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(54) Title: TRANSDERMAL MICRO-DOSING DELIVERY OF PSYCHEDELICS DERIVATIVES

(57) Abstract: The present disclosure relates to the transdermal administration of psychedelics, such as psilocybin, psilocin, lysergic acid diethyl amine (LSD), and/or ibogaine, and derivatives of these compounds, for the treatment and/or prevention and/or control of severe depression (treatment resistant), major depressive disorder, obsessive-compulsive disorder, quitting smoking, alcohol addiction, cocaine addiction, opioid addiction, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress.

TRANSDERMAL MICRO-DOSING DELIVERY OF PSYCHEDELICS DERIVATIVES:

This international application claims benefit of U.S. Serial No. 63/100,924 filed April 16, 2020, the entirety of which is incorporated herein by reference.

SPECIFICATION

BACKGROUND

The present disclosure relates to the transdermal administration of psychedelics, such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds, for the treatment and/or prevention and/or control of severe depression (treatment resistant), major depressive disorder, obsessive-compulsive disorder, quitting smoking, alcohol addiction, cocaine addiction, opioid addiction, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress.

The psychedelics, such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds may be used concomitantly with one or more other active pharmaceutical ingredients. Alternatively, the psychedelics, such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds may be formulated for administration separately, sequentially or simultaneously with one or more drugs or the combination may be provided in a single dosage form. Where psychedelics, such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds are formulated for administration separately, sequentially or simultaneously it may be provided as a kit or together with instructions to administer the one or more components in the manner as disclosed herein.

According to preliminary literature research, the maximum dose of psilocybin used in clinical trial is 0.6 mg/kg which is approximately 50 mg/70 kg. Furthermore, the lowest dose used in clinical trial was 1-3 mg/70 kg healthy volunteers. The present disclosure is directed to targeting, for example, 5 or 10 mg/day of active agent, such as for example psilocin, psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine (depending upon the ability of API to penetrate through the skin) delivery through the transdermal route.

There are several approaches that utilize these psychedelics, including:

1. Micro-dosing involves very small daily doses of the psychedelic. It could be twice a week, or potentially daily.

2. Larger single dose to treat more problematic mental illness like treatment resistant depression, which is administered under physician supervision and can last 6 to 8 hours.

In one aspect a transdermal matrix patch or transdermal semisolid formulation containing for example, psilocybin and psilocin can be prepared. In another aspect, two separate transdermal matrix patches can be prepared one containing psilocybin alone and a second containing psilocin alone as active ingredient. In this case both transdermal matrix patches could be applied at the same time and deliver psilocybin and psilocin. In yet another exemplary aspect two separate transdermal semisolid formulations can be prepared one containing psilocybin alone and a second containing psilocin alone as active ingredient. In this case both transdermal semisolid formulations could be applied at the same time and deliver psilocybin and psilocin.

It is projected that mental health disorders are growing in every country and will cost the global economy $16 trillion by 2030 affecting nearly 2 billion people every year. (The Lancet Commission on global mental health and sustainable development).

In the US, Substance Abuse and Mental Health Services Administration (SAMHSA) study indicates that every year, about 42.5 million Americans suffer from some mental illness, including conditions such as depression, addiction, anxiety, substance abuse, etc. In addition, about 9.3 American adults suffer from a serious mental illness which impedes day to day activities like going to work. Among the indications for which adminsitraiton of Where psychedelics, such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds may be useful include, but ar enot limited to, the following:

Major Depressive Disorder

According to the US National Institutes of Health (NIH), an estimated 17.3 million American adults had at least one depressive episode. According to the National Survey on Drug Use and Health (NSDUH), the study's definition of major depressive episode or Major Depressive Disorder is based mainly on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5):

- A period of at least two weeks when a person experienced a depressed mood or loss of interest or pleasure in daily activities, and had a majority of specified symptoms, such as problems with sleep, eating, energy, concentration, or self-worth.

- It goes beyond normal human sadness, and leads to the inability to function normally for everyday life.
- No exclusions were made for major depressive episode symptoms caused by medical illness, substance use disorders, or medication.

About 2-8% of of adults with major depression die by suicide, and about 50% of people who die by suicide had depression or another mood disorder. (Richards CS, O'Hara MW (2014). *The Oxford Handbook of Depression and Comorbidity*. Oxford University Press. p. 254. ISBN 978-0-19-979704-2. Strakowski S, Nelson E (2015). *Major Depressive Disorder*. Oxford University Press. p. PT27. ISBN 978-0-19-026432-1. Bachmann, S (6 July 2018). "Epidemiology of Suicide and the Psychiatric Perspective". *International Journal of Environmental Research and Public Health*. **15** (7): 1425. doi:10.3390/ijerph15071425. PMC 6068947. PMID 29986446). Half of all completed suicides are related to depressive and other mood disorders.

It is estimated that the economic cost of MDD in the US is $210 Billion. This encompasses absenteeism, reduced workplace productivity, and 45-47% is healthcare costs (shared by employer/employee/society).

Alcohol Use Disorder

Approximately 17 million American suffer from Alcohol Use Disorder (AUD) with significant costs to healthcare, productivity and families. AUD (which can include Alcoholism) occurs when an individual is having difficulty controlling their drinking, being preoccupied with drinking, continues to drink even when it causes problems, drinking more to get the same effect, and withdrawal symptoms when slowing or stopping. This can also include binge drinking which is classified as having more than 5 and 4 drinks in a single session (men and women respectively). Approximately US$250 Billion is spent on healthcare, lost productivity and criminal justice every year in the US. The current treatments have limitations. Only a handful of FDA treatments, and most are poorly tolerated. Alcoholics Anonymous (AA), also has low success rates.

Opioid Use Disorder (2 million Americans)

According to SAMHSA, approximately 11.4 million Americans misuse opioids. In addition, about 80% of Americans using heroin first started out using prescription pain relievers. The Centers for Diseases Control (CDC), estimate the all-in annual cost of opioid misuse in the US is $78.5 Billion, which includes costs of healthcare, lost productivity, treatment, and criminal

justice involvement. There are medications (mainly opioid antagonists) that are used, however given the significant size of the opioid overdose health crisis, and the limited success of these treatments, there is a huge unmet need. www.samhsa.gov/data/sites/default/files/nsduh-ppt-09-2018.pdf.

Anxiety Disorders (many form of anxiety)

Are the most common mental illnesses in the US affecting approximately 40 million American adults or 18% of the population. It is estimated to cost $42 Billion to $46 Billion every year.

The disclosure provides that the transdermal administration of psychedelics, such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds, are effective for the treatment and/or prevention of severe depression (treatment resistant), major depressive disorder, obsessive-compulsive disorder, quitting smoking, alcohol addiction, cocaine addiction, opioid addiction, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress.,

There is a need for an improved drug delivery system of psychedelics, such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds which can overcome the drawbacks associated with oral and IV routes. Transdermal delivery of psychedelics, such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds can address the challenges associated with oral and IV drug delivery. In exemplary embodiments as disclosed herein, the psychedelics, such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds, would be administered in the dosages as disclosed herein and would cause no or minmal hallucinogenic effect in a patient.

All references cited herein are incorporated herein by reference in their entireties.

BRIEF SUMMARY

The disclosure provides compositions and methods for the treatment and/or prevention and/or control of the treatment and/or prevention and/or control of severe depression (treatment resistant), major depressive disorder, obsessive-compulsive disorder, quitting smoking, alcohol addiction, cocaine addiction, opioid addiction, anxiety (stress), adult ADHD, cluster headaches,

and cancer related or other end-of-life psychological distress in a patient, using transdermal drug delivery. In Transdermal drug delivery, a transdermal patch or transdermal composition is applied topically to the skin surface. Throughout the duration of topical application of a transdermal patch or transdermal composition drug is continuously released and delivered through the intact skin (via transcellular, intercellular and transappendageal routes) to achieve systemic effect. Therefore, once applied transdermal composition or transdermal patch can deliver drug into systemic circulation throughout the day or even for more than one day depending on the duration of its application which can be even up to a week or up to 15 days.

