



(51) International Patent Classification:

A61K 31/496 (2006.01) A61P 25/30 (2006.01)
A61P 25/34 (2006.01)

(21) International Application Number:

PCT/EP2010/003965

(22) International Filing Date:

30 June 2010 (30.06.2010)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/269,870 30 June 2009 (30.06.2009) US

(71) Applicant (for all designated States except US): **MERZ PHARMA GMBH & CO. KGAA** [DE/DE]; Eckenheimer Landstrasse 100, 60318 Frankfurt am Main (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **FRANKE, Lutz** [DE/DE]; Bahnhofstrasse 2, 61118 Bad Vilbel (DE). **VALASTRO, Barbara** [IT/DE]; Kettenhofweg 123, 60325 Frankfurt am Main (DE).

(74) Agent: **RICKER, Mathias**; Wallinger Ricker Schlotter Foerstl, Zweibrückenstrasse 5-7, 80331 München (DE).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

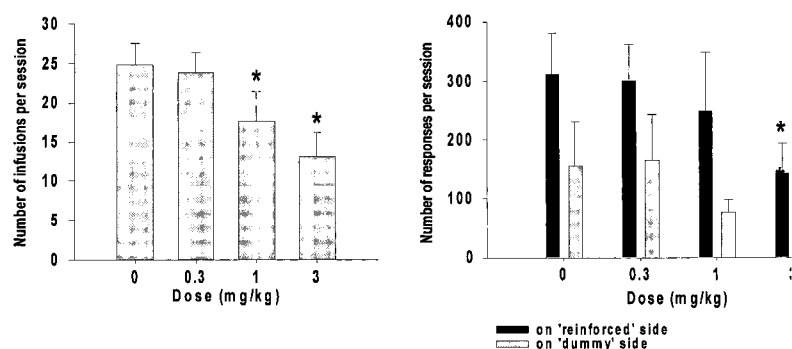
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: ELTOPRAZINE FOR THE TREATMENT OF DRUG ADDICTION

Figure 4



(57) Abstract: The present invention relates to the treatment of an individual afflicted with drug addiction, the instant treatment comprising administering to the individual an effective amount of eltoprazine or a pharmaceutically acceptable salt thereof.

ELTOPRAZINE FOR THE TREATMENT OF DRUG ADDICTION

FIELD OF THE INVENTION

[001] The present invention relates to the efficient treatment of an individual afflicted with drug addiction, the instant treatment comprising administering to the individual an effective amount of eltoprazine or a pharmaceutically acceptable salt thereof.

BACKGROUND OF THE INVENTION

[002] This invention relates to an innovative method of treating patients afflicted with drug addiction, such as cocaine or amphetamine addiction.

[003] Eltoprazine (1-(2,3-dihydro-1,4-benzodioxin-8-yl)piperazine) was synthesized more than two decades ago by scientists at Duphar International Research B. V., Netherlands, and was first described in EP 0138280 (published April 24, 1985) as intermediate for the synthesis of piperazine derivatives. European patent application EP 0189612 (filed December 16, 1985) disclosed for the first time the use of eltoprazine as a pharmaceutical compound. Eltoprazine and related compounds were characterized as compounds having psychotropic activity that could be used, for example, for treating aggressive behavior, and ED₅₀ values for a mouse model for fighting behavior were given in EP 0189612.

[004] The application mentioned further indications including other affections and diseases caused by disturbances in the central nervous system, such as psychoses, fear, depression, or the use as analgetics. Furthermore, the use of such compounds for treating hematological disorders was discussed based on the thrombolytic activity of the compounds. However, no data were given.

[005] Subsequently, the use of eltoprazine in the treatment of aggressive behaviour was tested in several clinical trials, for example in a trial of eltoprazine in the treatment of aggressive behavior in patients with epilepsy or Gilles de la Tourette's Syndrome (see Moriarty et al., Human Psychopharmacology: Clinical and Experimental, 9 (1994) 253-258), or in aggressive mentally handicapped patients (see de Koning et al., Int Clin Psychopharmacol. 9 (1994) 187-94). While these clinical trials did not result in an approval of eltoprazine in these indications, eltoprazine did prove to be clinically safe (de Koning, loc. cit.).

[006] Recently, eltoprazine has been studied in a phase IIa clinical trial for the treatment of ADHD patients (see US 2009/0104261; [http://www.psychogenics.com/pdf/Psychogenics%20-%20Eltoprazine%20Press%20Release%20Jun%2008 .pdf](http://www.psychogenics.com/pdf/Psychogenics%20-%20Eltoprazine%20Press%20Release%20Jun%2008.pdf)).

[007] Drug addiction is a pathological condition that involves the progression of acute drug use to the development of drug-seeking behavior, and the vulnerability to relapse. Furthermore drug addiction includes the decreased and retarded ability to respond to naturally rewarding stimuli. Drug addiction is mainly seen in the case of stimulants, sedatives, hypnotics, opiates and opioid analgesics.

[008] The present invention relates to the use of eltoprazine and its salts, solvates and conjugates, which we have determined possesses a unique receptor profile. Consequently, the present invention relates to the use of eltoprazine for the treatment of drug addiction.

SUMMARY OF THE INVENTION

[009] The present invention relates to a method of treating or preventing drug addiction in a subject in need thereof, comprising administering an

effective amount of eltoprazine or a pharmaceutically acceptable salt thereof.

[0010] A further aspect of the invention relates to such a method comprising administering an effective amount of eltoprazine hydrochloride.

[0011] A further aspect of the invention relates to such a method wherein eltoprazine is administered in a range from about 5 mg to about 75 mg/day.

[0012] A further aspect of the invention relates to such a method wherein eltoprazine is administered in a range from about 5 mg to about 50 mg/day.

[0013] A further aspect of the invention relates to such a method wherein eltoprazine is administered in a range from about 5 mg to about 60 mg/day.

[0014] A further aspect of the invention relates to such a method wherein eltoprazine is administered in a range from about 5 mg to about 40 mg/day.

[0015] A further aspect of the invention relates to such a method wherein eltoprazine is administered in a range from about 5 mg to about 20 mg/day.

[0016] A further aspect of the invention relates to such a method wherein eltoprazine is administered at about 20 mg/day.

[0017] A further aspect of the invention relates to such a method wherein eltoprazine is administered at about 40 mg/day.

[0018] A further aspect of the invention relates to such a method wherein eltoprazine is administered at about 60 mg/day.

[0019] A further aspect of the invention relates to such a method wherein eltoprazine is administered between about 10 and 15 mg/day.

[0020] A further aspect of the invention relates to such a method wherein eltoprazine or a pharmaceutically acceptable salt thereof is administered once a day, twice a day (b.i.d.), or three times a day.

