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WO-A1-2009/145900
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US-B1- 6 548 493
US-B2- 6 929 803

DESCRIPTION

FIELD OF THE INVENTION

[0001] The invention relates to particular substituted heterocycle fused gamma-carbolines of Formula Q as defined in the claims, in free, pharmaceutically acceptable salt form, pharmaceutical compositions thereof, and methods of use in the treatment of diseases involving 5-HT_{2A} receptor, serotonin transporter (SERT) and/or pathways involving dopamine D_2 receptor signaling systems, e.g., diseases or disorders such as anxiety, psychosis, schizophrenia, sleep disorders, sexual disorders, migraine, conditions associated with cephalic pain, social phobias, gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility and obesity; depression and mood disorders associated with psychosis or Parkinson's disease; psychosis such as schizophrenia associated with depression; bipolar disorder; and other psychiatric and neurological conditions, as well as to combinations with other agents.

BACKGROUND OF THE INVENTION

[0002] Certain substituted heterocycle fused gamma-carbolines have been reported to be agonists or antagonists of 5-HT2 receptors, particularly 5-HT_{2A} and 5-HT_{2C} receptors, in treating central nervous system disorders. These compounds have been disclosed in U.S. Pat. No. 6,548,493; 7,238,690; 6,552,017; 6,713,471; 7,183,282; U.S. RE39680, and U.S. RE39679, as novel compounds useful for the treatment of disorders associated with 5-HT_{2A} receptor modulation such as obesity, anxiety, depression, psychosis, schizophrenia, sleep disorders, sexual disorders migraine, conditions associated with cephalic pain, social phobias, gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility, and obesity. PCT/US08/03340 (WO 2008/112280) and U.S. Application Serial No. 10/786,935 (U.S. Pub. No. 2004/0209864) also disclose methods of making substituted heterocycle fused gamma-carbolines and uses of these gamma-carbolines as serotonin agonists and antagonists useful for the control and prevention of central nervous system disorders such as addictive behavior and sleep disorders. WO 2009/114181 also discloses of methods of preparing toluenesulfonic acid addition salt crystals of these substituted heterocycle fused gamma-carbolines.

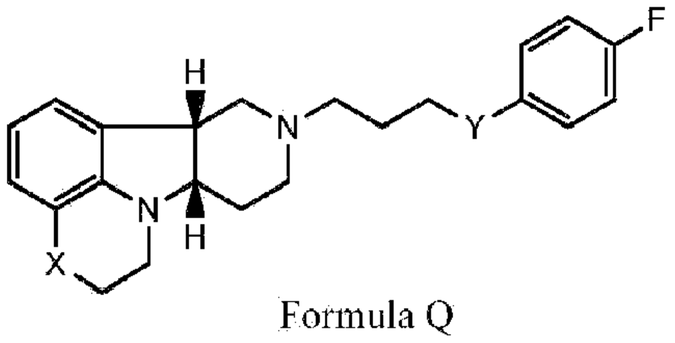
[0003] In addition, WO/2009/145900 discloses use of particular substituted heterocycle fused gamma-carbolines for the treatment of a combination of psychosis and depressive disorders as well as sleep, depressive and/or mood disorders in patients with psychosis or Parkinson's disease. In addition to disorders associated with psychosis and/or depression, this patent application discloses and claims use of these compounds at a low dose to selectively antagonize 5-HT_{2A} receptors without affecting or minimally affecting dopamine D_2 receptors, thereby useful for the treatment of sleep disorders without the side effects of the dopamine D_2 pathways or side effects of other pathways (e.g., $GABA_A$receptors) associated with convention

sedative-hypnotic agents (e.g., benzodiazepines) including but not limited to the development of drug dependency, muscle hypotonia, weakness, headache, blurred vision, vertigo, nausea, vomiting, epigastric distress, diarrhea, joint pains, and chest pains.

[0004] While these substituted heterocycle fused gamma-carbolines and their uses have been reported, particularly for the treatment of diseases such as schizophrenia, patient compliance in adhering to the medication schedule is a common and critical problem in therapy. According to one study, non-compliance with antipsychotic medication is observed in around 50% of people with schizophrenia. Such non-compliance is linked to the increase in re-hospitalizations and generally poorer outcome in people with psychotic disorders. Therefore, there exists a need for drugs, particularly anti-psychotic drugs that can overcome the non-compliance and provide prodrugs which have a sustained or delayed release profile.