Transdermal delivery can reduce the dosing frequency of psychedelics, such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds which is currently administered several times a day. Through transdermal delivery, transdermal compositions or transdermal formulations or transdermal patch of psychedelics, such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds, can be applied topically to skin thereby delivering the drug throughout the duration of topical application. Depending on the requirement, the duration of topical application can be once in a day, once in two days, once in three days, once in four days, once in five days, once in a week, once in a 15 days. Therefore, transdermal delivery can overcome the multiple dose regimen of oral delivery by reducing the dosing frequency.

Moreover, in transdermal drug delivery the drug is delivered slowly and continuously throughout the duration of topical application hence there are no peaks and troughs in drug plasma concentration which are associated with multiple dose administration in a day. Therefore, by transdermal delivery of psychedelics, such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds, patients can have the therapeutic effect of the drug for extended period of time without drastic changes in drug plasma concentration.

In transdermal delivery drug is delivered into systemic circulation through the skin, it escapes the first pass hepatic metabolism therefore to achieve the desired therapeutic activity less drug is required, resulting into less adverse effects or side effects.

Furthermore, transdermal delivery is easy, noninvasive and convenient. Administration of a transdermal patch or transdermal composition does not require medical supervision as patients

can topically apply the transdermal patch or transdermal composition themselves. Therefore, transdermal delivery can overcome the drawbacks of injections which are often painful and requires medical supervision.

With respect to psychedelics, such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds it is expected that interpatient variability in pharmacologic response will be less with transdermal delivery as drug plasma concentration can be controlled by controlling the rate of drug delivery from transdermal composition or transdermal patch. With transdermal delivery a small amount of psychedelics, such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds can be delivered for longer duration than oral administration. Transdermal formulations of psychedelics, such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds also provide more abuse deterrence than immediate release dosage forms.

Moreover, in case of any adverse effect, side effect or emergency transdermal delivery gives the liberty to terminate the therapy anytime by taking off the transdermal patch or transdermal composition from skin.

As per above stated reasons for the treatment and/or prevention and/or control of seizure disorders, transdermal delivery can provide patient friendly, simplified and convenient therapeutic regimen over traditional delivery systems. Transdermal delivery can reduce the dosing frequency of psychedelics, such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds. Depending on the necessity, dosing frequency can be once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in 15 days.

Through transdermal administration of drug combination, two or more drugs can be delivered simultaneously. Depending on the necessity, dosing frequency of transdermal patch or transdermal composition containing drug combination can be once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in 15 days. It would be a great addition to the patient compliance.

The disclosure provides a transdermal and/or topical pharmaceutical composition comprising: about 0.1 % to about 20 % of an active agent selected from the group consisting of psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, derivatives of these compounds, and combinations thereof; about 80% to about 99.9% of an adhesive and/or polymer; optionally, about 0.1 % to about 20% of a permeation enhancer; optionally, about 0.1% to about 20% of a solvent, wherein said pharmaceutical composition will have no or minimal hallucinogenic effect in a patient to whom the pharmaceutical composition is applied. The disclosure provides a transdermal and/or topical pharmaceutical composition wherein the adhesive is selected from the group consisting of pressure sensitive adhesives, silicone polymers, bio psa 4302, bio-psa 4202, acrylic pressure sensitive adhesives, duro –tak 87-2156, duro-tak 387-2287, duro-tak 87-9301, duro-tak 387-2051, polyisobutylene, polyisobutylene low molecular weight, polyisobutylene medium molecular weight, polyisobutylene 35000 mw, acrylic copolymers, rubber based adhesives, hot melt adhesives, styrene-butadiene copolymers, bentonite, all water and/or organic solvent swellable polymers and combinations thereof. The disclosure provides a transdermal and/or topical pharmaceutical composition wherein said polymer is present and is selected from the group consisting of natural polymers, polysaccharides. agar, alginic acid and derivatives, cassia tora, collagen, gelatin, gellum gum, guar gum, pectin, potassium cargeenan, sodium carageenan, tragacanth, xantham, gum copal, chitosan, resin, semisynthetic polymers, cellulose, methylcellulose, ethyl cellulose, carboxymethyl cellulose, hydroxylpropyl cellulose, hydroxylpropylmethyl cellulose, synthetic polymers, carboxyvinyl polymers, carbomers, carbopol 940, carbopol 934, carbopol 971p NF, polyethylene, clays, silicates, bentonite, silicon dioxide, polyvinyl alcohol, acrylic polymers (eudragit), acrylic acid esters, polyacrylate copolymers, polyacrylamide, polyvinyl pyrrolidone homopolymer, polyvinyl pyrrolidone copolymers, PVP, Kollidon 30, poloxamer, isobutylene, ethyl vinyl acetate copolymers, natural rubber, synthetic rubber, and combinations thereof. The disclosure provides a transdermal and/or topical pharmaceutical composition wherein said permeation enhancer is present, and is selected from the group consisting of dimethylsulfoxide, dimethylacetamide, dimethylformamide, decymethylsulfoxide, dimethylisosorbide, azone, pyrrolidones, N-methyl-2-pyrrolidone, 2-pyrrolidon, esters, fatty acid esters, propylene glycol monolaurate, butyl ethanoate, ethyl ethanoate, isopropyl myristate, isopropyl palmitate, methyl ethanoate, lauryl lactate, ethyl

oleate decyl oleate, glycerol monooleate, glycerol monolaurate, lauryl laurate, fatty acids, capric acid, caprylic acid, lauric acid, oleic acid, myristic acid, linoleic acid, stearic acid, palmitic acid, alcohols, fatty alcohols, glycols, oleyl alcohol, nathanol, dodecanol, propylene glycol, glycerol, ethers, alcohol, diethylene glycol monoethyl ether, urea, triglycerides, triacetin, polyoxyethylene fatty alcohol ethers, polyoxyethylene fatty acid esters, esters of fatty alcohols, essential oils, surfactant type enhancers, brij, sodium lauryl sulfate, tween, polysorbate, terpene, terpenoids, and combinations thereof. The disclosure provides a transdermal and/or topical pharmaceutical composition wherein said solvent is present, and is selected from the group consisting of methanol, ethanol, isopropyl alcohol, butanol, propanol, polyhydric alcohols, glycols, propylene glycol, polyethylene glycol, dipropylene glycol, hexylene glycol, butyene glycol, glycerine, derivative of glycols, pyrrolidone, N methyl 2- pyrrolidone, 2 pyrrolidone, sulfoxides, dimethyl sulfoxide, decymethylsulfoxide, dimethylisosorbide, mineral oils, vegetable oils, sesame oil water, polar solvents, semi polar solvents, non polar solvents, volatile chemicals, ethanol, propanol, ethyl acetate, acetone, methanol, dichloromethane, chloroform, toluene, IPA, hexane, acids, acetic acid, lactic acid, levulinic acid, bases, pentane, dimethylformamide, butane, lipids, and combinations thereof. The disclosure provides a transdermal and/or topical pharmaceutical composition formulated as a liquid formulation, transdermal semisolid formulation, or transdermal polymer matrix formulation, transdermal adhesive matrix formulation, film forming gel formulation, film forming spray formulation. The disclosure provides a transdermal and/or topical pharmaceutical composition which is formulated as a transdermal patch. The disclosure provides a transdermal and/or topical pharmaceutical composition formulated as a transdermal patch, wherein the transdermal patch is selected from the group such as to reservoir patch, a microreservoir patch, a matrix patch, a pressure sensitive adhesive patch, extended release transdermal film a liquid reservoir system, a microreservoir patch, a matrix patch, a pressure sensitive adhesive patch, a film forming gel, a film forming spray, a micro-dosing patch, a mucoadhesive patch, and combinations thereof. The disclosure provides a transdermal and/or topical pharmaceutical composition further comprising carriers or ingredients in effective amount selected from the group consisting of solvents, gelling agents, polymers, pressure sensitive adhesive, penetration enhancers, emollients, skin irritation reducing agents, buffering agents, pH stabilizers, solubilizers, suspending agents, dispersing agents, stabilizers, plasticizers, tackifier,

diluetns, surfactants, antioxidants, oxidants, and combinations thereof. The disclosure provides a transdermal and/or topical pharmaceutical composition indicated for the treatment and/or prevention and/or control of severe depression (treatment resistant), major depressive disorder, obsessive-compulsive disorder, post-traumatic stress disorder, quitting smoking, alcohol addiction, cocaine addiction, opioid addiction, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress in a patient. The disclosure provides a transdermal and/or topical pharmaceutical composition which is formulated as the transdermal formulation which can be administered in a dosage regimen selected from the group consisting of once daily, twice daily, three times a day, once in 1-8 hrs, once in 1-24 hrs, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in a 8 to about 13 days, once in two weeks, once in 15 days to about 30 days. The disclosure provides a transdermal and/or topical pharmaceutical composition which may be formulated as microneedles. The disclosure provides a transdermal and/or topical pharmaceutical composition wherein said psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, derivatives of these compounds, and combinations thereof is produced by a natural route or a synthetic route. The disclosure provides a transdermal and/or topical pharmaceutical composition co-administered with at least one additional active agent.

