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(54) Title: USE OF FLIBANSERIN IN THE TREATMENT OF OBESITY

(57) Abstract: The invention relates to a method for the treatment of obesity and related diseases comprising the administration of a therapeutically effective amount of Flibanserin.

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## Use of Flibanserin in the treatment of obesity

The invention relates to a method for the treatment of obesity and related diseases, comprising the administration of a therapeutically effective amount of Flibanserin. The invention relates further to new pharmaceutical compositions for the treatment of obesity and related diseases.

### Background of the Invention

The intake of food and its conversion in the body is an essential part of life for all living creatures. Therefore, deviations in the intake and conversion of food generally lead to problems and also illness. The changes in the lifestyle and nutrition of humans, particularly in industrialised countries, have promoted morbid overweight (also known as corpulence or obesity) in recent decades.

The prevalence of obesity has risen significantly in the past decade in the United States and many other developed countries, (Fiegal et al, Int. J. Obesity 22:39-47 (1998), Mokdad et al, JAMA 282:1519-1522 (1999)). Because obesity is associated with a significantly elevated risk for diabetes, especially for type 2 diabetes, dyslipidaemia, arteriosclerosis, coronary heart disease, hypertension, and numerous other major illnesses, and overall mortality from all causes (Must et al, JAMA 282:1523-1529 (1999), Calle et al, N. Engl. J. Med. 341:1097-1105 (1999)), weight reduction is critical for the obese patient (Blackburn, Am. J. Clin. Nutr. 69:347-349 (1999), Galuska et al, JAMA 282:1576 (1999)). Moreover, high body weight alone puts an increased strain on the support and mobility apparatus, which can lead to chronic pain and diseases such as arthritis or osteoarthritis. Thus, obesity is a serious health problem for society.

There is good evidence that pharmacotherapy can enhance weight loss when combined with interventions aimed at changing life style (National Heart, Lung and Blood Institute, Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report, NIH Publication No. 98-4083, September 1998). Yet, the available pharmacological therapies to facilitate weight loss fail to provide adequate benefit to many obese patients because of side effects, contraindications or lack of positive response (National Heart, Lung and Blood Institute, Clinical guidelines

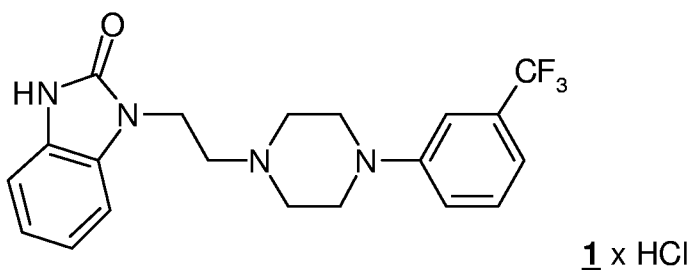
on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report, NIH Publication No. 98-4083, September 1998). Hence, there is impetus for developing new and alternative treatments for management of obesity.

- 5 Apart from physical activity and a change in nutrition, there is currently no convincing treatment option for effectively reducing body weight. However, as obesity is a major risk factor in the development of serious and even life-threatening diseases, it is all the more important to have access to pharmaceutical active substances for the prevention and/or treatment of obesity.

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### **Description of the invention**

The compound 1-[2-(4-(3-trifluoromethyl-phenyl)piperazin-1-yl)ethyl]-2,3-dihydro-1H-benzimidazol-2-one (Flibanserin) is disclosed in form of its hydrochloride in European  
15 Patent Application EP-A-526434 and has the following chemical structure:



- 20 Flibanserin shows affinity for the 5-HT<sub>1A</sub> receptor and the 5-HT<sub>2</sub>-receptor family. It is therefore a promising therapeutic agent for the treatment of a variety of diseases, for instance depression, schizophrenia and anxiety.

- Surprisingly it has been found that Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the  
25 hydrates and/or solvates thereof proved to be a weight-loss agent and therefore is useful to treat obesity and related diseases.

As used herein, the term "obesity" means an excess of adipose tissue in the body. In this connection, obesity is fundamentally to be seen as the increased level of fatness

which leads to a health risk. There is no sharp distinction between normal individuals, overweight individuals and those suffering from obesity, but the health risk accompanying obesity is presumed to rise continuously as the level of fatness increases. For simplicity's sake, in the present invention, individuals with a Body Mass Index (BMI), which is defined as the body weight measured in kilograms divided by the height (in metres) squared, above a value of 25 and more particularly above 30, are preferably regarded as suffering from obesity.

One object of the present invention is directed to the use of Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof, for the preparation of a medicament for the treatment and/or prevention of obesity.

The indication obesity includes in particular exogenic obesity, hyperinsulinaemic obesity, hyperplasmic obesity, hyperphyseal adiposity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, infantile obesity, upper body obesity, alimentary obesity, hypogonadal obesity and central obesity.

Therefore, the present invention is directed also to the use of Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof, for the preparation of a medicament for the treatment and/or prevention of exogenic obesity, hyperinsulinaemic obesity, hyperplasmic obesity, hyperphyseal adiposity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, infantile obesity, upper body obesity, alimentary obesity, hypogonadal obesity and central obesity.