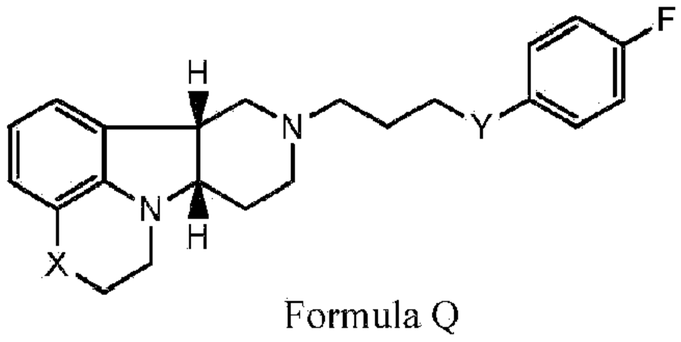
SUMMARY OF THE INVENTION

[0005] The present invention provides depot formulation of particular substituted heterocycle fused gamma-carbolines of Formula Q as defined in the claims that have altered pharmacokinetic profile, e.g., altered rate of absorption and distribution, and therefore may be useful for an improved formulation and/or for controlling the duration of the effect of the drug in the body (e.g., for sustained- or controlled release). the invention provides a pharmaceutical composition comprising a compound of the current invention as hereinbefore described, in admixture with a pharmaceutically acceptable diluent or carrier. Therefore, the invention provides the following: A Pharmaceutical Composition comprising the compound of Formula Q:



Formula Q

wherein X is -N(H)-, -N(CH_3)- or -O-; and Y is -C(=O), -O- or -C(H)(OH), in free or pharmaceutically acceptable salt form, in admixture with a pharmaceutically acceptable diluent or carrier. The invention provides a pharmaceutical composition, e.g., for sustained or delayed release, e.g., depot, formulation, comprising (i) the compound of Formula Q as described above; and (ii) a polymeric matrix:



Formula Q

wherein X is -N(H)-, -N(CH_3)- or -O-; and Y is -C(=O), -O- or -C(H)(OH), in free or pharmaceutically acceptable salt form.

[0006] In a further embodiment, the polymeric matrix comprises standard polymers used in depot formulations such as polymers selected from apolyester of a hydroxyfatty acid and

derivatives thereof, or a polymer of an alkyl alpha-cyanoacrylate, a polyalkylene oxalate, a polyortho ester, a polycarbonate, a polyortho-carbonate, a polyamino acid, a hyaluronic acid ester, and mixtures thereof. In a further embodiment, the polymer is selected from a group consisting of polylactide, poly d,l-lactide, poly glycolide, PLGA 50:50, PLGA 85:15 and PLGA 90:10 polymer. In another embodiment, the polymer is selected from poly(glycolic acid), poly-D,L-lactic acid, poly-L-lactic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxonone, poly(ortho carbonates), poly(acetals), poly(lactic acid-caprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, and natural polymers including albumin, casein, and waxes, such as, glycerol mono- and distearate, and the like. In a preferred embodiment, the polymeric matrix comprises poly(d,l-lactide-co-glycolide). For example, the Pharmaceutical Composition of Formula Q wherein said compound is dissolved or dispersed in a polymeric matrix which comprises a poly(d,l-lactide-co-glycolide).

[0007] The pharmaceutical compositions are particularly useful for sustained or delayed release, wherein the compound is released upon degradation of the polymeric matrix and/or the prodrug. Therefore, these compositions may be formulated for controlled- and/or sustained-release of the active compounds as described above over a period of up to 180 days, e.g., from about 7 to about 14 to about 30 to about 180 days. For example, the polymeric matrix may degrade and release the compounds disclosed herein over a period of about 7, about 14, about 30, about 60 or about 90 days. In another example, the polymeric matrix may degrade and release the compounds disclosed herein over a period of about 120, or about 180 days. Therefore, in one embodiment, the Pharmaceutical Composition releases the compound over a period of up to 180 days, about 120 days, about 90 days, about 60 days, about 30 days, about 14 days or about 7 days.