The disclosure provides a method for the treatment and/or prevention and/or control of severe depression (treatment resistant), major depressive disorder, obsessive-compulsive disorder, post-traumatic stress disorder, quitting smoking, alcohol addiction, cocaine addiction, opioid addiction, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress in a patient comprising: selecting a patient in need of treatment and/or prevention and/or control of severe depression (treatment resistant), major depressive disorder, obsessive-compulsive disorder, quitting smoking, alcohol addiction, cocaine addiction, opioid addiction, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress; topically applying the transdermal pharmaceutical composition as disclosed herein. wherein said patent experiences no or minimal hallucinogenic effects from said transdermal pharmaceutical composition. The disclosure provides a method wherein the topical application of a transdermal pharmaceutical composition for the treatment and/or prevention and/or control of severe depression (treatment resistant), major depressive disorder,

obsessive-compulsive disorder, post-traumatic stress disorder, quitting smoking, alcohol addiction, cocaine addiction, opioid addiction, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress in a patient, wherein the transdermal patch is applied at a time period selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in ten days, and once in fifteen days. The disclosure provides a method further providing a constant rate of delivery of the active components of the transdermal patch over a time period selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in ten days, and once in fifteen days. The disclosure provides a method further providing a steady absorption rates of the active components of the transdermal patch over a time period selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in ten days, and once in fifteen days. The disclosure provides a method further achieving a constant blood serum levels of the active components of the transdermal patch over a time period selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in ten days, and once in fifteen days. The disclosure provides a method further achieving a reduced variability in dosage of the active components of the transdermal patches over a time period selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in ten days, and once in fifteen days. The disclosure provides a method further providing a plasma concentration of the active components of the transdermal patch in a therapeutic range over a time period selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in ten days, and once in fifteen days. The disclosure provides a method further providing a plasma concentration of the active components of the transdermal patch in a therapeutic range of about 0.01 ng/mL to about 500 ng/mL.

DETAILED DESCRIPTION

It is to be understood that this invention is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of this invention will be limited only by the appended claims.

The detailed description of the invention is divided into various sections only for the reader's convenience and disclosure found in any section may be combined with that in another section. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a compound" includes a plurality of compounds.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. As used herein the following terms have the following meanings.

Active Agent

The term "active ingredient" refers to an agent, active ingredient compound or other substance, or compositions and mixture thereof that provide some pharmacological, often beneficial, effect. Reference to a specific active ingredient shall include where appropriate the active ingredient and it's pharmaceutically acceptable salts. Disclosure provides for, for example, transdermal formulations comprising one or more of the following active agents: Psilocybin, LSD, and ibogaine.

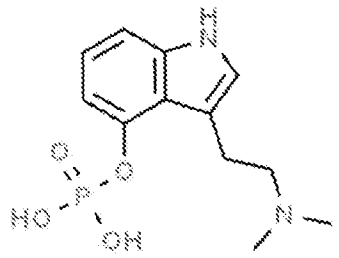
Psilocybin

Psilocybin is a naturally occurring psychedelic compound produced by more than 200 species of mushrooms, collectively known as psilocybin mushrooms. The most potent are members of the genus *Psilocybe*, such as *P. azurescens*, *P. semilanceata*, and *P. cyanescens*, but psilocybin has also been isolated from about a dozen other genera.

Once ingested, psilocybin is rapidly metabolized to psilocin, which then acts on serotonin receptors in the brain. The mind-altering effects of psilocybin typically last from two to six hours, although to individuals under the influence of psilocybin, the effects may seem to last much

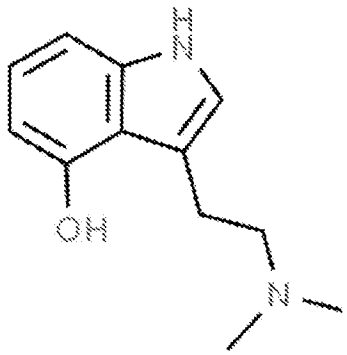
longer, since the drug can distort the perception of time. Psilocybin has a low toxicity and a relatively low harm potential, and reports of lethal doses of the drug are rare. Several modern bioanalytical methods have been adapted to rapidly and accurately screen the levels of psilocybin in mushroom samples and body fluids. Since the 1990s, there has been a renewal of scientific research into the potential medical and psychological therapeutic benefits of psilocybin for treating conditions including obsessive-compulsive disorder (OCD), cluster headaches, and anxiety related to terminal cancer.

Psilocybin is also referred to as [3-(2-dimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate, and given the CAS number 520-52-5.



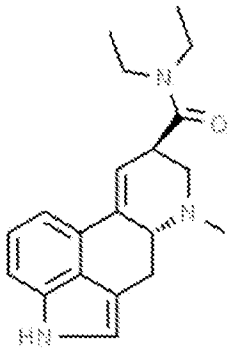
Psilocin (also known as 4-HO-DMT, psilocine, psilocyn, or psilotsin) is a substituted tryptamine alkaloid and a serotonergic psychedelic substance. It is present in most psychedelic mushrooms together with its phosphorylated counterpart psilocybin.

[0040] Psilocin also referred to as 4-hydroxy-N,N-dimethyltryptamine, and given the CAS number 520-53-6.



LSD

(+)-Lysergic acid diethylamide, 9,10-didehydro-N,N-diethyl-6-methylergoline-8β-carboxamide, known as LSD, is a hallucinogen which acts on the central nervous system and alters sensory perception. A concentration of from 20 to 80 µg of LSD is sufficient to induce hallucination (Nelson, C. and Foltz, R. Anal. Chem, 64, 1578-1585, 1992).

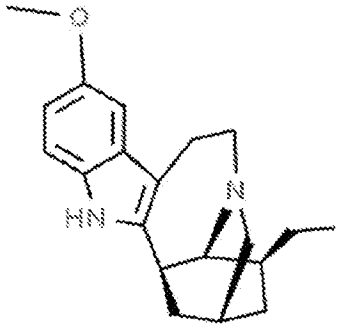


Ibogaine

Ibogaine has been used as a botanical preparation from the root bark of *iboga tabernathe* for over 100 years both as a crude preparation and as semisynthetic ibogaine, which was marketed in France until about 1970. High doses of ibogaine have been suggested to be useful as a treatment for pain and other conditions. However, the use of such high doses of ibogaine is associated with hallucinations and other negative side effects. In the United States, ibogaine is classified as a Schedule I controlled substance.

While ibogaine has been disclosed for treatment of substance addiction, its use in humans is complicated by the fact that the ranges in the prior art are exceptionally broad (0.01 to 1000 mg/kg body weight). Furthermore, human clinical studies demonstrate that the lower dosing of ibogaine has minimal impact on the alleviation of pain in patients. Thus, the previously disclosed broad range has now been found to be insufficient for human therapy at the lower end of this range.

Ibogaine



As used herein, the word active agent refers to all pharmaceutically acceptable forms of the active agent and its derivatives either alone or in combinations thereof, for example, in following forms but not limited to such as free base or salts or isomers or stereoisomers of polymorphs or amorphous or crystalline or co crystalline or ion pairs or solid solution or coated forms or prodrugs or analogs or derivatives or metabolites. For example, the active agent's free base or its salts or its isomers or its amorphous form or its crystalline form or its co crystalline form or its solid solution or its prodrugs or its analogs or its derivatives or synthetic forms. The compound may be in the form of, for example, a pharmaceutically acceptable salt, such as an acid addition salt or a base salt, or a solvate thereof, including a hydrate thereof. Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, p-toluenesulphonate and pamoate salts. Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts. The active ingredient(s) can be present in the form of a free base or in the form of pharmaceutically acceptable salts. Pharmaceutically acceptable salts forming part of this invention are intended to define but not limited to salts of the carboxylic acid moiety such as alkali metal salts like Li, Na and K salts; alkaline earth metal salts like Ca and Mg salts; salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline, and the like; ammonium or substituted ammonium salts and aluminium salts. Salts may be acid addition salts which defines but not limited to sulfates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates,

citrates, succinates, palmoates, methanesulfonates, benzoates, salicylates, hydroxynaphthoates, benzensulfonates, ascorbates, glycerophosphates, ketoglutarates and the like.