[0021] A further aspect of the invention relates to such a method wherein eltoprazine is administered in an oral formulation.

[0022] A further aspect of the invention relates to a composition comprising eltoprazine or a pharmaceutically acceptable salt thereof (e.g., eltoprazine hydrochloride) for the treatment of drug addiction.

[0023] A further aspect of the invention relates to the use of eltoprazine or a pharmaceutically acceptable salt thereof (e.g., eltoprazine hydrochloride) for the manufacture of a medicament for the treatment of drug addiction.

[0024] A further aspect of the invention relates to the above-defined composition or use wherein eltoprazine or a pharmaceutically acceptable salt thereof (e.g., eltoprazine hydrochloride) is for administration in a range from about 5 mg to about 150 mg/day, or in a range from about 5 mg to about 100 mg/day, or in a range from about 5 mg to about 75 mg/day, in a range from about 5 mg to about 75 mg/day, or in a range from about 5 mg to about 60 mg/day, or in a range from about 5 mg to about 50 mg/day, or in a range from about 5 mg to about 40 mg/day, or in a range from about 5 mg to about 20 mg/day, or in a range from about 5 mg to about 15 mg/day, or wherein eltoprazine is for administration at about 10 mg/day, wherein eltoprazine is for administration at about 15 mg/day, is for administration at about 20 mg/day, or eltoprazine is for administration at about 40 mg/day, or eltoprazine is for administration at about 60 mg/day, or eltoprazine is for administration at about 80 mg/day.

[0025] A further aspect of the invention relates to the above-defined composition or use wherein eltoprazine or a pharmaceutically acceptable

salt thereof (e.g., eltoprazine hydrochloride) is for administration once a day, twice a day (b.i.d.), or three times a day.

[0026] A further aspect of the invention relates to the above-defined composition or use wherein eltoprazine or a pharmaceutically acceptable salt thereof (e.g., eltoprazine hydrochloride) is for administration in an oral formulation.

[0027] A further aspect of the invention relates to a method comprising administering a therapeutically effective amount of eltoprazine or a pharmaceutically acceptable salt thereof in combination with at least one additional pharmaceutical agent which has been shown to be effective for the treatment of drug addiction.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] **Figure 1** shows the potency of eltoprazine on different serotonin receptors at relevant plasma concentration ($< 0.5\mu\text{M}$).

[0029] **Figure 2** shows the effect of eltoprazine on AIM scores in unilaterally 6-OHDA-lesioned rats.

[0030] **Figure 3** shows the effect of eltoprazine on turning behavior induced by high dose of L-DOPA in unilaterally 6-OHDA-lesioned rats.

[0031] **Figure 4** shows the effect of eltoprazine on self administration of nicotine in rats expressed as number of nicotine infusions (left) and responses to active and inactive holes (right). Values are shown as mean $\pm$ SEM and were analysed using one way ANOVA which was followed by posthoc analysis using Dunnett test. N = 13 per group. * - $p < 0.05$ vs. vehicle treatment.

DETAILED DESCRIPTION OF THE INVENTION

[0032] The peculiarity of this invention compared to former treatment approaches for drug addiction is the so far unknown therapeutic efficiency of eltoprazine, which is based on the unique receptor profile with several components potentiating each other in an unexpected way, as evidenced by the surprising activity of eltoprazine in a L-DOPA-induced dyskinesia model.

[0033] In the past, the pharmacological action of eltoprazine was mainly attributed to its agonistic effect on the 5-HT_{1a} and 5-HT_{1b} receptors (see Schipper J, Tulp MTM, Sijbesma H. Neurochemical profile of eltoprazine. Drug metabolism and Drug interactions 1990 8:85-114), while its effect on 5-HT_{2c} (initially designated 5-HT_{1c}) was characterized as antagonistic.

[0034] However, by using recombinant cell lines expressing the 5-HT_{1a}, 5-HT_{1b}, 5-HT_{2a}, 5-HT_{2b}, 5-HT_{2c} edited (data not shown) and 5-HT_{2c} non edited (ne) recombinant receptors in assays for testing the functional activity of eltoprazine, we have surprisingly found that eltoprazine acts primarily as a full agonist at the 5-HT_{2a} and 5-HT_{2c} receptors in human recombinant cell lines, in addition to its partial agonistic action on 5-HT_{1a} and 5-HT_{1b} receptors (see Figure 1).

[0035] Most drugs of abuse cause a locomotor stimulation, which appears, at least in part, to be mediated by increased accumbal dopamine (DA) overflow. Thus, locomotor stimulation has been suggested to be a putative endophenotype for drug addiction. Aripiprazole, a partial 5-HT_{1a} agonists and full 5-HT_{2a} agonist has been shown to antagonize drug-induced locomotor stimulation in mice (Jerlhag, Alcohol 42 (2008) 123-127) and is currently in phase II studies for the treatment of cocaine dependency.

[0036] The present invention relates to the use of eltoprazine and its salts, solvates and conjugates, which possesses a unique receptor profile targeting 5-HT_{2a} receptor as full agonist, and 5-HT_{1a} as partial agonist, besides 5-HT_{2c}, 5-HT_{1a} and 5-HT_{1b} receptors at relevant plasma concentration. Furthermore, eltoprazine is devoid of significant affinity for the dopamine D₂ receptor. In theory, the unique efficacy could be achieved also through a cocktail of drugs mimicking these composite effects, however, such a cocktail of several molecules cannot successfully be developed in a clinical setting obeying regulatory requirements.

[0037] In certain embodiments, the invention relates to the treatment of addiction to a drug taken from the list of stimulants, sedatives, hypnotics, opiates and opioid analgesics.

[0038] In particular such embodiments, the drug is cocaine, alcohol (ethanol), or an amphetamine, particularly alcohol (ethanol).

[0039] In another embodiment, the drug is nicotine.

[0040] In a particular embodiment, the drug is a drug targeting the neuronal nicotinic acetylcholine receptor.

[0041] In particular such embodiments, the drug is alcohol (ethanol) or nicotine.

[0042] It has been shown that in alcohol-preferring rats maintained on limited access to alcohol, acute treatment of nicotine (0.1 or 0.6 mg/kg) decreases the amount of alcohol consumed (Dyr W, Koros E, Bienkowski P, Kostowski W. Involvement of nicotinic acetylcholine receptors in the regulation of alcohol drinking in Wistar rats. *Alcohol* 1999;34(1):43 - 7). Similarly, a decrease in the alcohol intake was also observed after repeated treatment with nicotine (0.35 and 0.7 mg/kg sc for 3 and 1 weeks) in rats drinking 10% alcohol for 8 weeks (Sharpe AL, Samson HH. Repeated nicotine injections

decrease operant ethanol self-administration. Alcohol 2002;28(1):1-7). It is assumed that the neuronal nicotinic acetylcholine receptor is also a target site of alcohol and mediates some of its effects on the CNS (Aistrup GL, Marszalec W, Narahashi T. Ethanol modulation of nicotinic acetylcholine receptor currents in cultured cortical neurons. Mol Pharmacol 1999;55:39 – 49).