[0008] In still another further embodiment, the Pharmaceutical Compositions of the Invention are formulated for administration by injection. In another embodiment, the Pharmaceutical Compositions of the Invention may be formulated for oral administration. The Compound of Formula Q may be included as a depot formulation, e.g., by dispersing, dissolving or encapsulating the compounds of the Invention in a polymeric matrix such that the compound is continually released as the polymer degrades over time. The release of the compounds of the Invention or the Compound of Formula Q from the polymeric matrix provides for the controlled- and/or delayed- and/or sustained-release of the compounds, e.g., from the pharmaceutical depot composition, into a subject, for example a warm-blooded animal such as man, to which the pharmaceutical depot is administered. Thus, the pharmaceutical depot delivers the active compounds described hereinbefore or the Compound of Formula Q to the subject at concentrations effective for treatment of the particular disease or medical condition over a sustained period of time, e.g., 7-180 days, preferably about 7 or about 14 or about 30, about 60 or about 90 days.

[0009] alpha-hydroxycarboxylic acid polymer (preferably lactic acid-glycolic acid polymer), its ester, poly-alpha-cyanoacrylic acid esters, etc. may be used, and lactic acid-glycolic acid copolymer (also referred to as poly(lactide-alpha-glycolide) or poly(lactic-co-glycolic acid), and

hereinafter referred to as PLGA) are preferred. Thus, in one aspect the polymer useful for the polymeric matrix is PLGA. As used herein, the term PLGA includes polymers of lactic acid (also referred to as polylactide, poly(lactic acid), or PLA). Most preferably, the polymer is the biodegradable poly(d,l-lactide-co-glycolide) polymer.

[0010] In a preferred embodiment, the polymeric matrix of the invention is a biocompatible and biodegradable polymeric material. The term "biocompatible" is defined as a polymeric material that is not toxic, is not carcinogenic, and does not significantly induce inflammation in body tissues. The matrix material should be biodegradable wherein the polymeric material should degrade by bodily processes to products readily disposable by the body and should not accumulate in the body. The products of the biodegradation should also be biocompatible with the body in that the polymeric matrix is biocompatible with the body. The preferred polymer for use in the practice of this invention is dl(polylactide-co-glycolide). It is preferred that the molar ratio of lactide to glycolide in such a copolymer be in the range of from about 75:25 to 50:50.

[0011] Useful PLGA polymers may have a weight-average molecular weight of from about 5,000 to 500,000 daltons, preferably about 150,000 daltons. Dependent on the rate of degradation to be achieved, different molecular weight of polymers may be used. For a diffusional mechanism of drug release, the polymer should remain intact until all of the drug is released from the polymeric matrix and then degrade. The drug can also be released from the polymeric matrix as the polymeric excipient bioerodes.

[0012] The PLGA may be prepared by any conventional method, or may be commercially available. For example, PLGA can be produced by ring-opening polymerisation with a suitable catalyst from cyclic lactide, glycolide, etc. (see EP-0058481B2; Effects of polymerization variables on PLGA properties: molecular weight, composition and chain structure).

[0013] It is believed that PLGA is biodegradable by means of the degradation of the entire solid polymer composition, due to the break-down of hydrolysable and enzymatically cleavable ester linkages under biological conditions (for example in the presence of water and biological enzymes found in tissues of warm-blooded animals such as humans) to form lactic acid and glycolic acid. Both lactic acid and glycolic acid are water-soluble, non-toxic products of normal metabolism, which may further biodegrade to form carbon dioxide and water. In other words, PLGA is believed to degrade by means of hydrolysis of its ester groups in the presence of water, for example in the body of a warm-blooded animal such as man, to produce lactic acid and glycolic acid and create the acidic microclimate. Lactic and glycolic acid are by-products of various metabolic pathways in the body of a warm-blooded animal such as man under normal physiological conditions and therefore are well tolerated and produce minimal systemic toxicity.

[0014] In another embodiment, the polymeric matrix useful for the invention may comprise a star polymer wherein the structure of the polyester is star-shaped. These polyesters have a single polyol residue as a central moiety surrounded by acid residue chains. The polyol moiety may be, e. g., glucose or, e. g., mannitol. These esters are known and described in GB 2,145,422 and in U. S. Patent No. 5,538,739.