In another embodiment, this invention relates to the use of Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof, for the preparation of a medicament for promoting, increasing or facilitating weight loss.

Furthermore, this invention relates to the use of Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form

of the hydrates and/or solvates thereof, for the preparation of a medicament for prevention of body weight gain.

5 In another embodiment, this invention relates to the use of Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof, for the preparation of a medicament for inhibiting or reducing appetite.

10 In another embodiment, this invention relates to the use of Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof, for the preparation of a medicament for the treatment and/or prevention of diseases and/or disorders associated with obesity, such as the metabolic syndrome (syndromeX), hypertension, osteoarthritis, diabetes, especially type II diabetes, complications of diabetes including  
15 diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, pathological glucose tolerance, encephalorrhagia, heart diseases, cardiac insufficiency, arteriosclerosis, arthritis, gonitis, stroke and dyslipidaemia, preferably metabolic syndrome, diabetes and dyslipidaemia, comprising the administration of a therapeutically effective amount of Flibanserin, optionally in form of the free base, the  
20 pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof.

Another embodiment of the present invention relates to a method of treating and/or preventing the above mentioned diseases and/or disorders comprising the  
25 administration of a therapeutically effective amount of Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof.

For the treatment of the aforementioned diseases, Flibanserin, optionally in form of the  
30 free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof may also be co-administered with a second active substance selected from the group consisting of

- active substances for the treatment of diabetes,

- active substances for the treatment of diabetic complications,
- active substances for the treatment of obesity,
- active substances for the treatment of high blood pressure,
- active substances for the treatment of hyperlipidaemia, including arteriosclerosis,
- 5 - active substances for the treatment of dyslipidaemia, including arteriosclerosis,
- active substances for the treatment of arthritis.

Examples of active substances for the treatment of diabetes are insulin sensitisers, insulin secretion accelerators, biguanides, insulins,  $\alpha$ -glucosidase inhibitors,  $\beta$ 3 adreno-  
10 receptor agonists.

Insulin sensitisers include glitazones, particularly pioglitazone and its salts (preferably hydrochloride), troglitazone, rosiglitazone and its salts (preferably maleate), JTT-501, GI-262570, MCC-555, YM-440, DRF-2593, BM-13-1258, KRP-297, R-119702 and GW-  
15 1929.

Insulin secretion accelerators include sulphonylureas, such as for example tolbutamide, chloropropamide, tolazamide, acetohexamide, glycopyramide and its ammonium salts, glibenclamide, gliclazide, glimepiride. Further examples of insulin secretion accelerators  
20 are repaglinide, nateglinide, mitiglinide (KAD-1229) and JTT-608.

Biguanides include metformin, buformin and phenformin.

Insulins include those obtained from animals, particularly cattle or pigs, semisynthetic  
25 human insulins which are synthesised enzymatically from insulin obtained from animals, human insulin obtained by genetic engineering, e.g. from Escherichi coli or yeasts. Moreover, the term insulin also includes insulin-zinc (containing 0.45 to 0.9 percent by weight of zinc) and protamine-insulin-zinc obtainable from zinc chloride, protamine sulphate and insulin. Insulin may also be obtained from insulin fragments or derivatives  
30 (for example INS-1, etc.).

Insulin may also include different kinds, e.g. with regard to the onset time and duration of effect ("ultra immediate action type", "immediate action type", "two phase type",

"intermediate type", "prolonged action type", etc.), which are selected depending on the pathological condition of the patient.

$\alpha$ -Glucosidase inhibitors include acarbose, voglibose, miglitol, emiglitate.

5

$\beta_3$  Adreno receptor agonists include AJ-9677, BMS-196085, SB-226552, AZ40140.

Active substances for the treatment of diabetes other than those mentioned above include ergoset, pramlintide, leptin, BAY-27-9955 as well as glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, protein tyrosine phosphatase 1B inhibitors, dipeptidyl protease inhibitors, glipazide, glyburide.

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Active substances for the treatment of diabetic complications include for example aldose reductase inhibitors, glycation inhibitors and protein kinase C inhibitors, DPP-IV blockers, GLP-1 or GLP-2 analogues and SGLT-2 inhibitors.

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Aldose reductase inhibitors are for example tolrestat, epalrestat, imirestat, zenarestat, SNK-860, zopolrestat, ARI-50i, AS-3201.

An example of a glycation inhibitor is pimagedine.

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Protein Kinase C inhibitors are for example NGF, LY-333531.

DPP-IV blockers are for example LAF237 (Novartis), MK431 (Merck) as well as 815541, 823093 and 825964 (all GlaxoSmithkline).

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GLP-1 analogues are for example Liraglutide (NN2211) (NovoNordisk), CJC1131 (Conjuchem), Exenatide (Amylin).

SGLT-2 inhibitors are for example AVE-2268 (Aventis) and T-1095 (Tanabe, Johnson&Johnson).

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Active substances other than those mentioned above for the treatment of diabetic complications include alprostadil, thiapride hydrochloride, cilostazol, mexiletine hydrochloride, ethyl eicosapentate, memantine, pimagedine (ALT-711).