[0043] As used herein, the term "subject" encompasses mammals including animals and humans.

[0044] The term eltoprazine is known in the art and may also be known as DU-28853 and 1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine. As used herein, eltoprazine refers to the substance, as well as its pharmaceutically acceptable salts.

[0045] The term "agonist" refers to a substance that binds to a receptor and mimics the cellular effect of the native or endogenous ligand for the same receptor. The term agonist includes the class of agents called full agonists, which bind and display full efficacy at the receptor, and partial agonists, which have only partial efficacy at the receptor. Partial agonists may also be seen as competitive antagonists, competing away the endogenous ligand when it is in excess or give a sub maximal response when inadequate amount of endogenous ligand is present. The term "activation" refers to the state of a receptor when an agonist is bound to it.

[0046] The term "treat" is used herein to mean to relieve or alleviate at least one symptom of a disease in a subject. Within the meaning of the present invention, the term "treat" also denotes to arrest, delay the onset (*i.e.*, the period prior to clinical manifestation of a disease) and/or reduce the risk of developing or worsening a disease.

[0047] The term "therapeutically effective" applied to dose or amount refers to that quantity of a compound or pharmaceutical composition sufficient to result in a desired activity upon administration to a mammal in need thereof.

[0048] The phrase "pharmaceutically acceptable", as used in connection with compositions of the invention, refers to molecular entities and other ingredients of such compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a mammal (e.g., human). The term "pharmaceutically acceptable" may also mean approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in mammals, and more particularly in humans.

[0049] The term "salt" is defined as a chemical containing different charged components. The term salt also includes hydrates and solvates. Contemplated in the instant description are pharmaceutically acceptable salts, which salts may include, but are not limited to, acid addition salts, such as those made with hydrochloric, sulphuric, nitric, phosphoric, acetic, maleic, fumaric, tartaric, citric, benzoic, methane sulphonic, naphthalene sulphonic, p-toluene sulphonic acid. All of these salts (or other similar salts) may be prepared by conventional means. The nature of the salt is not critical, provided that it is non-toxic and does not substantially interfere with the desired pharmacological activity.

[0050] Eltoprazine may be used according to the invention in the form of any of pharmaceutically acceptable salts, solvates and conjugates. Any references to eltoprazine in this description should be understood as also referring to such salts, solvates and conjugates.

[0051] The term "carrier" applied to pharmaceutical compositions of the invention refers to a diluent, excipient, or vehicle with which an active compound (e.g., eltoprazine) is administered. Such pharmaceutical carriers may be sterile liquids, such as water, saline solutions, aqueous dextrose

solutions, aqueous glycerol solutions, and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by A.R. Gennaro, 20th Edition.

[0052] The term "about" or "approximately" usually means within 20%, alternatively within 10%, including within 5% of a given value or range. Alternatively, especially in biological systems, the term "about" means within about a log (*i.e.*, an order of magnitude), including within a factor of two of a given value.

[0053] In conjunction with the methods of the present invention, also provided are pharmaceutical compositions comprising a therapeutically effective amount of eltoprazine. The compositions of the invention may further comprise a carrier or excipient (all pharmaceutically acceptable). The compositions may be formulated *e.g.* for once-a-day administration, twice-a-day administration, or three times a day administration.

[0054] The active ingredient (*e.g.*, eltoprazine) or the composition of the present invention may be used for the treatment of at least one of the mentioned disorders, wherein the treatment is adapted to or appropriately prepared for a specific administration as disclosed herein (*e.g.*, to once-a-day, twice-a-day, or three times a day administration). For this purpose the package leaflet and/or the patient information contains corresponding information.

[0055] In another embodiment, a therapeutically effective amount of eltoprazine is administered twice per day. In particular, eltoprazine is administered once in the morning, and once in the middle of the day, particularly at about lunchtime, wherein the lunchtime treatment is between about 6 and 10, particularly between about 7 and 9 hours before the patient wishes to go to bed. Such an administration should allow for the eltoprazine

plasma level to ebb away during evening and at nighttime, reducing the risk of an impaired REM-(*rapid eye movement*)-activity.

[0056] In another embodiment, the first dosage of eltoprazine consist of about 55 to 65% of the total daily dosage amount, and the second dose of eltoprazine comprises the remaining total daily dosage amount.

[0057] The active ingredient (e.g., eltoprazine) or the composition of the present invention may be used for the manufacture of a medicament for the treatment of drug addiction, wherein the medicament is adapted to or appropriately prepared for a specific administration as disclosed herein (e.g., to once-a-day, twice-a-day, or three times a day administration). For this purpose the package leaflet and/or the patient information contains corresponding information.

[0058] According to the present invention, the dosage form of eltoprazine, or an eltoprazine salt, may be a solid, semisolid, or liquid formulation according to the following.

[0059] Eltoprazine may be administered orally, topically, parenterally, or mucosally (e.g., buccally, by inhalation, or rectally) in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers. In another embodiment, eltoprazine may be formulated as a flavored liquid (e.g., peppermint flavor). Eltoprazine may be administered orally in the form of a capsule, a tablet, granules, pellets or the like, or as a semi-solid, or liquid formulation (see Remington's Pharmaceutical Sciences, 20th Edition, by A.R. Gennaro).

[0060] For oral administration in the form of a tablet or capsule, eltoprazine may be combined with non-toxic, pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, sucrose, glucose, mannitol, sorbitol and other reducing and non-reducing

sugars, microcrystalline cellulose, calcium sulfate, or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc, or silica, steric acid, sodium stearyl fumarate, glyceryl behenate, calcium stearate, and the like); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate), coloring and flavoring agents, gelatin, sweeteners, natural and synthetic gums (such as acacia, tragacanth or alginates), buffer salts, carboxymethylcellulose, polyethyleneglycol, waxes, and the like.

[0061] The tablets may be coated with a concentrated sugar solution which may contain e.g., gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablets may be coated with a polymer that dissolves in a readily volatile organic solvent or mixture of organic solvents. In specific embodiments, eltoprazine is formulated in immediate-release (IR) or modified-release (MR) tablets. Immediate release solid dosage forms permit the release of most or all of the active ingredient over a short period of time, such as 60 minutes or less, and make rapid absorption of the drug possible. Modified release solid oral dosage forms permit the sustained release of the active ingredient over an extended period of time in an effort to maintain therapeutically effective plasma levels over similarly extended time intervals and/or to modify other pharmacokinetic properties of the active ingredient. For example, eltoprazine may be formulated in a modified release dosage form (including modified release tablets) to provide a dose of eltoprazine.