As used herein, the term "active agent" includes, for example, psychedelics, such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds, and the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, polymorphs forms therof, coated forms thereof, crystalline forms thereof, ion paris forms thereof, co crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, stereoisomers forms thereof, synthetic forms thereof, alone or in combinations thereof. In certain embodiments the active agent is highly purified. In certain embodiments the active agent is present as a highly purified extract of active agent which comprises at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.75% (w/w) of the formulation in certain embodiments, the dose of active agent is greater than, for example, about 0.001, 0.0025 0.005, 0.0075, 0.01, 0.025, 0.05, 0.075, 0.1, 0.25, 0.75, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, or 45 mg/kg/day. In certain embodiments, the dose of active agent is greater than, for example, about 0.001, 0.0025 0.005, 0.0075, 0.01, 0.025, 0.05, 0.075, 0.1, 0.25, 0.75, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 225, 250, or 275 mg/day. In exemplary embodiments, formulations of the disclosure may comprise active agent at a concentration of abount 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise active agent at a concentration of, for example, about 0.1 to about 20%, about 1 to 20%, of about 5% to 25%, about 10% to about 20%, about 15% to about 20%, about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, about 63.13%, or about 40% to about 64% w/w. In exemplary formulations of the disclosure, the active agent will represent approximately 1 wt %

to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 10 wt. % to 20 wt. % of the formulation.

In certain embodiments as disclosed herein the active agent s as disclosed hrein may be microdosed. Microdosing is born from the "set and setting" school of psychedelic therapy and one of its intellectual progeny, James Fadiman. The Stanford-trained Fadiman has worked with psychedelics for decades and runs a kind of cottage industry around espousing their powers. In his 2011 book *The Psychedelic Explorer's Guide* and at a conference talk that same year, Fadiman laid out the concept of microdosing. To microdose, one was to take a dose roughly 1/10th of a trip-inducing dose (10 micrograms of LSD) every three or four days, and go about their daily life. Most of what's known about the benefits of microdosing comes from self-reports Fadiman collected (and continues to collect) where microdosers described how the practice transformed their lives. In them, microdosers speak of anxiety and depression melting away, and feelings of determination and self-resolve that helped them achieve professional success. Some color-blind men even saw color for the first time."

As disclosed herein, the term "microdose" refers to a non-hallucinogenic dose of a pschyedelic active agent as disclosed herein. In exemplary embodiments, a microdose of the active agent psychedelics, such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds may, for example, a dose roughly 1/10th of a trip-inducing dose, or "macrodose", for example, 10 micrograms of LSD. In exemplary embodiments, these dosages would be administered to a patient, for example, every three or four days.

As used herein, the term "pharmaceutically acceptable salts" includes acid addition salts or addition salts of free bases. The term "pharmaceutically acceptable salts" of the psychedelics, such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds or any active agent herein within its scope all the possible isomers and their mixtures, and any pharmaceutically acceptable metabolite, bioprecursor and/or pro-drug, such as, for example, a compound which has a structural formula different from the one of the compounds of the disclosure, and yet is directly or indirectly converted in vivo into a compound of the disclosure, upon administration to a subject, such as a mammal, particularly a human being.

As used herein, the terms "subject" and "patient" are used interchangeably. As used herein, the term "patient" refers to an animal, preferably a mammal such as a non-primate (e.g., cows, pigs, horses, cats, dogs, rats etc.) and a primate (e.g., monkey and human), and most

preferably a human. In some embodiments, the subject is a non-human animal such as a farm animal (e.g., a horse, pig, or cow) or a pet (e.g., a dog or cat). In a specific embodiment, the subject is a human. As used herein, the term "agent" refers to any molecule, compound, methodology and/or substance for use in the prevention, treatment, management and/or diagnosis of a disease or condition. As used herein, the term "effective amount" refers to the amount of a therapy that is sufficient to result in the prevention of the development, recurrence, or onset of a disease or condition, and one or more symptoms thereof, to enhance or improve the prophylactic effect(s) of another therapy, reduce the severity, the duration of a disease or condition, ameliorate one or more symptoms of a disease or condition, prevent the advancement of a disease or condition, cause regression of a disease or condition, and/or enhance or improve the therapeutic effect(s) of another therapy.

As used herein, the phrase "pharmaceutically acceptable" means approved by a regulatory agency of the federal or a state government, or listed in the U.S. Pharmacopeia, European Pharmacopeia, or other generally recognized pharmacopeia for use in animals, and more particularly, in humans.

As used herein, the term "therapeutic agent" refers to any molecule, compound, and/or substance that is used for treating and/or managing a disease or disorder.

As used herein, the terms "therapies" and "therapy" can refer to any method(s), composition(s), and/or agent(s) that can be used in the prevention, treatment and/or management of a disease or condition, or one or more symptoms thereof. In certain embodiments, the terms "therapy" and "therapies" refer to small molecule therapy.

The term "derivative" or "derivatized" as used herein includes, for example, chemical modification of a compound of the disclosure, or extracted from botanical sources or pharmaceutically acceptable salts thereof or mixtures thereof. That is, a "derivative" may be a functional equivalent of a compound of the disclosure, which is capable of inducing the improved pharmacological functional activity in a given subject.

As used herein, the terms "composition" and "formulation" are used interchangeably.

As used herein, the term “transdermal delivery” means delivery of drug into systemic circulation through the skin.

As used herein, the term “hallucination” or "hallucinogenic effect" refers to symptoms in a patient who experience a perception without an object in the outside world. The hallucinations may include, for example, auditory hallucinations and visual hallucinations.

As used herein, the term "non-hallucinogenic" refers to an active agent as disclosed herein that will cause minimal or no hallucinogenic effects in a patient upon administration of the active agent at the doses as disclosed herein.

Additional Active Agents

As used herein the term "combination administration" of a compound, therapeutic agent or known drug with the combination of the present invention means administration of the drug and the one or more compounds at such time that both the known drug and/or combination will have a therapeutic effect. In some cases this therapeutic effect will be synergistic. Such concomitant administration can involve concurrent (i.e. at the same time), prior, or subsequent administration of the drug with respect to the administration of the composition and/or combination of the present invention. A person of ordinary skill in the art would have no difficulty determining the appropriate timing, sequence and dosages of administration for particular drugs of the present invention.

Further, active ingredient(s), where applicable, may be present either in the form of one substantially optically pure enantiomer or as a mixture of enantiomers or polymorphs thereof.

The active ingredient(s) may comprise one or more of the following therapeutic classes but not limited to adrenergic agent; adrenocortical steroid; adrenocortical suppressant; aldosterone antagonist; amino acid; anabolic; analeptic; analgesic; anesthetic; anorectic; anti-acne agent; anti-adrenergic; anti-allergic; anti-amebic; anti-anemic; anti-anginal; anti-arthritic; anti-asthmatic; anti-atherosclerotic; antibacterial; anticholinergic; anticoagulant; anticonvulsant; antidepressant; antidiabetic; antidiarrheal; antidiuretic; anti-emetic; anti-epileptic; antifibrinolytic; antifungal; antihemorrhagic; antihistamine; antihyperlipidemia; antihypertensive; antihypotensive; anti-infective; anti-inflammatory; antimicrobial; antimigraine; antimitotic; antimycotic, antinauseant, antineoplastic, antineutropenic, antiparasitic;

antiproliferative; antipsychotic; antirheumatic; antiseborrheic; antisecretory; antispasmodic; antithrombotic; anti-ulcerative; antiviral; appetite suppressant; blood glucose regulator; bone resorption inhibitor; bronchodilator; cardiovascular agent; cholinergic; depressant; diagnostic aid; diuretic; dopaminergic agent; estrogen receptor agonist; fibrinolytic; fluorescent agent; free oxygen radical scavenger; gastric acid supressant; gastrointestinal motility effector; glucocorticoid; hair growth stimulant; hemostatic; histamine H2 receptor antagonists; hormone; hypocholesterolemic; hypoglycemic; hypolipidemic; hypotensive; imaging agent; immunizing agent; immunomodulator; immunoregulator; immunostimulant; immunosuppressant; keratolytic; LHRH agonist; mood regulator; mucolytic; mydriatic; nasal decongestant; neuromuscular blocking agent; neuroprotective; NMDA antagonist; non-hormonal sterol derivative; plasminogen activator; platelet activating factor antagonist; platelet aggregation inhibitor; psychotropic; radioactive agent; scabicide; sclerosing agent; sedative; sedative-hypnotic; selective adenosine Al antagonist; serotonin antagonist; serotonin inhibitor; serotonin receptor antagonist; steroid; thyroid hormone; thyroid inhibitor; thyromimetic; tranquilizer; amyotrophic lateral sclerosis agent; cerebral ischemia agent; Paget's disease agent; unstable angina agent; vasoconstrictor; vasodilator; wound healing agent; xanthine oxidase inhibitor.