- 5 Active substances for the treatment of obesity, other than Flibanserin, include lipase inhibitors and anorectics.

A preferred example of a lipase inhibitor is orlistat.

- 10 Examples of preferred anorectics are phenetamine, mazindol, fluoxetine, sibutramine, baiamine, (S)-sibutramine, SR-141716, NGD-95-1.

Active substances other than those mentioned above for the treatment of obesity include lipstatin, Rimonabant and topiramate

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Moreover for the purposes of this application the active substance group of anti-obesity active substances also includes the anorectics, of which the  $\beta_3$  agonists, thyromimetic active substances and NPY antagonists should be emphasised. The range of substances which may be considered as preferred anti-obesity or anorectic active substances is indicated by the following additional list, by way of example:

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phenylpropanolamine, ephedrine, pseudoephedrine, phenetamine, a cholecystokin-A (hereinafter referred to as CCK-A) agonist, a monoamine reuptake inhibitor (such as for example sibutramine), a sympathomimetic active substance, a serotonergic active substance (such as for example dexfenfluramine, fenfluramine, a 5-HT<sub>2C</sub> agonist such as BVT.933 or APD356), a dopamine antagonist (such as for example bromocriptine or pramipexol), a melanocyte-stimulating hormone receptor agonist or mimetic, an analogue of melanocyte-stimulating hormone, a cannabinoid receptor antagonist (Rimonabant, ACOMPLIA TM), an MCH antagonist, the OB protein (hereinafter referred to as leptin), a leptin analogue, a fatty acid synthase (FAS) antagonist, a leptin receptor agonist, a galanine antagonist, a GI lipase inhibitor or reducer (such as for example orlistat). Other anorectics include bombesin agonists, dehydroepiandrosterone or its analogues, glucocorticoid receptor agonists and antagonists, orexin receptor antagonists, urocortin binding protein antagonists, agonists of the Glucagon-like

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Peptide-1 receptor, such as for example exendin, AC 2993, CJC-1131, ZP10 or GRT0203Y, DPPIV inhibitors and ciliary neurotrophic factors, such as for example axokines. In this context mention should also be made of the forms of therapy which produce weight loss by increasing the fatty acid oxidation in the peripheral tissue, such as for example inhibitors of acetyl-CoA carboxylase.

Active substances for the treatment of high blood pressure include inhibitors of angiotensin converting enzyme, calcium antagonists, potassium channel openers and angiotensin II antagonists.

Inhibitors of angiotensin converting enzyme include captopril, enalapril, alacepril, delapril (hydrochloride), lisinopril, imidapril, benazepril, cilazapril, temocapril, trandolapril, manidipine (hydrochloride).

Examples of calcium antagonists are nifedipine, amlodipine, efonidipine, nicardipine.

Potassium channel openers include levcromakalim, L-27152, AL0671, NIP -121.

Angiotensin II antagonists include telmisartan, losartan, candesartan cilexetil, valsartan, irbesartan, CS-866, E4177.

Active substances for the treatment of hyperlipidaemia, including arteriosclerosis, include HMG-CoA reductase inhibitors, fibrate compounds.

HMG-CoA reductase inhibitors include pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, lipantil, cerivastatin, itavastatin, ZD-4522 and their salts.

Fibrate compounds include bezafibrate, ciprofibrate, clofibrate and simfibrate.

Active substances for the treatment of dyslipidaemia, including arteriosclerosis, include e.g. medicaments which raise the HDL level, such as e.g. nicotinic acid and derivatives and preparations thereof, such as e.g. niaspan, as well as agonists of the nicotinic acid receptor.

Active substances for the treatment of arthritis include NSAIDs (non-steroidal antiinflammatory drugs), particularly COX2 inhibitors, such as for example meloxicam or ibuprofen.

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Accordingly, the invention also relates to combining separate pharmaceutical compositions in kit form which may be co-administered separately. Therefore, in a further embodiment the present invention provides a kit comprising a) a first pharmaceutical composition comprising an active substance being not flibanserin,  
10 selected from the group consisting of active substances for the treatment of diabetes, active substances for the treatment of diabetic complications, active substances for the treatment of obesity, active substances for the treatment of high blood pressure, active substances for the treatment of hyperlipidaemia, including arteriosclerosis active substances for the treatment of dyslipidaemia, including arteriosclerosis, active  
15 substances for the treatment of arthritis, b) a second pharmaceutical composition comprising Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof for the treatment of the above mentioned diseases; and a container for both compositions.

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In a preferred embodiment the present invention provides a kit comprising a) a first pharmaceutical composition comprising one or more, preferably one active substance for the treatment of obesity, preferably orlistat, phenetermine, sibutramine or topiramate; b) a second pharmaceutical composition comprising Flibanserin, optionally  
25 in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof for the treatment of the above mentioned diseases; and a container for both compositions

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The term "co-administration", within the present invention means that both active ingredients mentioned above can be taken from the kit and combined for administration together as a composition or as part of the same, unitary dosage form, such as an parenterally or orally administered solution. "Co-administration" also includes administering the components separately (e.g. as tablets or capsules), but as part of the

same therapeutic treatment program or regimen. Both components need not be administered at essentially the same time, although they can be if so desired. Thus "co-administration" includes, for example administering all active ingredients as separate dosages or dosage forms and at essentially the same time. The term also includes  
5 separate administration at different times, in any order, and if preferred by different routes of administration. An example of a kit is the so-called blister pack well known in the packaging industry particularly for packaging pharmaceutical dosage forms.