[0062] For the formulation of soft gelatin capsules, eltoprazine may be admixed with e.g., a vegetable oil or polyethyleneglycol. Hard gelatin capsules may contain granules of the active substances using either the above-mentioned excipients for tablets e.g., lactose, saccharose, sorbitol, mannitol, starches (e.g., potato starch, corn starch or amylopectin), cellulose derivatives or gelatine. Also liquids or semisolids of the drug may be filled into hard gelatine capsules.

[0063] Eltoprazine may also be introduced in microspheres or microcapsules, e.g., fabricated from polyglycolic acid/lactic acid (PGLA) (see, e.g., U.S. Patents No. 5,814,344; 5,100,669 and 4,849,222; PCT Publications No. WO 95/11010 and WO 93/07861). Biocompatible polymers may be used in achieving controlled release of a drug, include for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, poly(epsilon-caprolactone), polyhydroxybutyric acid, polyorthoesters, polyacetals, polyhydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

[0064] Formulation of eltoprazine in a semi-solid or liquid form may also be used. Eltoprazine may constitute between 0.1 and 99% by weight of the formulation, more specifically between 0.5 and 20% by weight for formulations intended for injection and between 0.2 and 50% by weight for formulations suitable for oral administration.

[0065] In one embodiment of the invention, eltoprazine is administered in a modified release formulation. Modified release dosage forms provide a means for improving patient compliance and for ensuring effective and safe therapy by reducing the incidence of adverse drug reactions. Compared to immediate release dosage forms, modified release dosage forms may be used to prolong pharmacologic action after administration, and to reduce variability in the plasma concentration of a drug throughout the dosage interval, thereby eliminating or reducing sharp peaks.

[0066] A modified release dosage form may comprise a core either coated with or containing a drug. The core is then coated with a release-modifying polymer within which the drug is dispersed. The release-modifying polymer disintegrates gradually, releasing the drug over time. Thus, the outer-most layer of the composition effectively slows down and thereby regulates the diffusion of the drug across the coating layer when the composition is exposed to an aqueous environment, i.e. the gastrointestinal tract. The net rate of diffusion of the drug is mainly dependent on the ability of the gastric

fluid to penetrate the coating layer or matrix and on the solubility of the drug itself.

[0067] In another embodiment of the invention, eltoprazine is formulated in an oral, liquid formulation. Liquid preparations for oral administration may take the form of, for example, solutions, syrups, emulsions or suspensions, or they may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Preparations for oral administration may be suitably formulated to give controlled or postponed release of the active compound.

[0068] For oral administration in liquid form, eltoprazine may be combined with non-toxic, pharmaceutically acceptable inert carriers (e.g., ethanol, glycerol, water), suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats), emulsifying agents (e.g., lecithin or acacia), non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol or fractionated vegetable oils), preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid), and the like. Stabilizing agents such as antioxidants (BHA, BHT, propyl gallate, sodium ascorbate, citric acid) may also be added to stabilize the dosage forms. For example, solutions may contain from about 0.2% to about 20% by weight of eltoprazine, with the balance being sugar and mixture of ethanol, water, glycerol and propylene glycol. Optionally, such liquid formulations may contain coloring agents, flavoring agents, saccharine and carboxymethyl-cellulose as a thickening agent or other excipients.

[0069] In another embodiment, a therapeutically effective amount of eltoprazine is administered in an oral solution containing a preservative, a sweetener, a solubilizer, and a solvent. The oral solution may include one or more buffers, flavorings, or additional excipients. In a further embodiment, a peppermint or other flavoring is added to the eltoprazine oral liquid formulation.

[0070] For administration by inhalation, eltoprazine may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0071] Solutions for parenteral applications by injection may be prepared in an aqueous solution of the compound or of a water-soluble pharmaceutically acceptable salt of the active substances, for example in a concentration of from about 0.5% to about 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules.

[0072] The formulations of the invention may be delivered parenterally, i.e., by intravenous (i.v.), intracerebroventricular (i.c.v.), subcutaneous (s.c.), intraperitoneal (i.p.), intramuscular (i.m.), subdermal (s.d.), or intradermal (i.d.) administration, by direct injection, via, for example, bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0073] The invention also provides a pharmaceutical pack or kit comprising one or more containers containing eltoprazine and, optionally, more of the ingredients of the formulation. In a specific embodiment, eltoprazine is provided as an oral solution for administration with the use of a 2-teaspoon capacity syringe (dosage KORC®). Each oral syringe has hatch marks for

measurement, with lines on the right side of the syringe (tip down) representing tsp units, and those on the left representing ml units.

[0074] The optimal therapeutically effective amount may be determined experimentally, taking into consideration the exact mode of administration, form in which the drug is administered, the indication toward which the administration is directed, the subject involved (e.g., body weight, health, age, sex, etc.), and the preference and experience of the physician or veterinarian in charge.

[0075] Dosage units for rectal application may be solutions or suspensions or may be prepared in the form of suppositories or retention enemas comprising eltoprazine in a mixture with a neutral fatty base, or gelatin rectal capsules comprising the active substances in admixture with vegetable oil or paraffin oil.

[0076] Toxicity and therapeutic efficacy of the compositions of the invention may be determined by standard pharmaceutical procedures in experimental animals, e.g., by determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index and it may be expressed as the ratio LD₅₀/ED₅₀. Compositions that exhibit large therapeutic indices are preferred.

[0077] Suitable daily doses of the active ingredient of the invention (eltoprazine) in therapeutic treatment of humans are within the range from about 5 mg to about 150 mg per day, such as from about 5 mg to about 120 mg, from about 5 mg to about 100 mg, or from about 5 mg to about 75 mg, or from about 5 mg to about 60 mg, or from about 5 mg to about 50 mg, or from about 10 mg to about 20 mg, or from about 10 mg to about 15 mg, such as 10mg or 15 mg or 20 mg or 30 mg or 40 mg or 60mg or 80mg, per day. For example the daily dose may be body weight-adjusted such as 40 mg/day up to 80 kg body weight or 60 mg/day for patients with a body weight of $\geq$

80 kg. In modified release formulations the amounts of active ingredient per day could also be higher due to reduced bioavailability, e.g. up to 200 mg/day. An equimolar amount of another pharmaceutically acceptable salt, a solvate, a conjugate or a derivative thereof, such as eltoprazine hydrochloride, is also suitable. For pediatric subjects aged 4-14, eltoprazine may be administered as an oral, liquid dosage form, at reduced amounts, for example from about 1 mg/day, up to about 5 mg/day.

