB_1 receptor antagonist that reduces the appetite. However, in the administration of cannabinoid receptor antagonists there is a risk of the occurrence of psychiatric side effects. A well known potent cannabinoid CB_1 receptor antagonist is rimonabant i.e. N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide [European Patent No. 656 354] that is rather effective in the reduction of obesity, however, produces adverse psychiatric effects especially anxiety,

depression, suicidal ideation etc. Thus, in the treatment of obese patients with rimonabant, there is a relatively high risk of psychiatric side effects. [FDA Briefing Document NDA 21-888, Zimulti (rimonabant) Tablets, 20 mg, issued by Advisory Committee, June 13, 2007].

O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic amidoxime) (abbreviated as BGP-15) was patented in 1976 as a new compound useful in the treatment of diabetic angiopathy, a complication of diabetes resulting in the damage of blood vessels. The basic patent is, among others, US-P No. 4,187,220.

US-P No. 6,306,878 refers to a method for the protection of the mitochondrial genome and/or mitochondrion from damage leading to myopathies and neurodegenerative diseases which comprises administering an effective non-toxic dose to a patient susceptible to such damage of an amidoximic acid derivative including BGP-15. A preferred myopathy is cardiomyopathy. Neurodegenerative diseases include Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis.

US-P No. 6,458,371 refers to a composition comprising 0.1-30 % of a hydroximic acid derivative including BGP-15 as the active ingredient and a carrier that is in the form of a cream, lotion, foam or spray. The composition is suitable for reducing the incidence of photodamage by radiation with UV-B.

US-P No. 6,884,424 refers to a method for preventing actinic keratosis by applying a hydroximic acid derivative including BGP-15 to the affected skin surface.

US-P No. 6,451,851 refers to a method of treating a patient suffering from a viral infection comprising administering to the patient a pharmaceutically effective amount of a known antivirally active agent together with a hydroximic acid derivative including BGP-15.

US-P No. 6,440,998 refers to a pharmaceutical composition having antitumor activity with reduced side effect comprising cisplatin or carboplatin and a hydroximic acid derivative including BGP-15. US-P No. 6,656,955 refers to a pharmaceutical composition having antitumor activity with reduced side effect comprising paclitaxel or docetaxel and a hydroximic acid derivative including BGP-15. US-P No. 6,720,337 refers to a pharmaceutical composition having antitumor activity with reduced side effect comprising oxaliplatin and a hydroximic acid derivative including BGP-15. US-P No. 6,838,469 refers to a pharmaceutical composition having antitumor activity with reduced side effect comprising pyrimidine derivatives and BGP-15.

PCT Patent Application published under No. WO 00/07580 disclosed experimental data for the antidiabetic

effect of BGP-15 in the treatment of type 1 diabetes mellitus. It is to be noted that type 1 diabetes mellitus is an autoimmune disease occuring at young age, while type 2 diabetes mellitus is a metabolic disease occuring at higher age.

PCT Application published under No. WO 03/007951 refers to a pharmaceutical combination of hydroximic acid derivatives including BGP-15 and an antidiabetic or anti-hyperlipidemic active agent for the prevention or treatment of a prediabetic state, metabolic X-syndrome or diabetes mellitus as well as disorders which are associated with the states listed above, namely endogenic metabolic disorders, insulin resistance, dislipidemia, alopecia, diffuse effluvium and/or female endocrine disorders based on androgenic preponderance. In the description, laboratory data indicate that BGP-15 enhances, synergistically, the effect of the known antidiabetic agent metformin and troglitazone, respectively. The laboratory data also show that BGP-15 in itself enhances the insulin sensitivity (thus, reduces the insulin resistance) in both normal and hyper-cholesterolemic animals relative to the control.

PCT Application published under No. WO 2005/122678 refers to the use of BGP-15 in a pharmaceutical composition having prokinetic effect (i.e. induces activity in the stomach and intestines. Prokinetic effect includes possible treatment of reflux esophagitis, gastroparesis, influencing bile flow from the gall bladder etc.

PCT Application published under No. WO 2005/123049 refers to the use of BGP-15 for mitochondrial genesis i.e. to

increase the number of mitochondria in the cells resulting in a roborating effect.

PCT Application published under No. WO 2006/079910 refers to the use of BGP-15 for the treatment of lesions in the oral cavity, especially periodontal disease.