Instead of a kit, Flibanserin and the second active substance according to the invention  
10 can be combined in one dosage form. Therefore, the present invention also relates to compositions comprising Flibanserin optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof and a second active substance active being not flibanserin, selected from the group consisting of active substances for the treatment of  
15 diabetes, active substances for the treatment of diabetic complications, active substances for the treatment of obesity, active substances for the treatment of high blood pressure, active substances for the treatment of hyperlipidaemia, including arteriosclerosis active substances for the treatment of dyslipidaemia, including arteriosclerosis, active substances for the treatment of arthritis in one dosage form.

20 Preferably, the present invention also relates to compositions comprising a) one or more, preferably one active substance for the treatment of obesity preferably orlistat, phenetermine, sibutramine or topiramate and b) Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form  
25 of the hydrates and/or solvates thereof.

Above mentioned kits and compositions can be used for the treatment and/or prevention of obesity like exogenic obesity, hyperinsulinaemic obesity, hyperplasmic obesity, hyperphyseal adiposity, hypoplasmic obesity, hypothyroid obesity,  
30 hypothalamic obesity, symptomatic obesity, infantile obesity, upper body obesity, alimentary obesity, hypogonadal obesity and central obesity as well as for promoting, increasing or facilitating of weight loss, for the prevention of body weight gain, and for inhibiting or reducing appetite.

Furthermore the above mentioned kits and compositions can be used for the treatment and/or prevention of diseases and/or disorders associated with obesity, such as the metabolic syndrome (syndromeX), hypertension, osteoarthritis, diabetes, especially type II diabetes, complications of diabetes including diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, pathological glucose tolerance, encephalorrhagia, heart diseases, cardiac insufficiency, arteriosclerosis, arthritis, gonitis, stroke and dyslipidaemia, preferably metabolic syndrome, diabetes and dyslipidaemia.

As already mentioned above, Flibanserin may be used in form of the free base, optionally in form of its pharmaceutically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof. Suitable acid addition salts include for example those of the acids selected from, succinic acid, hydrobromic acid, acetic acid, fumaric acid, maleic acid, methanesulphonic acid, lactic acid, phosphoric acid, hydrochloric acid, sulphuric acid, tartaric acid and citric acid. Mixtures of the abovementioned acid addition salts may also be used. From the aforementioned acid addition salts the hydrochloride and the hydrobromide, particularly the hydrochloride, are preferred. If Flibanserin is used in form of the free base, it is preferably used in form of Flibanserin polymorph A as disclosed in WO 03/014079.

The active substances which are suitable to be combined with Flibanserin within the teaching of the instant invention and which are mentioned hereinbefore may also be capable of forming acid addition salts with pharmaceutically acceptable acids.

Representative salts include the following: Acetate, Benzenesulfonate, Benzoate,

Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycolylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isothionate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, Mesylate,

Methylbromide, Methylnitrate, Methylsulfate, Mucate, Napsylate, Nitrate, N-methylglucamine ammonium salt, Oleate, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Salicylate, Stearate, Sulfate, Subacetate, Succinate, Tannate, Tartrate, Teoclate, Tosylate, Triethiodide and

Valerate.

Furthermore, where the other anti-obesity compounds carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e. g., calcium or magnesium salts; and salts  
5 formed with suitable organic ligands, e.g., quaternary ammonium salts.

The active substances which are suitable to be combined with Flibanserin may have chiral centers and occur as racemates, racemic mixtures and as individual

10 diastereomers, or enantiomers with all isomeric forms being included in the present invention. Therefore, where a compound is chiral, the separate enantiomers, substantially free of the other, are included within the scope of the invention. Further included are all mixtures of the two enantiomers. Also included within the scope of the invention are polymorphs and hydrates of the compounds of the instant invention.

15 The present invention includes within its scope prodrugs of Flibanserin and of the active substances which are suitable to be combined with Flibanserin. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible in vivo into the required compound.

20 Flibanserin, optionally used in form of its pharmaceutically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof, or in form of Flibanserin polymorph A, as well as the other anti-obesity compounds may be incorporated into the conventional pharmaceutical preparation in solid, liquid or spray  
25 form. The compositions may, for example, be presented in a form suitable for oral, rectal, parenteral administration or for nasal inhalation: preferred forms includes for example, capsules, tablets, coated tablets, ampoules, suppositories and nasal spray.