[0078] In particular embodiments, the daily dosage of eltoprazine is between about 10 and 20 mg/day.

[0079] The daily doses indicated herein may be administered, for example, as one or two dosing units once, twice or three times per day. Suitable doses per dosage unit may therefore be the daily dose divided (for example, equally) between the number of dosage units administered per day, and will thus typically be about equal to the daily dose or one half, one third, one quarter or one sixth thereof. Dosages per dosage unit may thus be calculated from each daily dosage indicated herein. A daily dose of 5 mg, for example may be seen as providing a dose per dosage unit of, for example, about 5 mg, 2.5 mg, 1.67 mg, 1.25 mg and 0.83 mg, depending upon the dosing regimen chosen. Correspondingly, a dosage of 50 mg per day corresponds to dosages per dosing unit of, for example, about 50 mg, 25 mg, 16.7 mg, 12.5 mg, and 8.33 mg for corresponding dosing regimens. In other embodiments, especially in cases where only two daily doses are administered, an unequal split of the first and the second dosage is envisaged. In such cases, for example, the first dosage comprises about 55 to 65% of the total daily dosage. For example, a daily dosage of 10 mg is split into a first dosage of 6 mg and a second dosage of 4 mg. In cases, in which more than two administration per day are envisaged, the dosage might be split also unequally, wherein the second and further dosages are reduced in comparison to the dosage before. For example, if three dosages per day are administered, the first dosage could be about one half of the total daily dosage, i.e. between about 40% to 60%, the second dosage could

be about one third of the total daily dosage, i.e. between about 20% to 40%, and the third dosage could be about one sixth of the total daily dosage, i.e. between about 5% to 20%. For example, a daily dosage of 10 mg could be split into a first dosage of 6 mg, a second dosage of 3 mg and a third dosage of 1 mg.

[0080] Treatment duration may be short-term, e.g., several weeks (for example 8-14 weeks), or long-term until the attending physician deems further administration no longer is necessary.

[0081] Eltoprazine may be administered as a single anti-addiction agent or in combination with other anti-addiction agents .

[0082] The term "combination" applied to active ingredients is used herein to define two separate pharmaceutical compositions, each comprising an active agent (e.g. eltoprazine, and another pharmaceutical composition comprising another agent prescribed for the treatment of drug addiction, to be administered conjointly.

[0083] Within the meaning of the present invention, the term "conjoint administration" is used to refer to administration of eltoprazine, and a second active agent simultaneously in different compositions, or sequentially. For the sequential administration to be considered "conjoint", however, eltoprazine, and the second active agent must be administered separated by a time interval, which still permits the resultant beneficial effect for treating L-DOPA-induced dyskinesias in a mammal.

EXAMPLES

[0084] The following examples illustrate the invention without limiting its scope.

EXAMPLE 1: Neurochemical profile of eltoprazine

5-HT_{1a} and 5-HT_{1b} receptors

[0085] Eltoprazine was tested for activity on the human serotonin 5-HT_{1a} and 5-HT_{1b} receptors using a GTP γ S assay. Recombinant membranes obtained from CHO-K1 cells expressing either the 5-HT_{1a} or 5-HT_{1b} receptors were mixed with GDP (volume:volume) and incubated for at least 15 min on ice. In parallel, GTP γ [35S] was mixed with the beads (volume:volume) just before starting the reaction. The following reagents were successively added in the wells of an Optiplate (Perkin Elmer): 50 μ l of test compound, 20 μ l of the membranes:GDP mix, 10 μ l of assay buffer (for agonist testing) and 20 μ l of the GTP γ [35S]:beads mix. The plates were covered with a top seal, shaken on an orbital shaker for 2 min, and then incubated for 1 h at room temperature. Then the plates were centrifuged for 10 min at 2000 rpm, incubated at room temperature 1 h and counted for 1 min/well with a PerkinElmer TopCount reader.

5-HT_{2a}, 5-HT_{2b} and 5-HT_{2c} non-edited receptor

[0086] Aequorin cell lines expressing the 5-HT_{2a}, 5-HT_{2b} and 5-HT_{2c} non-edited (ne) recombinant receptors were used to evaluate the functional activity of eltoprazine. Aequorin cells grown 18 h prior to the test in media without antibiotics were detached by gentle flushing with PBS-EDTA (5 mM EDTA), recovered by centrifugation and resuspended in "assay buffer" (DMEM/HAM's F12 with HEPES + 0.1% BSA protease free). Cells were incubated at room temperature for at least 4h with Coelenterazine h (Molecular Probes). The reference agonist used were 5-HT and α -methyl-5-HT. For agonist testing, 50 μ l of cell suspension were injected on 50 μ l of

test compound or reference agonist plated in a 96-well plate. The resulting emission of light was recorded using the Hamamatsu Functional Drug Screening System 6000 (FDSS 6000).

Results

[0087] **Figure 1** illustrates the potency of eltoprazine on different serotonergic receptor activated at relevant plasma concentration.

EXAMPLE 2: Effect of eltoprazine on L-DOPA Induced Dyskinesia in the 6-hydroxydopamine (6-OHDA)-lesioned rat model of Parkinson's disease

Materials and Methods

Animals

[0088] Male Sprague Dawley rats (Elevage Janvier, Le Genest Saint Isle, France) weighing between 220 and 250 g at the beginning of the study are used in these experiments. They are housed under a 12 h light/dark cycle with free access to standard pelleted food and tap water. Animal treatment and experimental procedures are approved by local ethical committees (Regierungspräsidium Darmstadt; Germany).

Dopamine-denervating lesions

[0089] Dopamine-denervating lesions are performed on rats anaesthetized with a 5:1 mixture of ketamine and xylazine (1 ml/kg, i.p.). All rats receive unilateral injection of 6-hydroxydopamine (6-OHDA-HCl) (3 µg/µl in 0.02% ascorbate-saline) into the right ascending DA fibre bundle at the following coordinates (in mm relative to bregma and the dural surface): (1) A = - 4.4, L = -1.2, V = -7.8, tooth bar -2.3 (7.5 µg deposit); (2) A = -4.0, L = -0.75, V = -8.0, tooth bar = +3.4 (6 µg deposit). Injections are performed at the rate of 1 µl/min (allowing an additional 3 min before retracting the needle) using a 10 µl Hamilton microsyringe with a 26-gauge steel cannula. In order to assess

the efficacy of the lesions, all rats are tested for amphetamine-induced rotation 2 weeks after the 6-OHDA injections. The animals' turning behaviour is recorded in an automated rotometer (TSE Rotameter System, TSE-Systems GmbH, Bad Homburg, Germany) over a 90 min period after the intraperitoneal (i.p.) injection of 2.5 mg/kg dexamphetamine sulphate dissolved in saline. Only the rats showing rotational scores > 5 net full turns/min in the direction ipsilateral to the lesion are selected for the study.