Examples of active ingredients comprises, but is not limited to any of the following, for example, alone or in combination: 16-alpha fluorocstradiol, 16alpha-gitoxin, 16-epiestriol, 17 alpha dihydroequilenin, 17 alpha estradiol, 17 beta estradiol, 17 hydroxy progesterone, 1alpha-hydroxyvitamin D2, 1-dodecpyrrolidinone, 20-epi-1,25 dihydroxyvitamin D3, 22-oxacalcitriol, 2CVV, 2'-nor-cGMP, 3-isobutyl GABA, 5-ethynyluracil, 6-FUDCA, 7-methoxytacrine, Abamectin, abanoquil, abecarnil, abiraterone, Ablukast, Ablukast Sodium, Acadesine, acamprosate, Acarbose, Acebutolol, Acecainide Hydrochloride, Aceclidine, aceclofenae, Acedapsone, Aceglutamide Aluminum, Acemannan, Acetaminophen, Acetazolamide, Acetohexamide, Acetohydroxamic Acid, acetomepregenol, Acetophenazine Maleate, Acetosulfone Sodium, Acetylcholine Chloride, Acetylcysteine, acetyl-L-carnitine, acetylmethadol, Acifran, acipimox, acitemate, Acitretin, Acivicin, Aclarubicin, aclatonium, Acodazole Hydrochloride, aconiazide, Acrisorcin, Acrivastine, Acronine, Actisomide, Actodigin, Acyclovir, acylfulvene, adafenoxate, adapalene, Adapalene, adatanserin, Adatanserin Hydrochloride, adecypenol, adecypenol, Adefovir, adelmidrol, ademetionine, Adenosine,

Adinazolam, Adipheinine Hydrochloride, adiposin, Adozelesin, adrafinil, Adrenalone, airbutamine, alacepril, Alamecin, Alanine, Alaproclate, alaptide, Albendazole, albolabrin, Albuterol, Albutoin, Alclofenae, Alclometasone Dipropionate, Alcloxa, aldecalmycin, Aldesleukin, Aldioxa, Alendronate Sodium, alendronic acid, alentemol, Alentemol Hydrobromide, Aletamine Hydrochloride, Aleuronium Chloride, Alexidine, alfacalcidol, Alfentanil Hydrochloride, alfuzosin, Algestone Acetonide, alglucerase, Aliflurane, alinastine, Alipamide, Allantoin, Allobarbital, Allopurinol, ALL-TK antagonists, Alonimid, alosetron, Alosetron Hydrochloride, Alovudine, Alpertine, Alpha Amylase, alpha idosone, Alpidem, Alprazolam, Alprenolol Hydrochloride, Alprenoxime Hydrochloride, Alprostadil, Alrestatin Sodium, Altanserin Tartrate, Alteplase, Althiazide, Altretamine, altromycin B, Alverinc Citrate, Alvircept Sudotox, Amadinone Acetate, Amantadine Hydrochloride, ambamustine, Ambomycin, Ambruticin, Ambuphylline, Ambuside, Amcinafal, Amcinonide, Amdinocillin, Amdinocillin Pivoxil, Amedalin Hydrochloride, amelometasone, Ameltolide, Amesergide, Ametantrone Acetate, amezinium metilsulfate, amfebutamone, Amfenac Sodium, Amflutizole, Amicycline, Amidephrine Mesylate, amidox, Amifloxacin, amifostine, Amikacin, Amiloride Hydrochloride, Aminacrine Hydrochloride, Aminobenzoate Potassium, Aminobenzoate Sodium, Aminocaproic Acid, Aminoglutethimide, Aminohippurate Sodium, aminolevulinic acid, Aminophylline, A minorex, Aminosalicylate sodium, Aminosalicylic acid, Amiodarone, Amiprilose Hydrochloride, Amiquinsin Hydrochloride, amisulpride, Amitraz, Amitriptyline Hydrochloride, Amlexanox, amlodipine, Amobarbital Sodium, Amodiaquine, Amodiaquine Hydrochloride, Amorolfine, Amoxapine, Amoxicillin, Amphecloral, Amphetamine Sulfate, Amphomycin, Amphotericin B, Ampicillin, ampiroxicam, Ampyzine Sulfate, Amquinate, Amrinone, amrinone, amrubicin, Amsacrine, amylin, amythiamicin, Anagestone Acetate, anagrelide, Anakinra, ananain, anaritide, Anaritide Acetate, Anastrozole, Anazolene Sodium, Ancrod, andrographolide, Androstenedione, angiogenesis inhibitors, Angiotensin Amide, Anidoxime, Anileridine, Anilopam Hydrochloride, Aniracetam, Anirolac, Anisotropine Methylbromide, Anistreplase, Anitrazafen, anordrin, antagonist D, antagonist G, antarelix, Antazoline Phosphate, Anthelmycin, Anthralin, Anthramycin, antiandrogen, Acedapsone, Felbamate, antiestrogen, antineoplaston, Antipyrine, antisense oligonucleotides, apadoline, apafant, Apalcillin Sodium, apaxifylline, Apazone, aphidicolin glycinate, Apixifylline, Apomorphine Hydrochloride, apraclonidine, Apraclonidine

Hydrochloride, Apramycin, Aprindine, Aprindine Hydrochloride, aprosulate sodium, Aprotinin, Aptazapine Maleate, aptiganel, apurinic acid, apurinic acid, aranidipine, Aranotin, Arbaprostil, arbekicin, arbidol, Arbutamine Hydrochloride, Arclofenin, Ardeparin Sodium, argatroban, Arginine, Argipressin Tannate, Arildone, aripiprazol, arotinolol, Arpinocid, Arteflene, Artilide Fumarate, asimadoline, aspalatone, Asparaginase, Aspartic Acid, Aspartocin, asperfuran, Aspirin, aspoxicillin, Asprelin, Astemizole, Astromicin Sulfate, asulacrine, atamestane, Atenolol, atevirdine, Atipamezole, Atiprosin Maleate, Atolide, Atorvastatin Calcium, Atosiban, Atovaquone, atpenin B, Atracurium Besylate, atrimustine, atrinositol, Atropine, Auranofin, aureobasidin A, Aurothioglucose, Avilamycin, Avoparcin, Avridine, Axid, axinastatin 1, axinastatin 2, axinastatin 3, Azabon, Azacitidinie, Azaclorzine Hydrochloride, Azaconazole, azadirachtine, Azalanstat Dihydrochloride, Azaloxan Fumarate, Azanator Maleate, Azanidazole, Azaperone, Azaribine, Azaserine, azasetron, Azatadine Maleate, Azathioprine, Azathioprine Sodium, azatoxin, azatyrosine, azelaic acid, azelastine, azelnidipine, Azepindole, Azetepa, azimilide, Azithromycin, Azlocillin, Azolimine, Azosemide, Azotomycin, Aztreonam, Azumolene Sodium, Bacampicillin Hydrochloride, baccatin III, Bacitracin, Baclofen, bacoside A, bacoside B, bactobolamine, balanol, balazipone, balhimycin, balofloxacin, balsalazide, Bambermycins, bambuterol, Bamethan Sulfate, Bamifylline Hydrochloride, Bamidazole, baohuoside 1, Barmastine, barnidipine, Basifungin, Batanopride Hydrochloride, batebulast, Batelapine Maleate, Batimastat, beauvericin, Becanthone Hydrochloride, becaplermin, becliconazole, Beclomethasone Dipropionate, befloxatone, Beinserazide, Belfosdil, Belladonna, Beloxamide, Bemesetron, Bemitradine, Bemoradan, Benapryzine Hydrochloride, Benazepril Hydrochloride, Benazeprilat, Bendacalol Mesylate, Bendazac, Bendroflumethiazide, benflumetol, benidipine, Benorterone, Benoxaprofen, Benoxaprofen, Benoxinate Hydrochloride, Benperidol, Bentazepam, Bentiromide, Benurestat, Benzbromarone, Benzethonium Chloride, Benzetimide Hydrochloride, Benzilonium Bromide, Benzindopyrine Hydrochloride, benzisoxazole, Benzocaine, benzochlorins, Benzoctamine Hydrochloride, Benzodepa, benzoidazoxan, Benzonatate, Benzoyl Peroxide, Benzoylpas Calcium, benzoylstaurosporine, Benzquinamide, Benzthiazide, benztropine, Benztropine Mesylate, Benzydamine Hydrochloride, Benzylpenicilloyl Polylysine, bepridil, Bepridil Hydrochloride, Beractant, Beraprost, Berefrine, berlafenone, bertosamil, Berythromycin, besipirdine, beta-alethine, betaclamycin B,