30 The active ingredients may be incorporated in excipients or carriers conventionally used in pharmaceutical compositions such as, for example, talc, arabic gum, lactose, gelatine, magnesium stearate, corn starch, aqueous or non aqueous vehicles, polyvinyl pyrrolidone, semisynthetic glycerides of fatty acids, benzalconium chloride, sodium phosphate, EDTA, polysorbate 80. The compositions are advantageously

formulated in dosage units, each dosage unit being adapted to supply a single dose of the active ingredient.

Within the instant invention flibanserin is preferably administered in such an amount that per single dosage between 0.01 to 400 mg of flibanserin are applied. Preferred are ranges of between 1.0 to 300 mg, particular preferred 2.0 to 200 mg of flibanserin. Suitable dosage forms may contain for instance 5, 10, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 mg of flibanserin. The dose range applicable per day is between 0.1 to 400, preferably between 1.0 to 300, more preferably between 2 to 200 mg. The aforementioned values are based on flibanserin in form of the free base. If flibanserin is applied in form of one of its acid addition salts, the corresponding values are readily calculable from the aforementioned values. Advantageously, flibanserin may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily.

The dosage of the active ingredients suitable for coadministration with flibanserin in the compositions of this invention may be varied. However, it is necessary that the amount of the active ingredients be such that a suitable dosage form is obtained. The selected dosage and the dosage form depend upon the desired therapeutic effect, on the route of administration and on the duration of the treatment. Dosage ranges in the combination are approximately one tenth to one times the clinically effective ranges required to induce the desired therapeutic effect, respectively when the compounds are used singly.

In case of the preferred compound orlistat particularly preferred doses per day are in the range of about 100 to 400 mg. In case of the preferred compound sibutramine particularly preferred doses per day are in the range of about 5 to 15 mg. In case of the preferred compound phenentermine particularly preferred doses per day are in the range of about 30 to 90 mg. Suitable dosage forms may contain for instance 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 mg of the above mentioned compounds. Advantageously, the compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily.

Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium

phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

5

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

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Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. of a flavouring such as vanilline or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

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Solutions for injection are prepared in the usual way, e.g. with the addition of preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, and transferred into injection vials or ampoules.

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Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

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Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

30

The Examples which follow illustrate the present invention without restricting its scope:

#### Examples of pharmaceutical formulations

A)	<u>Tablets</u>	<u>per tablet</u>
5	Flibanserin hydrochloride	100 mg
	lactose	240 mg
	corn starch	340 mg
	polyvinylpyrrolidone	45 mg
	magnesium stearate	15 mg
10		<hr/> <hr/> 740 mg

The finely ground active substance, lactose and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

B)	<u>Tablets</u>	<u>per tablet</u>
20	Flibanserin hydrochloride	80 mg
	corn starch	190 mg
	lactose	55 mg
	microcrystalline cellulose	35 mg
	polyvinylpyrrolidone	15 mg
25	sodium-carboxymethyl starch	23 mg
	magnesium stearate	<u>2 mg</u>
		400 mg

The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened. The sodium-carboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.





sodium chloride	50 mg
water for inj.	5 ml

The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilised and sealed by fusion.

#### F) Suppositories

Flibanserin hydrochloride	50 mg
solid fat	<u>1650 mg</u>
	1700 mg

The hard fat is melted. At 40°C the ground active substance is homogeneously dispersed. It is cooled to 38°C and poured into slightly chilled suppository moulds.

In a particular preferred embodiment of the instant invention, Flibanserin is administered in form of specific film coated tablets. Examples of these preferred formulations are listed below. The film coated tablets listed below can be manufactured according to procedures known in the art (see hereto WO 03/097058).

#### G) Film coated tablet

##### Core

<b><u>Constituents</u></b>	<b>mg/tablet</b>
Flibanserin	25.000
Lactose monohydrate	71.720
Microcrystalline cellulose	23.905
HPMC (Methocel E5)	1.250
Carboxymethylcellulose sodium	2.500

<b>Magnesium stearate</b>	0.625
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Coating

<b><u>Constituents</u></b>	<b>mg/ tablet</b>
HPMC (Methocel E5)	1.440
Polyethylene Glycol 6000	0.420
Titanium dioxide	0.600
Talc	0.514
Iron oxide red	0.026

<b>Total Film coated tablet</b>	<b>128.000</b>
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5

H) Film coated tabletCore

<b><u>Constituents</u></b>	<b>mg/tablet</b>
Flibanserin	50.000
Lactose monohydrate	143.440
Microcrystalline cellulose	47.810
HPMC (e.g. Pharmacoat 606)	2.500
Carboxymethylcellulose sodium	5.000
<b>Magnesium stearate</b>	1.250

Coating

<b><u>Constituents</u></b>	<b>mg/ tablet</b>
HPMC (e.g. Pharmacoat 606)	2.400
Polyethylene Glycol 6000	0.700
Titanium dioxide	1.000
Talc	0.857
Iron oxide red	0.043

<b>Total Film coated tablet</b>	<b>255.000</b>
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10

I) Film coated tabletCore

<b><u>Constituents</u></b>	<b>mg/tablet</b>
Flibanserin	100.000
Lactose monohydrate	171.080
Microcrystalline cellulose	57.020
HPMC (e.g. Methocel E5)	3.400
Carboxymethylcellulose sodium	6.800
<b>Magnesium stearate</b>	1.700