[0015] The star polymers may be prepared using polyhydroxy compounds, e. g., polyol, e. g., glucose or mannitol as the initiator. The polyol contains at least 3 hydroxy groups and has a molecular weight of up to about 20,000 Daltons, with at least 1, preferably at least 2, e. g. , as a mean 3 of the hydroxy groups of the polyol being in the form of ester groups, which contain polylactide or co-polylactide chains. The branched polyesters, e. g., poly (d, l-lactide-co-glycolide) have a central glucose moiety having rays of linear polylactide chains.

[0016] The depot composition of the invention as herein before described may comprise the polymer in the form of microparticles or nanoparticles, or in a liquid form, with the compounds of the Invention dispersed or encapsulated therein. "Microparticles" is meant solid particles that contain the compounds of the Invention either in solution or in solid form wherein such compound is dispersed or dissolved within the polymer that serves as the matrix of the particle. By an appropriate selection of polymeric materials, a microparticle formulation can be made in which the resulting microparticles exhibit both diffusional release and biodegradation release properties.

[0017] When the polymer is in the form of microparticles, the microparticles may be prepared using any appropriate method, such as by a solvent evaporation or solvent extraction method. For example, in the solvent evaporation method, the compounds of the Invention and the polymer may be dissolved in a volatile organic solvent (for example a ketone such as acetone, a halogenated hydrocarbon such as chloroform or methylene chloride, a halogenated aromatic hydrocarbon, a cyclic ether such as dioxane, an ester such as ethyl acetate, a nitrile such as acetonitrile, or an alcohol such as ethanol) and dispersed in an aqueous phase containing a suitable emulsion stabiliser (for example polyvinyl alcohol, PVA). The organic solvent is then evaporated to provide microparticles with the compounds of the Invention encapsulated therein. In the solvent extraction method, the compounds of the Invention and polymer may be dissolved in a polar solvent (such as acetonitrile, dichloromethane, methanol, ethyl acetate or methyl formate) and then dispersed in an aqueous phase (such as a water/PVA solution). An emulsion is produced to provide microparticles with the compounds of the Invention encapsulated therein. Spray drying is an alternative manufacturing technique for preparing the microparticles.

[0018] Another method for preparing the microparticles of the invention is also described in both U.S. Pat. No. 4,389,330 and U.S. Pat. No. 4,530,840.

[0019] The microparticle of the present invention can be prepared by any method capable of producing microparticles in a size range acceptable for use in an injectable composition. One preferred method of preparation is that described in U.S. Pat. No. 4,389,330. In this method the active agent is dissolved or dispersed in an appropriate solvent. To the agent-containing medium is added the polymeric matrix material in an amount relative to the active ingredient that provides a product having the desired loading of active agent. Optionally, all of the ingredients of the microparticle product can be blended in the solvent medium together.

[0020] Solvents for the compounds of the Invention or the compound of Formula Q and the polymeric matrix material that can be employed in the practice of the present invention include organic solvents, such as acetone; halogenated hydrocarbons, such as chloroform, methylene chloride, and the like; aromatic hydrocarbon compounds; halogenated aromatic hydrocarbon compounds; cyclic ethers; alcohols, such as, benzyl alcohol; ethyl acetate; and the like. In one embodiment, the solvent for use in the practice of the present invention may be a mixture of benzyl alcohol and ethyl acetate. Further information for the preparation of microparticles useful for the invention can be found in U.S. Patent Publication Number 2008/0069885, the contents of which are incorporated herein by reference in their entirety.

[0021] The amount of the compounds of the Invention or the compounds of Formula Q incorporated in the microparticles usually ranges from about 1 wt % to about 90 wt. %, preferably 30 to 50 wt. %, more preferably 35 to 40 wt. %. By weight % is meant parts of the compounds of the Invention per total weight of microparticle.

[0022] The pharmaceutical depot may comprise a pharmaceutically-acceptable diluent or carrier, such as a water miscible diluent or carrier.

[0023] A "therapeutically effective amount" is any amount of the compounds of the invention (for example as contained in the pharmaceutical depot) which, when administered to a subject suffering from a disease or disorder, is effective to cause a reduction, remission, or regression of the disease or disorder over the period of time as intended for the treatment.