Betamethasone, betamipron, betaxolol, Betaxolol Hydrochloride, Bethanechol Chloride, Bethanidine Sulfate, betulinic acid, bevantolol, Bevantolol Hydrochloride, Bezafibrate, bFGF inhibitor, Bialamicol Hydrochloride, Biapenem, Bicalutamide, Bicifadine Hydrochloride, Biclodil Hydrochloride, Bidisomide, bifemelane, Bifonazole, bimakalim, bimithil, Bindarit, Biniramycin, binospirone, bioxalomycin alpha2, Bipenamol Hydrochloride, Biperiden, Biphenamine Hydrochloride, biriperone, bisantrene, bisaramil, bisaziridinylspermine, bis-benzimidazole A, bis-benzimidazole B, bisnafide, Bisobrin Lactate, Bisoprolol, Bispyrithione Magsulfex, bistramide D, bistramide K, bistratene A, Bithionolate Sodium, Bitolterol Mesylate, Bivalirudin, Bizelesin, Bleomycin Sulfate, Bolandiol Dipropionate, Bolasterone, Boldenone Undecylenate, boldine, Bolenol, Bolmantalate, bopindolol, Bosentan, Boxidine, brefeldin, breflate, Brequinar Sodium, Bretazenil, Bretylium Tosylate, Brifentanil Hydrochloride, brimonidine, Brinolase, Brocresine, Brocrinat, Brofoxine, Bromadoline Maleate, Bromazepam, Bromchlorenone, Bromelains, bromfenac, Brominidione, Bromocriptine, Bromodiphenhydramine Hydrochloride, Bromoxanide, Bromperidol, Bromperidol Decanoate, Brompheniramine Maleate, Broperamole, Bropirimine, Brotizolam, Bucainide Maleate, bucindolol, Buclizine Hydrochloride, Bucromarone, Budesonide, budipine, budotitane, Buformin, Bumetamide, Bunaprolast, bunazosin, Bunolol Hydrochloride, Bupicomide, Bupivacaine Hydrochloride, Buprenorphine Hydrochloride, Bupropion Hydrochloride, Buramate, Buserelin Acetate, Buspirone Hydrochloride, Busulfan, Butabarbital, Butacetin, Butaclamol Hydrochloride, Butalbital, Butamben, Butamirate Citrate, Butaperazine, Butaprost, Butedronate Tetrasodium, butenafine, Buterizine, buthionine sulfoximine, Butikacin, Butilfenin, Butirosin Sulfate, Butixirate, butixocort propionate, Butoconazole Nitrate, Butonate, Butopamine, Butoprozine Hydrochloride, Butorphanol, Butoxamine Hydrochloride, Butriptyline Hydrochloride, Cactinomycin, Cadexomer Iodine, Caffeine, calanolide A, Calcifediol, Calcipotriene, calcipotriol, Calcitonin, Calcitriol, Calcium Undecylenate, calphostin C, Calusterone, Cambendazole, camonagrel, camptothecin derivatives, canarypox IL-2, candesartan, Candicidin, candoxatril, candoxatrilat, Caniglibose, Canrenoate Potassium, Canrenone, capecitabine, Capobenate Sodium, Capobenic Acid, Capreomycin Sulfate, capromab, capsaicin, Captopril, Capuride, Caracemide, Carbachol, Carbadox, Carbamazepine, Carbamide Peroxide, Carbantel Lauryl Sulfate, Carbaspirin Calcium, Carbazeran, carbazomycin C, Carbenicillin

Potassium, Carbenoxolone Sodium, Carbetimer, carbetocin, Carbidopa, Carbidopa-Levodopa, Carbinoxamine Maleate, Carbiphene Hydrochloride, Carbocloral, Carbocysteine, Carbol-Fuchsin, Carboplatin, Carboprost, carbovir, carboxamide-amino-triazo-le, carboxyamidotriazole, carboxymethylated beta-1,3-glucan, Carbuterol Hydrochloride, CaRest M3, Carfentanil Citrate, Carisoprodol, Carmantadine, Carmustine, CARN 700, Camidazole, Caroxazone, carperitide, Carphenazine Maleate, Carprofen, Carsatrin Succinate, Cartazolate, carteolol, Carteolol Hydrochloride, cartilage derived inhibitor, Carubicin Hydrochloride, Carumonam Sodium, carvedilol, carvotroline, Carvotroline Hydrochloride, carzelesin, casein kinase inhibitors (ICOS), castanospermine, caurumonam, cebaracetam, cecropin B, Cedefingol, Cefaclor, Cefadroxil, Cefamandole, Cefaparole, Cefatrizine, Cefazaflur Sodium, Cefazolin, Cefbuperazone, cefcapene pivoxil, cefdaloxime pentexil tosilate, Cefdinir, cefditoren pivoxil, Cefepime, cefetamet, Cefetecol, cefixime, cefluprenam, Cefinenoxime Hydrochloride, Cefinetazole, cefminlox, cefodizime, Cefonicid Sodium, Cefoperazone Sodium, Ceforamide, cefoselis, Cefotaxime Sodium, Cefotetan, cefotiam, Cefoxitin, cefozopran, cefpimizole, Cefpiramide, cefpirome, cefpodoxime proxetil, cefprozil, Cefroxadine, cefsulodin, Ceftazidime, cefteram, ceftibuten, Ceftizoxime Sodium, ceftriaxone, Cefuroxime, celastrol, celikalim, celiprolol, cepacidiine A, Cephacetrile Sodium, Cephalexin, Cephaloglycin, Cephaloridine, Cephalothin Sodium, Cephapirin Sodium, Cephradine, cericlamine, cerivastatin, Ceronapril, certoparin sodium, Ceruletide, Cetaben Sodium, Cetalkonium Chloride, Cetamolol Hydrochloride, cetiedil, cetirizine, Cetophenicol, Cetraxate Hydrochloride, cetrorelix, Cetylpyridinium Chloride, Chenodiol, Chlophedianol Hydrochloride, Chloral Betaine, Chlorambucil, Chloramphenicol, Chlordantoin, Chlordiazepoxide, Chlorhexidine Gluconate, chlorins, Chlormadinone Acetate, chloroorienticin A, Chloroprocaine Hydrochloride, Chloropropamide, Chloroquine, chloroquinoxaline sulfonamide, Chlorothiazide, Chlorotrianisene, Chloroxine, Chloroxylenol, Chlorphenesin Carbamate, Chlorpheniramine Maleate, Chlorpromazine, Chlorpropamide, Chlorprothixene, Chlortetracycline Bisulfate, Chlorthalidone, Chlorzoxazone, Cholestyramine Resin, Chromonar Hydrochloride, cibenzoline, cicaprost, Ciclafrine Hydrochloride, Ciclazindol, ciclesonide, cicletanine, Ciclopirox, Ciclopro fen, ciclo prolol, Cidofovir, Cidoxepin Hydrochloride, Cifenline, Ciglitazone, Ciladopa Hydrochloride, cilansetron, Cilastatin Sodium, Cilazapril, cilnidipine, Cilobamine Mesylate, cilobradine, Cilofungin, cilostazol, Cimaterol,