Experimental Design and Drug Treatment

[0090] At 6-8 weeks post-lesion, rats are treated for 21 days with a single daily i.p. injection of 6 mg/kg of L-DOPA mixed with 15 mg/kg of the peripheral DOPA-decarboxylase inhibitor benserazide hydrochloride or with saline (vehicle controls). L-DOPA and benserazide are dissolved in a physiological saline solution. Chronic treatment with this dose of L-DOPA has been shown to induce gradual development of dyskinetic-like movements in 6-OHDA-lesioned rats. After approx. 3 weeks of the daily treatment, rats are injected 30 min before the evaluation of abnormal involuntary movement (AIM)s with different doses of eltoprazine hydrochloride (0.08, 0.3, 1.25 and 5 mg/kg, s.c.), followed by L-DOPA (L-DOPA 6 mg/kg, and benserazide 15 mg/kg), i.p., 10 min before the beginning of the test.

Behavioral Test

[0091] In order to evaluate the severity of LID, AIMs are recorded every second day as described by Cenci et al. (1998). Cenci MA, Lee CS, Björklund A. L-DOPA-induced dyskinesia in the rat is associated with striatal overexpression of prodynorphin- and glutamic acid decarboxylase mRNA. Eur J Neurosci 1998 10:2694-2706. Briefly, rats are observed individually for 1 min every 10th minute during 3 h following a daily L-DOPA dose. Repetitive movements affecting the side of the body contralateral to the lesion that could not be ascribed to any normal behavioural pattern are classified into four different subtypes: locomotive AIMs, i.e., increased locomotion with contralateral side bias; axial dystonia, i.e., contralateral twisted posturing of

the neck and upper body; orolingual AIMs, i.e., stereotyped jaw movements and contralateral tongue protrusion; and forelimb dyskinesia, i.e., repetitive jerks of the contralateral forelimb, sometimes combined with grabbing movements of the paw. Each rat is scored on a severity scale from 0 to 4 based on its frequency and persistence (1 = occasional; 2 = frequent; 3 = continuous but interrupted by sensory distraction; 4 = continuous, severe and not interrupted by sensory distraction). The axial, orolingual and forelimb (AOL) AIMs are presented together as a mean (mean AIM score) per time point. In this experiment, L-DOPA (6.25 mg/kg + Benserazide 15 mg/kg) is injected alone or in combination with eltoprazine at 0.08, 0.3, 1.25 and 5 mg/kg.

[0092] In order to evaluate the effect of eltoprazine on parkinsonian symptoms and its interaction with L-DOPA, rotational behaviour is evaluated. The numbers of ipsilateral and contralateral turns are recorded in an automated rotometer (TSE Rotameter System, TSE –Systems GmbH, Bad Homburg, Germany) over a period of 180 min. For the effect on parkinsonian symptoms, eltoprazine is administered at 0.3, 1.25 and 5 mg/kg 30 min before the test.

Statistical Analysis

[0093] ANOVA and two-way ANOVA are used to evaluate the significance of the results. Post hoc Tukey test is performed where appropriate.

[0094] **Figure 2** illustrates the effect of increasing doses of eltoprazine on AIM scores in 6-OHDA-lesioned rats. The data are expressed as % of AIM scores compared to L-DOPA - vehicle-treated animals. * indicates a significant difference with $p < 0.05$ between L-DOPA - vehicle-treated animals (ANOVA).

[0095] This result demonstrates that eltoprazine significantly reverses, in a dose-dependent manner, the AIMs that arise in 6-OHDA-lesioned rats after 21 days of treatment with L-DOPA. The effect of amantadine (40 mg/kg) and

buspirone (1 mg/kg) in the dyskinetic rat model are presented on the same graph for comparison.

[0096] **Figure 3** illustrates the effect of eltoprazine on the turning behaviour induced by high dose of L-DOPA in 6-OHDA-lesioned rats. * indicates a significant difference with $p < 0.05$ versus vehicle-treated animals, # indicates a significant different with $p < 0.05$ versus eltoprazine-treated animals (2-way ANOVA followed by Tukey's Post hoc test).

[0097] This result demonstrates that eltoprazine does not interfere with the antiparkinsonian effect of L-DOPA.

EXAMPLE 3: Eltoprazine in *in vivo* model for the treatment of nicotine abuse

Materials and Methods

Animals

[0098] Experimentally naive adult male Wistar rats (180-220 g, State Breeding Farm "Rappolovo", St. Petersburg, Russia; N=109) were used. The rats were housed at a colony room temperature and humidity of $20 \pm 1^\circ\text{C}$ and $60 \pm 3\%$, respectively. Food and water were available *ad libitum* and the animals were kept under an alternating 12 h / 12 h day-night cycle (lights on at 07.00) for at least 6 days before the experiments were started. All experiments were conducted during the light period of the day-night cycle.

Drug Treatment

[0099] Animals were implanted with jugular vein catheters. One week later animals were placed in test chambers (equipped with two nose poke holes, one active and one inactive) and trained for nose pokes to the active hole, which produced delivery of 10 μg of nicotine through the catheter. After

stable responses were obtained, animals were treated with different doses of eltoprazine (see below). Schedule of reinforcement was set at a fixed ratio of 5 times in 60 seconds. Only the fifth nose poke was reinforced. Nose pokes outside of the 60 s period were recorded, but not reinforced.

[00100] Eltoprazine hydrochloride was administered at 0.1, 0.3 and 1 mg/kg i.p. 60 min before the test.

[00101] To assess the effect on nicotine self-administration, i.e. the reinforcing property of nicotine, the number of nose pokes (in active and inactive hole) and injections are recorded.

Results and discussion

[00102] As shown in Figure 4, eltoprazine showed inhibitory effect on nicotine reinforcing activity at the dose of 1 mg/kg, and thus, anti-abuse potential against nicotine.

* * * * *

[00103] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

[00104] All patents, applications, publications, test methods, literature, and other materials cited herein are hereby incorporated by reference.