Summary of the invention

It has been found that O-(3-piperidino-2-hydroxypropyl)-nicotinic amidoxime or a pharmaceutically suitable acid addition salt thereof can be used for increasing the effect of cannabinoid CB_1 antagonists, especially rimonabant, synergistically. Due to the dose reduction of the cannabinoid CB_1 antagonists in the treatment of overweight or obesity, also the psychiatric side effects that occur in the treatment with cannabinoid CB_1 antagonists, especially rimonabant, can be reduced by the simultaneous administration of O-(3-piperidino-2-hydroxypropyl)-nicotinic amidoxime or a pharmaceutically suitable acid addition salt thereof.

Described herein is a use of O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic amidoxime or a pharmaceutically acceptable acid addition salt thereof for the preparation of a pharmaceutical composition suitable for enhancing, synergistically, the effect of a cannabinoid CB_1 receptor agonist in reduction of overweight or obesity.

Also described is a use of O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic amidoxime or a pharmaceutically acceptable acid addition salt thereof for the preparation of a pharmaceutical composition suitable for reducing the

unfavourable psychiatric side effect of a known cannabinoid CB_1 receptor antagonist.

Also described is a pharmaceutical composition comprising a known cannabinoid CB_1 receptor antagonist and O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic amidoxime or a pharmaceutically acceptable acid addition salt thereof in admixture with one or more conventional carrier(s).

Also described is a pharmaceutical composition for the treatment of overweight or obesity comprising a known cannabinoid CB_1 receptor antagonist and O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic amidoxime or a pharmaceutically acceptable acid addition salt thereof in admixture with one or more conventional carrier(s).

Also described is a pharmaceutical composition for the treatment of overweight or obesity and having reduced psychiatric side effect comprising a known cannabinoid CB_1 receptor antagonist and O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic amidoxime or a pharmaceutically acceptable acid addition salt thereof in admixture with one or more conventional carrier(s).

In various embodiments the cannabinoid CB_1 receptor antagonist is preferably rimonabant or a pharmaceutically acceptable acid addition salt and/or solvate thereof.

In various embodiments the psychiatric side effects comprise, in particular, anxiety, depression and suicidal ideation.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description, and from the claims.

Description of preferred embodiments

The cannabinoid CB_1 receptor antagonist includes any known active agent that antagonizes the cannabinoid CB_1 receptor. Preferred cannabinoid CB_1 receptor antagonists include N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide (rimonabant) and N-piperidino-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethyl-pyrazole-3-carboxamide or a pharmaceutically suitable acid addition salt thereof or a solvate of the base or a solvate of the acid addition salt.

A pharmaceutically suitable acid addition salt is a salt formed with an inorganic acid such as hydrochloric acid, sulfuric acid etc. or with an organic acid such as acetic acid, lactic acid, tartaric acid etc. Preferred acid addition salts include hydrochlorides, acetates, maleates etc. A preferred acid addition salt of O-(3-piperidino-2-hydroxy-1-propyl)nicotinic amidoxime is the dihydrochloride thereof.

BGP-15 can be prepared by the process described in e.g. US-P No. 4,187,220.

In one embodiment, a conventional dose of a known cannabinoid CB_1 receptor antagonist, preferably rimonabant, is administered to a patient requiring treatment of overweight or obesity, and, simultaneously, a dose of BGP-15 or a

pharmaceutically suitable acid addition salt thereof is administered. This non-toxic dose of BGP-15 increases the effect of the cannabinoid CB_1 receptor antagonist synergistically, and reduces, effectively, the psychotic side effect associated with the administration of the cannabinoid CB_1 receptor antagonist.

In some embodiments, the known cannabinoid CB_1 receptor antagonist such as rimonabant is not administered simultaneously with BGP-15. Thus, while the two active agents in the combination therapy, e.g. rimonabant and BGP-15, can be administered simultaneously, they need not be. For example, administration of a first active agent can precede the administration of a second active agent by some time e.g. some minutes. While in many cases it is desirable that the two active agents used in a combination therapy be present in the patient's body at the same time, this need not be so. Combination therapy can also include two or more administrations of one of the active agents or both active agents used in the combination.

Combination therapy can also include the administration of the two active agents via different routes or locations. For example, one active agent is administered orally and the other active agent is administered parenterally or one active agent is administered orally and the other active agent is administered locally. In each case, the active agents can be administered either simultaneously or sequentially.

Generally, the daily dose of the known cannabinoid CB_1 receptor antagonist, preferably rimonabant, for an adult person of about 70 kg body weight amounts to 1-1000 mg, preferably 1-100 mg, in general, 2-20 mg. The similar daily dose of BGP-15 (as dihydrochloride) is, in general, 5-1000 mg, preferably 50-500 mg.