Cimetidine, cimetropium bromide, Cinalukast, Cinanserin Hydrochloride, Cinepazet Maleate, Cinflumide, Cingestol, cinitapride, Cinnamedrine, Cinnarizine, cinolazepam, Cinoxacin, Cinperene, Cinromide, Cintazone, Cintriamide, Cioteronel, Cipamfylline, Ciprefadol Succinate, Ciprocinonide, Ciprofibrate, Ciprofloxacin, ciprostene, Ciramadol, Cirolemycin, cisapride, cisatracurium besilate, Cisconazole, Cisplatin, cis-porphyrin, cistinexine, citalopram, Citenamide, citicoline, citreamicin alpha, cladribine, Clamoxyquin Hydrochloride, Clarithromycin, clausenamide, Clavulanate Potassium, Clazolam, Clazolimine, clebopride, Clemastine, Clentiazem Maleate, Clidinium Bromide, clinafloxacin, Clindamycin, Clioquinol, Clioxanide, Cliprofen, clobazam, Clobetasol Propionate, Clobetasone Butyrate, Clocortolone Acetate, Clodanolene, Clodazon Hydrochloride, clodronic acid, Clofazimine, Clofibrate, Clofilium Phosphate, Clogestone Acetate, Clomacran Phosphate, Clomegestone Acetate, Clometherone, clomethiazole, clomifene analogues, Clominorex, Clomiphene, Clomipramine Hydrochloride, Clonazepam, Clonidine, Clonitrate, Clonixeril, Clonixin, Clopamide, Clopenthixol, Cloperidone Hydrochloride, clopidogrel, Clopimozide, Clopipazan Mesylate, Clopirac, Cloprednol, Cloprostenol Sodium, Clorazepate Dipotassium, Clorethate, Clorexolone, Cloroperone Hydrochloride, Clorprenaline Hydrochloride, Clorsulon, Clortermine Hydrochloride, Closantel, Closiramine Aceturate, Clothiapine, Clothixamide Maleate Cloticasone Propionate, Clotrimazole, Cloxacillin Benzathine, Cloxyquin, Clozapine, Cocaine, Coccidioidin, Codeine, Codoxime, Colchicine, colestimide, Colestipol Hydrochloride, Colestolone, Colforsin, Colfosceril Palmitate, Colistimethate Sodium, Colistin Sulfate, collismycin A, collismycin B, Colterol Mesylate, combretastatin A4, combretastatin analogue, complestatin, conagenin, Conorphone Hydrochloride, contignasterol, contortrostatin, Cormethasone Acetate, Corticorelin Ovine Triflutate, Corticotropin, Cortisone Acetate, Cortivazol, Cortodoxone, cosalane, costatolide, Cosyntropin, cotinine, Coumadin, Coumermycin, crambescidin 816, Crilvastatin, crisnatol, Cromitrile Sodium, Cromolyn Sodium, Crotamiton, cryptophycin 8, cucumariosid, Cuprimyxin, curacin A, curdlan sulfate, curiosin, Cyclacillin, Cyclazocine, cyclazosin, cyclic HPMPC, Cyclindole, Cycliramine Maleate, Cyclizine, Cyclobendazole, cyclobenzaprine, cyclobut A, cyclobut G, cyclocapron, Cycloguanil Pamoate, Cycloheximide, cyclopentanthraquinones, Cyclopenthiazide, Cyclopentolate Hydrochloride, Cyclophenazine Hydrochloride, Cyclophosphamide, cycloplatam, Cyclopropane, Cycloserine,

cyclosin, Cyclosporine, cyclothialidine, Cyclothiazide, cyclothiazomycin, Cyheptamide, cypemycin, Cypenamine Hydrochloride, Cyprazepam, Cyproheptadine Hydrochloride, Cyprolidol Hydrochloride, cyproterone, Cyproximide, Cysteamine, Cysteine Hydrochloride, Cystine, Cytarabine, Cytarabine Hydrochloride, cytarabine ocfosfate, cytochalasin B, cytolytic factor, cytostatin, Dacarbazine, dacliximab, dactimicin, Dactinomycin, daidzein, Daledalin Tosylate, dalfopristin, Dalteparin Sodium, Daltroban, Dalvastatin, danaparoid, Danazol, Dantrolene, daphlnodorin A, dapiprazole, dapitant, Dapoxetine Hydrochloride, Dapsone, Daptomycin, Darglitazone Sodium, darifenacin, darlucin A, Darodipine, darsidomine, Daunorubicin Hydrochloride, Dazadrol Maleate, Dazepinil Hydrochloride, Dazmegrel, Dazopride Fumarate, Dazoxiben Hydrochloride, Debrisoquin Sulfate, Decitabine, deferiprone, deflazacort, Dehydrocholic Acid, dehydrodidemnin B, Dehydroepiandrosterone, delapril, Delapril Hydrochloride, Delavirdine Mesylate, delequamine, delfaprazine, Delmadinone Acetate, delmopinol, delphinidin, Demecarium Bromide, Demeclocycline, Demecycline, Demoxepam, Denofungin, deoxypyridinoline, Depakote, deprodone, Deprostil, depsidomycin, deramciclane, dermatan sulfate, Desciclovir, Descinolone Acetonide, Desflurane, Desipramine Hydrochloride, desirudin, Deslanoside, deslorelin, desmopressin, desogestrel, Desonide, Desoximetasone, desoxoamiodarone, Desoxycorticosterone Acetate, detajmium bitartrate, Deterenol Hydrochloride, Detirelix Acetate, Devazepide, Dexamethasone, Dexamisole, Dexbrompheniramine Maleate, Dexchlorpheniramine Maleate, Dexclamol Hydrochloride, Dexetimide, Dexfenfluramine Hydrochloride, dexifosfamide, Deximafen, Dexivacaine, dexketoprofen, dexloxiglumide, Dexmedetomidine, Dexormaplatin, Dexoxadrol Hydrochloride, Dexpanthenol, Dexpemedolac, Dexpropranolol Hydrochloride, Dexrazoxane, dexsotalol, dextrin 2-sulphate, Dextroamphetamine, Dextromethorphan, Dextrorphan Hydrochloride, Dextrothyroxine Sodium, dexverapamil, Dezaguanine, dezinamide, dezocine, Diacetolol Hydrochloride, Diamocaine Cyclamate, Diapamide, Diatrizoate Meglumine, Diatrizoic Acid, Diaveridine, Diazepam, Diaziquone, Diazoxide, Dibenzepin Hydrochloride, Dibenzothiophene, Dibucaine, Dichliorvos, Dichloralphenazone, Dichlorphenamide, Dicirenone, Diclofenac Sodium, Dicloxacillin, dicranin, Dicumarol, Dicyclomine Hydrochloride, Didanosine, didemnin B, didox, Dienestrol, dienogest, Diethylcarbamazine Citrate, diethylhomospermine, diethylnorspermine, Diethylpropion Hydrochloride, Diethylstilbestrol, Difenoximide

Hydrochloride, Difenoxin, Diflorasone Diacetate, Difloxacin Hydrochloride, Difluanine Hydrochloride, Diflucortolone, Diflumidone Sodium, Diflunisal, Difluprednate, Diftalone, Digitalis, Digitoxin,