[0024] Dosages employed in practicing the present invention will of course vary depending, e.g. on the particular disease or condition to be treated, the particular compound of the Invention used, the mode of administration, and the therapy desired. Unless otherwise indicated, an amount of the compound of the Invention for administration (whether administered as a free base or as a salt form) refers to or is based on the amount of the active drug compound in free base form or in pharmaceutically acceptable salt form (i.e., the calculation of the amount is based on the free base amount or pharmaceutically acceptable salt amount and in a non-prodrug form). Therefore, the dosage is based on the amount of the compound of Formula Q, wherein X is $-N(CH_3)-$ and Y is -C(=O), in free base form. In another embodiment, the dosage is based on the amount of the compound of Formula Q, wherein X is $-N(CH_3)-$ and Y is -C(=O), in pharmaceutically acceptable salt.

[0025] The compounds of the Invention may be administered by any satisfactory route, including orally, parenterally (intravenously, intramuscular or subcutaneous) or transdermally, but are preferably administered orally. In certain embodiment, the compounds of the Invention, e.g., in depot formulation, is preferably administered parenterally, e.g., by injection.

[0026] In general, satisfactory results for use of the compounds of the Invention or the compounds of Formula Q as hereinbefore described, e.g. for the treatment of a combination of diseases such as a combination of at least depression, psychosis, e.g., (1) psychosis, e.g., schizophrenia, in a patient suffering from depression; (2) depression in a patient suffering from

psychosis, e.g., schizophrenia; (3) mood disorders associated with psychosis, e.g., schizophrenia, or Parkinson's disease; and (4) sleep disorders associated with psychosis, e.g., schizophrenia, or Parkinson's disease, as set forth above are indicated to be obtained on oral administration at dosages of the order from about 1 mg to 100 mg once daily, preferably 2.5mg-50mg, e.g., 2.5mg, 5mg, 10mg, 20mg, 30mg, 40mg or 50mg in free base or pharmaceutically acceptable, non-prodrug form, once daily, preferably via oral administration. Preferably, the daily dosage is 20mg-40mg in free base or pharmaceutically acceptable, non-prodrug form. For example, the method of treating schizophrenia or dementia comprises a daily dosage of 20-40mg in free base or pharmaceutically acceptable, non-prodrug form.

[0027] Satisfactory results for use of the compounds of the Invention or compounds or Formula Q as hereinbefore described, e.g. for the treatment of sleep disorder alone are indicated to be obtained on oral administration at dosages of the order from about 2.5mg-5mg, e.g., 2.5mg, 3mg, 4mg or 5mg, of a compound of the Invention, in free or pharmaceutically acceptable salt form, once daily, preferably via oral administration.

[0028] For treatment of the disorders disclosed herein wherein the depot composition is used to achieve longer duration of action, the dosages will be higher relative to the shorter action composition, e.g., higher than 1-100mg, e.g., 25mg, 50mg, 100mg, 500mg, 1,000mg, or greater than 1000mg in free base or pharmaceutically acceptable, non-prodrug form. For example, for the treatment of psychosis, schizophrenia or dementia (Methods I or III), the weekly biweekly and monthly dosages may be about 100mg-300mg (e.g., 140mg-160mg), about 250mg-600mg (e.g., 280-300mg) and about 500-1,240mg (e.g., 600mg-620mg) of the compound of the invention based on the free base or pharmaceutically acceptable salt and non-prodrug form. Duration of action of the compounds of the Invention may be controlled by manipulation of the polymer composition, i.e., the polymer:drug ratio and microparticle size. Wherein the composition of the invention is a depot composition, administration by injection is preferred.

[0029] The pharmaceutically acceptable salts of the compounds of the Invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free base forms of these compounds with a stoichiometric amount of the appropriate acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Further details for the preparation of these salts, e.g., toluenesulfonic salt in amorphous or crystal form, may be found in PCT/US08/03340 and/or U.S. Provisional Appl. No. 61/036,069.

[0030] Pharmaceutical compositions comprising compounds of the Invention may be prepared using conventional diluents or excipients (an example include, but is not limited to sesame oil) and techniques known in the galenic art. Thus oral dosage forms may include tablets, capsules, solutions, suspensions and the like.