5 Coating

<b><u>Constituents</u></b>	<b>mg/ tablet</b>
HPMC (e.g. Methocel E5)	3.360
Polyethylene Glycol 6000	0.980
Titanium dioxide	1.400
Talc	1.200
Iron oxide red	0.060

<b>Total Film coated tablet</b>	<b>347.000</b>
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J) Film coated tablet10 Core

<b><u>Constituents</u></b>	<b>mg/tablet</b>
Flibanserin	2.000
Dibasic Calciumphosphate, anhydrous	61.010
Microcrystalline cellulose	61.010
HPMC (Methocel E5)	1.950
Carboxymethylcellulose sodium	2.600

<b>Colloidal silicon dioxide</b>	0.650
<b>Magnesium stearate</b>	0.780

Coating

<b><u>Constituents</u></b>	<b>mg/ tablet</b>
HPMC (Methocel E5)	1.440
Polyethylene Glycol 6000	0.420
Titanium dioxide	0.600
Talc	0.514
Iron oxide red	0.026

<b>Total Film coated tablet</b>	<b>133.000</b>
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5

K) Film coated tabletCore

<b><u>Constituents</u></b>	<b>mg/tablet</b>
Flibanserin	100.000
Dibasic Calciumphosphate, anhydrous	69.750
Microcrystalline cellulose	69.750
HPMC (e.g. Methocel E5)	2.750
Carboxymethylcellulose sodium	5.000
<b>Colloidal silicon dioxide</b>	1.250
<b>Magnesium stearate</b>	1.500

10 Coating

<b><u>Constituents</u></b>	<b>mg/ tablet</b>
HPMC (e.g. Methocel E5)	2.400
Polyethylene Glycol 6000	0.700
Titanium dioxide	1.043
Talc	0.857

<b>Total Film coated tablet</b>	<b>255.000</b>
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L) Film coated tablet

5 Core

<b><u>Constituents</u></b>	<b>mg/tablet</b>
Flibanserin	20.000
Lactose monohydrate	130.000
Microcrystalline cellulose	43.100
Hydroxypropyl Cellulose (e.g. Klucel LF)	1.900
Sodium Starch Glycolate	4.000
<b>Magnesium stearate</b>	<b>1.000</b>

Coating

<b><u>Constituents</u></b>	<b>mg/ tablet</b>
HPMC (e.g. Methocel E5)	2.400
Polyethylene Glycol 6000	0.700
Titanium dioxide	1.043
Talc	0.857

<b>Total Film coated tablet</b>	<b>205.000</b>
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10 M)

Core

<b><u>Constituents</u></b>	<b>mg/tablet</b>
Flibanserin (free base)	50.000
Orlistat	120.000
Anhydrous dibasic calcium phosphate	100.000
Microcrystalline cellulose	203.090
HPMC (Methocel E5)	6.615
Croscarmellose sodium	8.820

<b>Magnesium stearate</b>	2.250
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Coating

<b>Constituents</b>	<b>mg/ tablet</b>
HPMC (Methocel E5)	4.320
Polyethylene Glycol 6000	1.260
Titanium dioxide	1.800
Talc	1.542
Iron oxide red	0.078

<b>Total Film coated tablet</b>	<b>499.775</b>
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5

N)Core:

<b>Constituents</b>	<b>mg/tablet</b>
Flibanserin (free base)	50.000
Sibutramine	10.000
Lactose monohydrate	133.750
Microcrystalline cellulose	40.000
Hydroxypropylcellulose	2.500
Corn starch	12.500
<b>Magnesium stearate</b>	1.250

10 Coating

<b>Constituents</b>	<b>mg/ tablet</b>
HPMC (e.g. Pharmacoat 606)	2.400
Polyethylene Glycol 6000	0.700
Titanium dioxide	1.000
Talc	0.857
Iron oxide yellow	0.043

<b>Total Film coated tablet</b>	<b>255.000</b>
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Q)

Core

<b>Constituents</b>	<b>mg/tablet</b>
Flibanserin (free base)	50.000
Phenetermine	30.000
Lactose monohydrate	143.490
Microcrystalline cellulose	47.810
HPMC (e.g. Pharmacoat 606)	2.500
Carboxymethylcellulose sodium	5.000
Mannitol	60.000
Corn starch	36.500
Povidone	1.000
Colloidal silicon dioxide	1.000
<b>Magnesium stearate</b>	<b>1.700</b>

5

Coating

<b>Constituents</b>	<b>mg/ tablet</b>
HPMC (e.g. Methocel E5)	3.360
Polyethylene Glycol 6000	0.980
Titanium dioxide	1.400
Talc	1.200
Iron oxide red	0.060
<b>Total Film coated bilayer tablet</b>	<b>386.000</b>

10 Pharmacological Experiments:

To test the efficacy of Flibanserin in the treatment of obesity groups of the rats per sex per group (gang-housed) received Flibnanserin at dosages of 0 (control), 100, 200, and 600 mg/kg/day via dietary admixture. The test compound was mixed with the food to obtain a 3% premix. This premix was prepared in week -1 and drug week 7 and was

15



used to prepare the substance/food mixtures for all individual groups. The substance/food concentration was calculated using the mean daily food intake from the study week before. The substance/food mixture was made weekly for every dose group and stored under darkness in the animal room. The concentration, homogeneity and stability of the test substance in the food was checked during study week 2 with reanalysis one and four weeks later. One further check of concentration and homogeneity was performed in week 13. The body weight of each animal was determined and recorded once a week including the pretest acclimation period, in the morning on the same day of the week.