CLAIMS

1. A method of treatment or prevention of drug addiction in a subject in need thereof, comprising administering an effective amount of eltoprazine or a pharmaceutically acceptable salt thereof.
2. A composition comprising eltoprazine or a pharmaceutically acceptable salt thereof for the treatment or prevention of drug addiction.
3. Use of eltoprazine or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention of drug addiction.
4. The method according to Claim 1, the composition according to Claim 2, or the use according to Claim 3, wherein the substance eltoprazine is eltoprazine hydrochloride.
5. The method/composition/use according to any of the preceding claims, wherein eltoprazine is for administration in a range from about 5 mg to about 75 mg/day, or in a range from about 5 mg to about 60 mg/day, or in a range from about 5 mg to about 50 mg/day, or in a range from about 5 mg to about 40 mg/day, or in a range from about 5 mg to about 20 mg/day, or in a range from about 5 mg to about 15 mg/day.
6. The method/composition/use according to Claim 5, wherein eltoprazine is for administration in a range from about 10 mg to about 15 mg/day.
7. The method/composition/use according to Claim 5, wherein eltoprazine is for administration at about 5 mg/day, or eltoprazine is for administration at about 10 mg/day, or eltoprazine is for administration at about 15 mg/day, or eltoprazine is for administration at about 20 mg/day, or eltoprazine is for administration at about 40 mg/day, or eltoprazine is for administration at about 60 mg/day.

8. The method/composition/use according to any of the preceding claims, wherein eltoprazine or a pharmaceutically acceptable salt thereof is for administration once a day, twice a day (b.i.d.), or three times a day.
9. The method/composition/use according to Claim 8, wherein eltoprazine or a pharmaceutically acceptable salt thereof is for administration twice a day (b.i.d.).
10. The method/composition/use according to Claim 9, wherein the daily dosage for said administration twice a day (b.i.d.) is split into a first dose of about 55 to 65% of the total daily dosage amount, and a second dose comprising the remaining total daily dosage amount.
11. The method/composition/use according to claim 9, wherein the second dosage is administered at about lunchtime.
12. The method/composition/use according to any of the preceding claims, wherein the subject to be treated suffers from drug addiction.
13. The method/composition/use according to Claim 12, wherein the drug is nicotine.
14. The method/composition/use according to any of the preceding claims in the form of an oral formulation.

Figure 1

Assays	Potency data (EC₅₀; μM)	MOA
Serotonin 5-HT _{2c} (non-edited)	0.031	full agonist
Serotonin 5-HT _{2a}	0.092	full agonist
Serotonin 5-HT _{1b}	0.163	partial agonist
Serotonin 5-HT _{1a}	0.381	partial agonist
Serotonin 5-HT _{2b}	0.464	partial agonist