REFERENCES CITED IN THE DESCRIPTION

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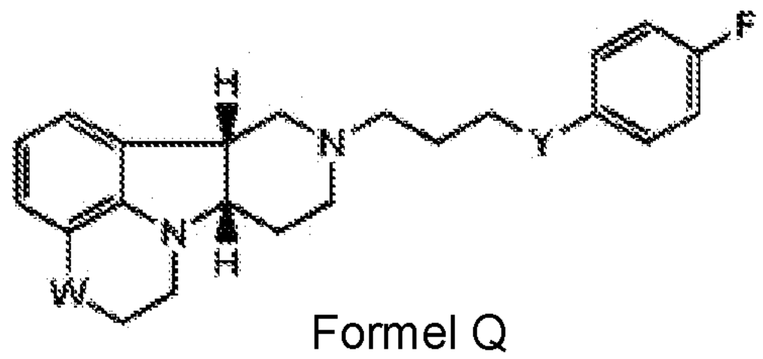
ORGANISKE FORBINDELSER

Patentkrav

1. En farmaceutisk sammensætning omfattende den kemiske forbindelse for Formel Q:



Formel Q

hvori W er −N(CH_3)-; og Y er −C(=O), i fri eller farmacewutisk acceptabel saltform; og (ii) en polymer matrix, hvori den polymere matrix er en biologisk nedbrydelig poly(d,l-lactid-co-glycolid)mikrosfære.

2. Den farmaceutiske sammensætning i henhold til krav 1, hvori den kemiske forbindelse for Formel Q er i fri form.

3. Den farmaceutiske sammensætning i henhold til krav 1, hvori den kemiske forbindelse for Formel Q er i toluensulfonsyreadditionssaltform

4. Den farmaceutiske sammensætning i henhold til et hvilket som helst af kravene 1 til 3, i tilsætning med et farmaceutisk acceptabelt fortyndingsmiddel eller bærer.

5. Den farmaceutiske sammensætning i henhold til et hvilket som helst af kravene1-4, hvori nævnte sammensætning frigiver den aktive sammensætning over en periode på cirka 7 dage, cirka 14 dage, cirka 30 dage, cirka 60 dage eller cirka 90 dage.

6. En farmaceutisk sammensætning i henhold til et hvilket som helst af kravene 1-5 til anvendelse i behandling eller profylakse af en lidelse i centralnervesystemet.

7. Den farmaceutiske sammensætning til anvendelse i henhold til krav 6, hvori nævnte lidelse vælges fra en gruppe bestående af overvægt, angst, depression, psykose, skizofreni, søvnforstyrrelser, seksuelle lidelser, migræne, tilstande forbundet med

cephale smerter, sociale fobier og gastrointestinale lidelser, såsom dysfunktion i mavetarmkanalens motilitet.

8. Den farmaceutiske sammensætning til anvendelse i henhold til patentkrav 6, hvori nævnte lidelse er en lidelse, som involverer serotonin 5-HT_2A, dopamin D2 og/eller vejen for serotonin-genooptagelsestransporteren (SERT).

9. Den farmaceutiske sammensætning til anvendelse i henhold til krav 6, hvori nævnte lidelse er en lidelse udvalgt blandt følgende: (i) psykose, fx skizofreni, hos en patient, der lider af depression; (2) depression hos en patient, der lider af psykose, fx skizofreni; (3) stemningsforstyrrelser associeret med psykose, fx skizofreni eller Parkinsons sygdom og (4) søvnforstyrrelser associeret med psykose, fx skizofreni eller Parkinsons sygdom.

10. Den farmaceutiske sammensætning til anvendelse i henhold til krav 9, hvori lidelsen er psykose.

11. Den farmaceutiske sammensætning til anvendelse i henhold til krav 9, hvori lidelsen er skizofreni.

12. Den farmaceutiske sammensætning til anvendelse i henhold til krav 9, hvori lidelsen er depression.

13. Den farmaceutiske sammensætning til anvendelse i henhold til patentkrav 6 omfattende administration til en patient med behov derfor en effektiv mængde; eventuelt hvor nævnte lidelse vælges fra en gruppe bestående af overvægt, angst, depression (for eksempel refraktær depression og svær depressiv lidelse), psykose, skizofreni, søvnforstyrrelser (især søvnforstyrrelser forbundet med skizofreni og andre psykiatriske og neurologiske sygdomme), seksuelle lidelser, migræne, tilstande forbundet med cephalisk smerte, sociale fobier, agitation i demens (fx agitation i Alzheimers sygdom), agitation i autisme og beslægtede autistiske lidelser samt gastrointestinale lidelser, såsom dysfunktion i mavetarmkanalens motilitet.