The following tables presents the results of the above described experiments as absolute body weights at start of treatment (week -1) as well as in drug week 6 and 13, including percentage change compared to controls. (in parentheses).

Table 1:

Table. Mean absolute body weights of males<sup>#</sup> in grams and percent change to controls

Drug week	Dosage BIMT 17 BS (mg/kg/day)			
	0 (Controls)	100	200	600
-1	191.3	188.1 (-1.7)	189.3 (-1.0)	186.8 (-2.4)
6	368.2	340.9 (-7.4)↓	340.4 (-7.5)↓	284.8 (-22.7)↓
13	440.4	397.4 (-9.8)↓	400.9 (-9.0)↓	333.2 (-24.3)↓

↓: significantly decreased compared to controls ( $p < 0.05$ ; t-test, pooled variance)

<sup>#</sup>: n=10/group

Table 2:

Table. Mean absolute body weights of females<sup>#</sup> in grams and percent change to controls

Drug week	Dosage BIMT 17 BS (mg/kg/day)			
	0 (Controls)	100	200	600
-1	141.2	141.3 (+0.1)	142.2 (+0.7)	140.7 (-0.4)
6	229.1	213.6 (-6.8)↓	209.7 (-8.5)↓	196.0 (-14.4)↓
13	261.5	234.5 (-10.3)↓	234.9 (-10.2)↓	225.8 (-13.7)↓

↓: significantly decreased compared to controls ( $p < 0.05$ ; t-test, pooled variance)

<sup>#</sup>: n=10/group

From Tables 1 and 2 it can be taken that the body weight gain of males and females were significantly decreased in almost all drug weeks. At study end the difference

compared to controls was 10%, 9% and 24% in males and 10%, 10% and 14% in females at 100, 200 and 600 mg/kg/day, respectively.

This pharmacological data provide evidence for the efficacy of Flibanserin in the treatment of obesity and can be used for the preparation of a medicament for  
5 promoting, increasing or facilitating weight loss and for inhibiting or prevention of body weight gain.

## Patent Claims

- 1) Use of Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof, for the preparation of a medicament for the treatment and/or prevention of obesity.  
5
- 2) Use according to claim 1 or 2 for the treatment and/or prevention of obesity selected from the group consisting of exogenic obesity, hyperinsulinaemic obesity, hyperplasmic obesity, hyperphyseal adiposity, hypoplastic obesity, hypothyroid  
10 obesity, hypothalamic obesity, symptomatic obesity, infantile obesity, upper body obesity, alimentary obesity, hypogonadal obesity and central obesity.
- 3) Use of Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof, for the preparation of a medicament for promoting, increasing or facilitating  
15 weight loss.
- 4) Use of Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof, for the preparation of a medicament for inhibiting or prevention of body weight  
20 gain.
- 5) Use of Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof, for the preparation of a medicament for inhibiting or reducing appetite.  
25
- 6) Use of Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof, for the preparation of a medicament for the treatment and/or prevention  
30 diseases and/or disorders associated with obesity.

7) Use according to claim 6 wherein the diseases and/or disorders associated with obesity are selected from the group consisting of metabolic syndrome (syndromeX), hypertension, osteoarthritis, diabetes, especially type II diabetes, complications of diabetes including diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, pathological glucose tolerance, encephalorrhagia, heart diseases, cardiac insufficiency, arteriosclerosis, arthritis, gonitis and dyslipidaemia.

8) A kit comprising

a) a first pharmaceutical composition comprising an active substance being not flibanserin, selected from the group consisting of active substances for the treatment of diabetes, active substances for the treatment of diabetic complications, active substances for the treatment of obesity, active substances for the treatment of high blood pressure, active substances for the treatment of hyperlipidaemia, including arteriosclerosis active substances for the treatment of dyslipidaemia, including arteriosclerosis, active substances for the treatment of arthritis,

b) a second pharmaceutical composition comprising Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof for the treatment of the above mentioned diseases; and a container for both compositions; and

c) a container for both compositions.

9) A kit according to claim 8, wherein the anti-obesity compound is selected from the group consisting of orlistat, phenetamine, sibutramine and topiramate or a pharmaceutical acceptable salt thereof.

10) A pharmaceutical composition comprising a) an active substance being not flibanserin, selected from the group consisting of active substances for the treatment of diabetes, active substances for the treatment of diabetic complications, active substances for the treatment of obesity, active substances for the treatment of high

blood pressure, active substances for the treatment of hyperlipidaemia, including  
arteriosclerosis active substances for the treatment of dyslipidaemia, including  
arteriosclerosis, active substances for the treatment of arthritis and b) Flibanserin,  
optionally in form of the free base, the pharmacologically acceptable acid addition salts  
5 and/or optionally in form of the hydrates and/or solvates thereof.