According to an especially preferred method of the invention, 5-20 mg of rimonabant and 50-500 mg of BGP-15 dihydrochloride are administered to an adult, daily.

In case of the pharmaceutical composition of the invention

either each of the two active agents (i.e. the known cannabinoid CB_1 receptor antagonist and BGP-15) has been converted, one by one, to separate pharmaceutical compositions using one or more conventional carrier(s) and any of the usual processes of drug manufacture, and in this case the two sorts of pharmaceutical composition obtained are administered to the patient simultaneously or one after the other;

or the two active agents have been converted to one single pharmaceutical composition that can be administered to the patient being in need thereof. In the latter case, the pharmaceutical composition may contain a mixture of the two active agents, or each of the active agents may be present at a different site in the pharmaceutical composition, e.g. one of them in the tablet core and the other in a coating of the tablet core. Of course, one or more conventional carriers and any of

the usual processes of drug manufacture are used to prepare this single pharmaceutical composition.

The pharmaceutical composition of the invention contains an effective non-toxic amount of a known cannabinoid CB_1 receptor antagonist, preferably rimonabant, or a pharmaceutically suitable acid addition salt and/or a solvate thereof and an effective non-toxic amount of BGP-15 or a pharmaceutically suitable acid addition salt thereof in addition to one or more pharmaceutically acceptable carrier(s). The pharmaceutical composition may include any dosage form suitable for peroral, parenteral, transdermal or rectal administration or for local treatment, and can be solid or liquid.

The solid pharmaceutical compositions suitable for peroral administration may be powders, capsules, tablets, film-coated tablets, microcapsules etc., and can comprise binding agents such as gelatine, sorbitol, poly(vinylpyrrolidone) etc.; filling agents such as lactose, glucose, starch, calcium phosphate etc.; auxiliary substances for tabletting such as magnesium stearate, talc, poly(ethylene glycol), silica etc.; wetting agents such as sodium laurylsulfate etc. as the carrier.

The liquid pharmaceutical compositions suitable for peroral administration may be solutions, suspensions or emulsions and can comprise e.g. suspending agents such as gelatine, carboxymethylcellulose etc.; emulsifiers such as sorbitane monooleate etc.; solvents such as water, oils, glycerol, propylene glycol, ethanol etc.; preservatives such as methyl p-hydroxybenzoate etc. as the carrier.

Pharmaceutical compositions suitable for parenteral administration consist of sterile solutions of the active ingredients, in general.

Dosage forms listed above as well as other dosage forms are known *per se*, see e.g. Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, USA.

The pharmaceutical composition contains dosage unit, in general. The daily dose can be administered in one or more portions. The actual dosage depends on many factors and is determined by the doctor.

The pharmaceutical composition is prepared by admixing the active ingredients to one or more carrier(s), and converting the mixture obtained to a pharmaceutical composition in a manner known *per se*. Useful methods are known from the literature, e.g. Remington's Pharmaceutical Sciences mentioned above.

A preferred pharmaceutical composition of the invention contains a known cannabinoid CB_1 receptor antagonist selected from the group consisting of rimonabant and N-piperidino-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethyl-pyrazole-3-carboxamide or a pharmaceutically acceptable acid addition salt and/or a solvate thereof in addition to BGP-15 or a pharmaceutically suitable acid addition salt thereof, preferably BGP-15 dihydrochloride.

The invention is further illustrated by means of the following Example.

Example

Inhibition of body weight gain in high fat diet exposed mice by rimonabant and BGP-15

OF-1 female mice weighing about 18-20 g at the beginning of the experiment were used in the study. A group of 9 mice were kept on standard laboratory chaw, while the other experimental groups were exposed to high fat diet and to daily oral treatment with the following compounds: vehicle, rimonabant 2 mg/kg, rimonabant 10 mg/kg, BGP-15 dihydrochloride 20 mg/kg and rimonabant 2 mg/kg + BGP-15 dihydrochloride 20 mg/kg. The high fat diet consisted of palatable food that contained 50 % fat. The group on standard laboratory chaw was also treated with vehicle. Treatment was performed with all of the drugs, orally, at 5 ppm. The weight of the animals was measured weekly. The body weight gain (BWG) data at the end of the second and third week are shown in Table 1.