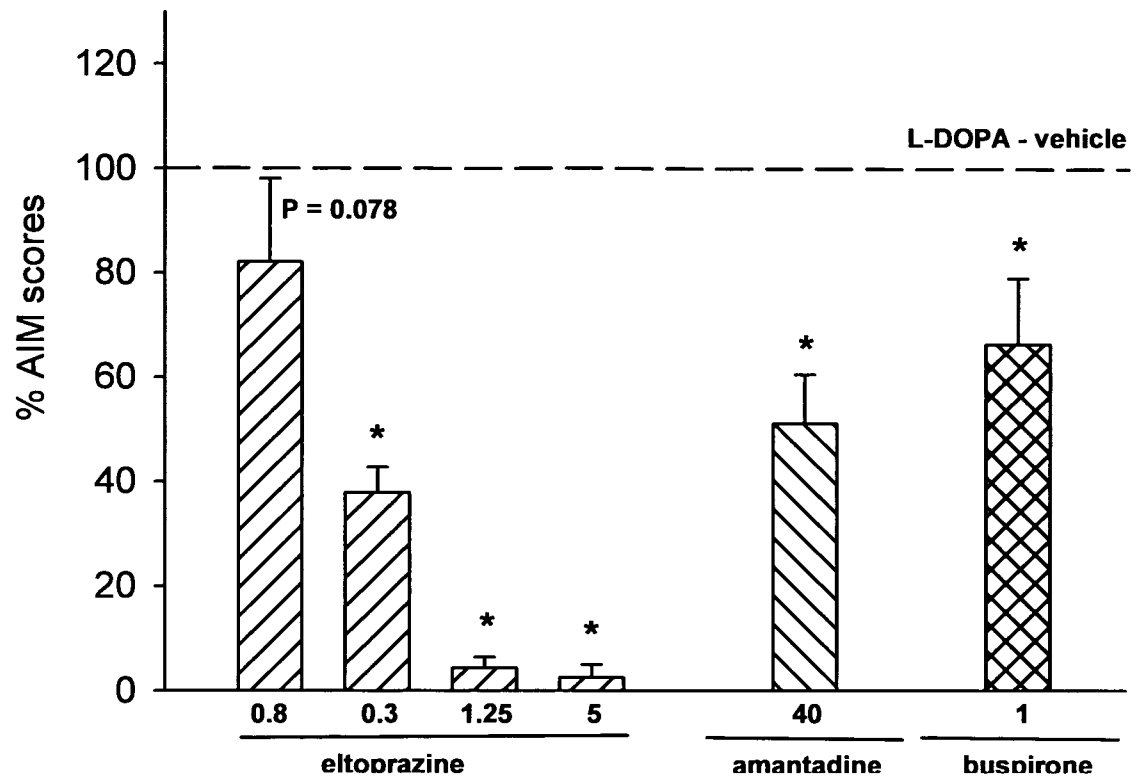
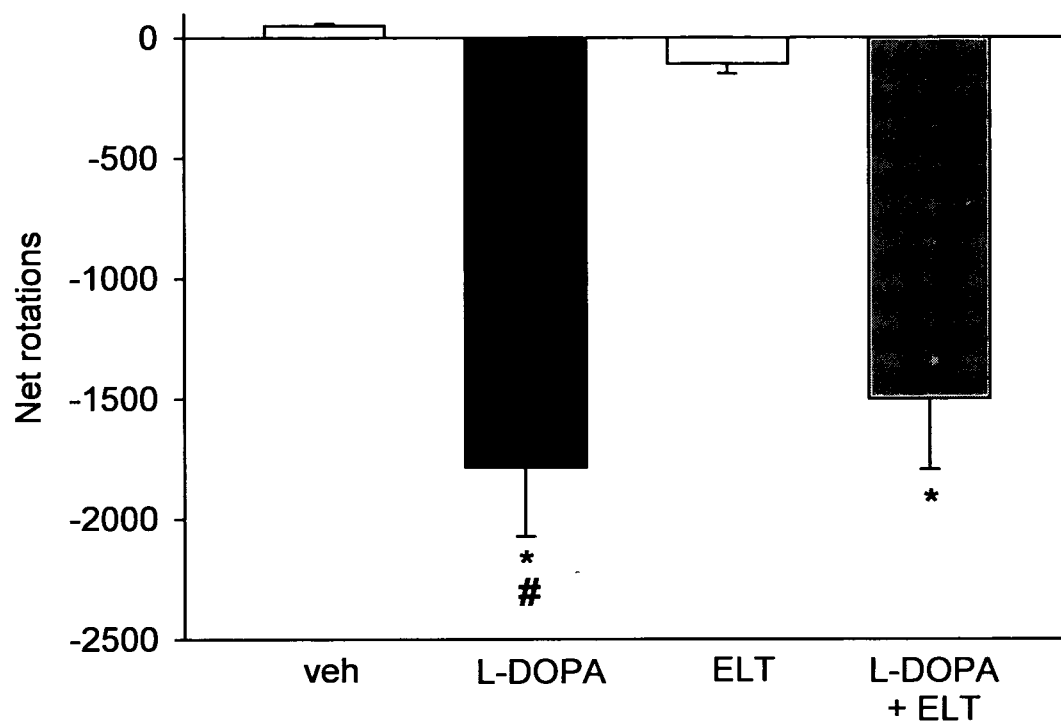
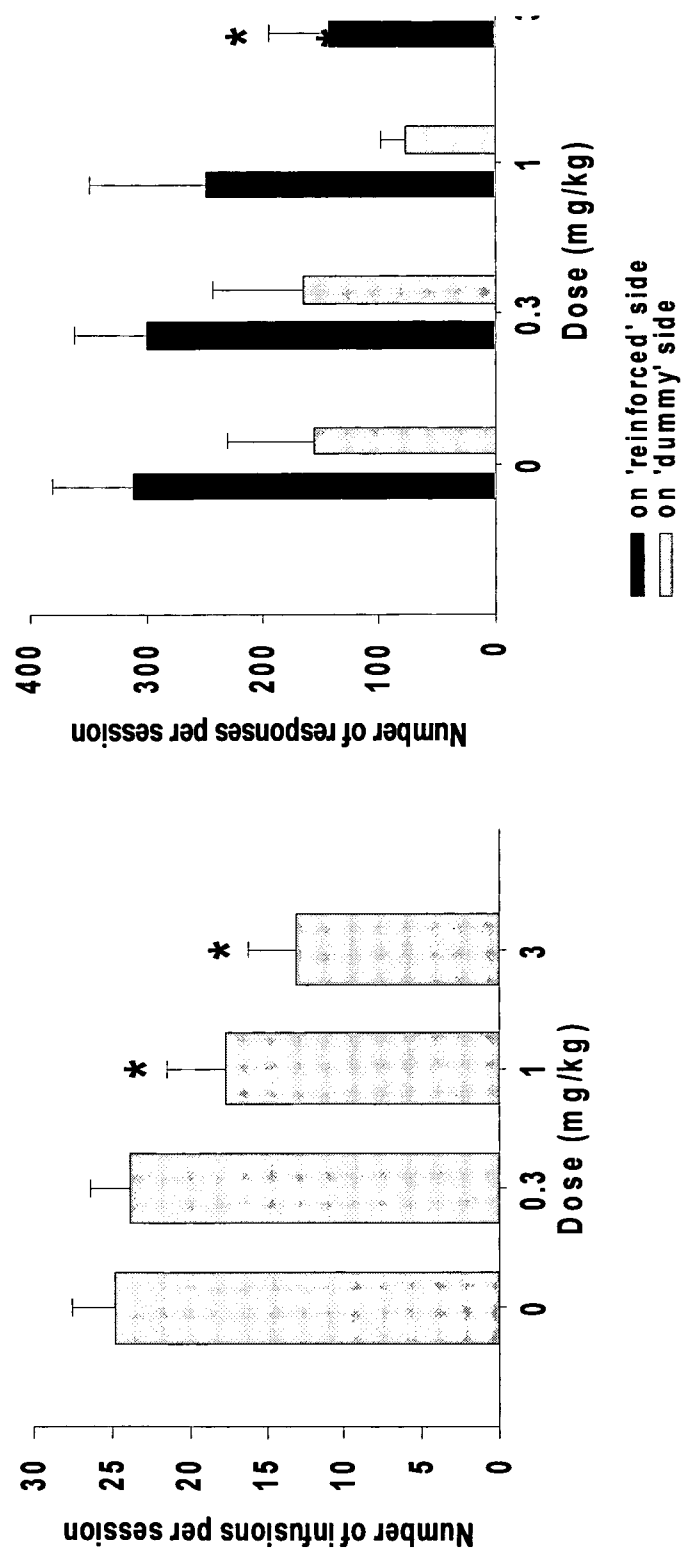
Figure 2

Figure 3

* - $p < 0.05$ vs. vehicle, # - $p < 0.05$ vs. eltoprazine;
ANOVA on ranks followed by Tukey's test

Figure 4



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/003965

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/496 A61P25/34 A61P25/30
ADD.

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 A61P

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, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2009/148891 A1 (PSYCHOGENICS INC [US]; LEAHY EMER [US]; DAY MARK [US]) 10 December 2009 (2009-12-10) paragraphs [0027], [0037], [0068], [0076], [00104], [00105]; claims 1,5,13,33,34	1-14
A	EP 0 189 612 A1 (DUPHAR INT RES [NL]) 6 August 1986 (1986-08-06)	1-14
A	WO 97/03067 A1 (KNOLL AG [DE]; KERRIGAN FRANK [GB]; CHEETHAM SHARON CRAWFORD [GB]; WAT) 30 January 1997 (1997-01-30)	1-14



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
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *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

13 October 2010

Date of mailing of the international search report

29/10/2010

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Ansaldo, M

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2010/003965

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009148891 A1	10-12-2009	US 2009298850 A1	03-12-2009
EP 0189612 A1	06-08-1986	AT 81975 T	15-11-1992
		AU 588015 B2	07-09-1989
		AU 5139185 A	26-06-1986
		CA 1271475 A1	10-07-1990
		DE 3586794 D1	10-12-1992
		DE 3586794 T2	27-05-1993
		DK 586085 A	22-06-1986
		ES 8702143 A1	16-03-1987
		GR 853064 A1	09-04-1986
		IE 61723 B1	30-11-1994
		IL 77395 A	16-08-1991
		JP 61152655 A	11-07-1986
		NZ 214610 A	29-09-1988
		PH 24503 A	18-07-1990
WO 9703067 A1	30-01-1997	AR 002830 A1	29-04-1998
		AU 6517196 A	10-02-1997
		DE 69615376 D1	25-10-2001
		DE 69615376 T2	05-09-2002
		EP 0839144 A1	06-05-1998
		HR 960349 A2	30-04-1998
		JP 4108747 B2	25-06-2008
		JP 11508888 T	03-08-1999
		JP 2008150387 A	03-07-2008
		US 6114334 A	05-09-2000