11) A pharmaceutical composition according to claim 10, wherein the active  
substance for the treatment of obesity is selected from the group consisting of orlistat,  
phenetamine, sibutramine and topiramate or a pharmaceutical acceptable salt thereof.

12) Use of Flibanserin, optionally in form of the free base, the pharmacologically  
acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates  
thereof, for the preparation of a medicament for the treatment of a condition selected  
from the group consisting of selected from the group consisting of obesity, exogenic  
15 obesity, hyperinsulinaemic obesity, hyperplasmic obesity, hyperphyseal adiposity,  
hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity,  
infantile obesity, upper body obesity, alimentary obesity, hypogonadal obesity and  
central obesity in combination with a second active ingredient selected from the group  
consisting of active substances for the treatment of diabetes, active substances for the  
20 treatment of diabetic complications, active substances for the treatment of obesity,  
active substances for the treatment of high blood pressure, active substances for the  
treatment of hyperlipidaemia, including arteriosclerosis active substances for the  
treatment of dyslipidaemia, including arteriosclerosis, active substances for the  
treatment of arthritis.

13) Use of Flibanserin, optionally in form of the free base, the pharmacologically  
acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates  
thereof, for the preparation of a medicament for promoting, increasing or facilitating  
weight loss in combination with a second active ingredient selected from the group  
30 consisting of active substances for the treatment of diabetes, active substances for the  
treatment of diabetic complications, active substances for the treatment of obesity,  
active substances for the treatment of high blood pressure, active substances for the  
treatment of hyperlipidaemia, including arteriosclerosis active substances for the

treatment of dyslipidaemia, including arteriosclerosis, active substances for the treatment of arthritis.

- 14) Use of Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof, for the preparation of a medicament for inhibiting or prevention of body weight gain in combination with a second active ingredient selected from the group consisting of active substances for the treatment of diabetes, active substances for the treatment of diabetic complications, active substances for the treatment of obesity, active substances for the treatment of high blood pressure, active substances for the treatment of hyperlipidaemia, including arteriosclerosis active substances for the treatment of dyslipidaemia, including arteriosclerosis, active substances for the treatment of arthritis.
- 15) Use of Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof, for the preparation of a medicament for inhibiting or reducing appetite in combination with a second active ingredient selected from the group consisting of active substances for the treatment of diabetes, active substances for the treatment of diabetic complications, active substances for the treatment of obesity, active substances for the treatment of high blood pressure, active substances for the treatment of hyperlipidaemia, including arteriosclerosis active substances for the treatment of dyslipidaemia, including arteriosclerosis, active substances for the treatment of arthritis.
- 16) Use of Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof, for the preparation of a medicament for the treatment and/or prevention diseases and/or disorders associated with obesity in combination with a second active ingredient selected from the group consisting of active substances for the treatment of diabetes, active substances for the treatment of diabetic complications, active substances for the treatment of obesity, active substances for the treatment of high blood pressure, active substances for the treatment of hyperlipidaemia, including

arteriosclerosis active substances for the treatment of dyslipidaemia, including  
arteriosclerosis, active substances for the treatment of arthritis.

17) Use according to claim 16 wherein the diseases and/or disorders associated with  
5 obesity are selected from the group consisting of metabolic syndrome (syndromeX),  
hypertension, osteoarthritis, diabetes, especially type II diabetes, complications of  
diabetes including diabetic retinopathy, diabetic neuropathy, diabetic nephropathy,  
insulin resistance, pathological glucose tolerance, encephalorrhagia, heart diseases,  
cardiac insufficiency, arteriosclerosis, arthritis, gonitis and dyslipidaemia.

18) Use according to any of the claims 12 to 17, wherein the active substance for the  
10 treatment of obesity is selected from the group consisting of orlistat, phenetermine,  
sibutramine and topiramate or a pharmaceutical acceptable salt thereof.

# INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/064825

## A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/496 A61K31/365 A61K31/137 A61K31/34 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, WPI Data, BIOSIS, EMBASE, SCISEARCH

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CREMERS.B. & BÖHM, M.: "Non erectile dysfunction application of sildenafil" HERZ, vol. 28, no. 4, 2003, pages 325-333, XP002404204 page 329 - page 331	8,10
P,X	WO 2005/102342 A (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [US]; BOEHR) 3 November 2005 (2005-11-03) example 1	8,10
A	EP 1 256 343 A1 (BECK JUERGEN K DR [DE]) 13 November 2002 (2002-11-13) claims	1-18
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☒ Further documents are listed in the continuation of Box C.

☒ 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

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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.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

24 October 2006

Date of mailing of the international search report

17/11/2006

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# INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2006/064825

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	<p>WO 2006/019715 A (BOEHRINGER INGELHEIM PHARMA [US]; PYKE ROBERT [US]) 23 February 2006 (2006-02-23) claims</p> <p>-----</p>	1-18

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/064825

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