Table 1

Group	Body weight gain in g	
	after 2 weeks	after 3 weeks
Standard laboratory chaw + vehicle (control)	8.7	10.6
High fat diet (HFD)+ vehicle ($control_{HFD}$)	12.6	15.9
HFD + rimonabant 2 mg/kg	10.6	14.1
HFD + rimonabant 10 mg/kg	10.2	13.0
HFD + BGP-15 dihydrochloride 20 mg/kg	10.4	13.6
HFD + rimonabant 2 mg/kg + BGP-15 dihydrochloride 20 mg/kg	9.4	11.8

From Table 1 it can be seen that, in the control group, high fat diet caused a body weight gain of 44 % after 2 weeks, and 50 % after 3 weeks, in relation to the weight gain in the control group in which the animals were fed with standard laboratory chaw. Consequently, the high fat diet produced obese mice. In the test group treated with high fat diet and 2 mg/kg of rimonabant, the weight gain was 22 % after 2 weeks, and 33 % after 3 weeks, in relation to that of the control group fed with standard laboratory chaw. In the test group treated with high fat diet and 10 mg/kg of rimonabant, a weight gain of 17 %

after 2 weeks, and 22.6 % after 3 weeks was obtained, in relation to that of the control group fed with standard laboratory chaw. In the test group treated with high fat diet and 20 mg/kg of BGP-15 dihydrochloride, the weight gain was 19.5 % after 2 weeks, and 28.3 % after 3 weeks, in relation to that of the control group fed with standard laboratory chaw. Thus, it can be stated that neither rimonabant nor BGP-15, alone, could inhibit the weight gain sufficiently to compensate the effect of high fat diet in the test groups.

However, in the test group treated with both BGP-15 dihydrochloride and the lower dose of rimonabant, the weight gain was as low as 8 % after 2 weeks, and 11.3 % after 3 weeks, in relation to that of the control group fed with standard laboratory chaw. Thus, it is evident, that the weight gain produced by a high fat diet can be compensated by a combined treatment with a lower dose of rimonabant and with BGP-15 dihydrochloride within about 10 %.

Consequently, BGP-15 produces synergism with rimonabant regarding the weight reducing effect. Since, in the method of the invention, it is sufficient to administer a lower dose of rimonabant in the treatment of overweight and obesity, a lower incidence of the unfavourable psychiatric side effect of rimonabant can be expected.

Claims:

1. Use of O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic amidoxime or a pharmaceutically acceptable acid addition salt thereof for the preparation of a pharmaceutical composition suitable for enhancing, synergistically, the effect of a cannabinoid CB_1 receptor agonist in reduction of overweight or obesity.

2. Use of O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic amidoxime or a pharmaceutically acceptable acid addition salt thereof for the preparation of a pharmaceutical composition suitable for reducing the unfavourable psychiatric side effect of a known cannabinoid CB_1 receptor antagonist.

3. A use of Claim 2 in which the psychiatric side effect is anxiety.

4. A use of Claim 2 in which the psychiatric side effect is depression.

5. A use of any of Claims 1-4 in which the known cannabinoid CB_1 receptor antagonist is rimonabant or a pharmaceutically acceptable acid addition salt and/or a solvate thereof.

6. A use of any of Claims 1-4 in which the known cannabinoid CB_1 receptor antagonist is N-piperidino-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxamide or a pharmaceutically acceptable acid addition salt and/or a solvate thereof.

7. A pharmaceutical composition comprising a known cannabinoid CB_1 receptor antagonist and O-(3-piperidino-2-

hydroxy-1-propyl)-nicotinic amidoxime or a pharmaceutically acceptable acid addition salt thereof in admixture with one or more conventional carrier(s).

8. A pharmaceutical composition of Claim 7 comprising rimonabant or a pharmaceutically acceptable acid addition salt and/or a solvate thereof and O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic amidoxime dihydrochloride.

9. A pharmaceutical composition of Claim 7 comprising N-piperidino-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxamide or a pharmaceutically acceptable acid addition salt and/or a solvate thereof and O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic amidoxime dihydrochloride.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/454 A61K31/4545 A61K45/06 A61P3/04

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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	page 22 - page 24 claims 1-34	1-9
Y	WO 2007/033366 A (CONCERT PHARMACEUTICALS INC [US]; TUNG ROGER [US]) 22 March 2007 (2007-03-22) abstract page 40, paragraph 137 - page 41, paragraph 138 page 47, paragraph 169 page 1; compound 1	1-9

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/HU2008/000147

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/HU2008/000147

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