Digoxin, Dihexyverine Hydrochloride, dihydrexidine, dihydro-5-azacytidine, Dihydrocodeine Bitartrate, Dihydroergotamine Mesylate, Dihydroestosterone, Dihydrostreptomycin Sulfate, Dihydrotachysterol, dihydrotaxol, 9-, Dilantin, Dilevalol Hydrochloride, Diltiazem Hydrochloride, Dimefadane, Dimefline Hydrochloride, Dimenhydrinate, Dimercaprol, Dimethadione, Dimethindene Maleate, Dimethisterone, dimethyl prostaglandin A1, Dimethyl Sulfoxide, dimethylhomospermine, dimiracetam, Dimoxamine Hydrochloride, Dinoprost, Dinoprostone, Dioxadrol Hydrochloride, dioxamycin, Diphenhydramine Citrate, Diphenidol, Diphenoxylate Hydrochloride, diphenyl spiromustine, Dipivefin Hydrochloride, Dipivefrin, dipliencyprone, diprafenone, dipropylnorspermine, Dipyridamole, Dipyrithione, Dipyrone, dirithromycin, discodermolide, Disobutamide, Disofenin, Disopyramide, Disoxaril, disulfiram, Ditekiren, Divalproex Sodium, Dizocilpine Maleate, Dobutamine, docarpamine, Docebenone, Docetaxel, Doconazole, docosanol, dofetilide, dolasetron, Ebastine, ebiratide, ebrotidine, ebselen, ecabapide, ecabet, ecadotril, ecdisteron, echicetin, echistatin, Echothiophate Iodide, Eclanamine Maleate, Eclazolast, ecomustine, Econazole, ecteinascidin 722, edaravone, Edatrexate, edelfosine, Edifolone Acetate, edobacomab, Edoxudine, edrecolomab, Edrophonium Chloride, edroxyprogesteone Acetate, efegatran, eflornithine, efonidipine, egualcen, Elantrine, eleatonin, elemene, eletriptan, elgodipine, eliprodil, Elsamitrucin, eltenae, Elucaine, emalkalim, emedastine, Emetine Hydrochloride, emiglitate, Emilium Tosylate, emitefur, emoctakin, Enadoline Hydrochloride, enalapril, Enalaprilat, Enalkiren, enazadrem, Encyprate, Endralazine Mesylate, Endrysone, Enflurane, englitazone, Enilconazole, Enisoprost, Enlimomab, Enloplatin, Enofelast, Enolicam Sodium, Enoxacin, enoxacin, enoxaparin sodium, Enoxaparin Sodium, Enoximone, Enpiroline Phosphate, Enprofylline, Enpromate, entacapone, enterostatin, Enviradene, Enviroxime, Ephedrine, Epicillin, Epimestrol, Epinephrine, Epinephryl Borate, Epipropidine, Epirizole, epirubicin, Epitetracycline Hydrochloride, Epithiazide, Epoetin Alfa, Epoetin Beta, Epoprostenol, Epoprostenol Sodium, epoxymexrenone, epristeride, Eprosartan, eptastigmine, equilenin, Equilin, Erbulozole, erdosteine, Ergoloid Mesylates, Ergonovine Maleate, Ergotamine Tartrate, ersentilide, Ersofermin, erythritol, Erythrityl Tetranitrate, Erythromycin, Esmolol

Hydrochloride, Esorubicin Hydrochloride, Esproquin Hydrochloride, Estazolam, Estradiol, Estramustine, estramustine analogue, Estrazinol Hydrobromide, Estriol, Estrofurate, estrogen agonists, estrogen antagonists, Estrogens, Conjugated, Estrogens, Esterified, Estrone, Estropipate, esuprone, Etafedrine Hydrochloride, Etanidazole, etanterol, Etarotene, Etazolate Hydrochloride, Eterobarb, ethacizin, Ethacrynate Sodium, Ethacrynic Acid, Ethambutol Hydrochloride, Ethamivan, Ethanolamine Oleate, Ethehlorvynol, Ether, Ethinyl estradiol, Ethiodized Oil, Ethionamide, Ethonam Nitrate, Ethopropazine Hydrochloride, Ethosuximide, Ethotoin, Ethoxazene Hydrochloride, Ethybenztropine, Ethyl Chloride, Ethyl Dibunate, Ethylestrenol, Ethyndiol, Ethynerone, Ethynodiol Diacetate, Etibendazole, Etidocaine, Etidronate Disodium, Etidronic Acid, Etifenin, Etintidine Hydrochloride, etizolam, Etodolac, Etofenamate, Etoformin Hydrochloride, Etomidate, Etonogestrel, Etoperidone Hydrochloride, Etoposide, Etoprine, Etoxadrol Hydrochloride, Etozolin, etrabamine, Etretinate, Etryptamine Acetate, Eucatropine Hydrochloride, Eugenol, Euprocin Hydrochloride, eveminomicin, Exametazime, examorelin, Exaprolol Hydrochloride, exemestane, fadrozole, faeriefungin, Famciclovir, Famotidine, Fampridine, fantofarone, Fantridone Hydrochloride, faropenem, fasidotril, fasudil, fazarabine, fedotozine, felbamate, Felbinac, Felodipine, Felypressin, Fenalamide, Fenamole, Fenbendazole, Fenbufen, Fencibutirol, Fenclofenac, Fenclonine, Fenclorac, Fendosal, Fenestrel, Fenethylline Hydrochloride, Fenfluramine Hydrochloride, Fengabine, Fenimide, Fenisorex, Fenmetozole Hydrochloride, Fenmetramide, Fenobam, Fenoctimine Sulfate, fenofibrate, fenoldopam, Fenoprofen, Fenoterol, Fenpipalone, Fenprinast Hydrochloride, Fenprostalene, Fenquizone, fenretinide, fenspiride, Fentanyl Citrate, Fentiazac, Fenticlor, fenticonazole, Fenyripol Hydrochloride, fepradinol, ferpifosate sodium, ferristene, ferrixan, Ferrous Sulfate, Dried, Ferumoxides, ferumoxsil, Fetoxylate Hydrochloride, fexofenadine, Fezolamine Fumarate, Fiacitabine, Fialuridine, Fibrinogen 1 125, filgrastim, Filipin, finasteride, Flavodilol Maleate, flavopiridol, Flavoxate Hydrochloride, Flazalone, flecainide, flerobuterol, Fleroxacin, flesinoxan, Flestolol Sulfate, Fletazepam, flezelastine, flobufen, Floctafenine, flomoxef, Flordipine, florfenicol, florifenine, flosatidil, Flosequinan, Floxacillin, Floxuridine, fluasterone, Fluazacort, Flubanilate Hydrochloride, Flubendazole, Flucindole, Flucloronide, Fluconazole, Flucytosine, Fludalanine, Fludarabine Phosphate, Fludazonium Chloride, Fludeoxyglucose F 18, Fludorex, Fludrocortisone Acetate, Flufenamic Acid, Flufenisal, Flumazenil, flumecinol, Flumequine,

Flumeridone, Flumethasone, Flumetramide, Flumezapine, Fluminorex, Flumizole, Flumoxonide, flunarizine, Flunidazole, Flunisolide, Flunitrazepam, Flunixin, fluocalcitriol, Fluocinolone Acetonide, Fluocinonide, Fluocortin Butyl, Fluocortolone, Fluorescein, fluorodaunorunicin hydrochloride, Fluorodopa F 18, Fluorometholone, Fluorouracil, Fluotracen Hydrochloride, Fluoxetine, Fluoxymesterone, fluparoxan, Fluperamide, Fluperolone Acetate, Fluphenazine Decanoate, flupirtine, Fluprednisolone, Fluproquazone, Fluprostenol Sodium, Fluquazone, Fluradoline Hydrochloride, Flurandrenolide, Flurazepam Hydrochloride, Flurbiprofen, Fluretofen, flurithromycin, Flurocitabine, Flurofamide, Flurogestone Acetate, Flurothyl, Fluroxene, Fluspiperone, Fluspirilene, Fluticasone Propionate, flutrimazole, Flutroline, fluvastatin, Fluvastatin Sodium, fluvoxamine, Fluzinamide, Folic Acid, Follicle regulatory protein, Folliculostatin, Fomepizole, Fonazine Mesylate, forasartan, forfenimex, forfenirmex, formestane, Formocortal, formoterol, Fosarilate, Fosazepam, Foscarnet Sodium, fosfomycin, Fosfonet Sodium, fosinopril, Fosinoprilat, fosphenyloin, Fosquidone, Fostedil, fostriecin, fotemustine, Fuchsin, Basic, Fumoxicillin, Fungimycin, Furaprofen, Furazolidone, Furazolium Chloride, Furegrelate Sodium, Furobufen, Furodazole, Furosemide, Fusidate Sodium, Fusidic Acid, gabapentin, Gadobenate Dimeglumine, gadobenic acid, gadobutrol, Gadodiamide, gadolinium texaphyrin, Gadopentetate Dimeglumine, gadoteric acid, Gadoteridol, Gadoversetamide, galantamine, galdansetron, Galdansetron Hydrochloride, Gallamine Triethiodide, gallium nitrate, gallopamil, galocitabine, Gamfexine, gamolenic acid, Ganciclovir, ganirelix, gelatinase inhibitors, Gemcadiol, Gemcitabine, Gemeprost, Gemfibrozil, Gentamicin Sulfate, Gentian Violet, gepirone, Gestaclone, Gestodene, Gestonorone Caproate, Gestrinone, Gevotroline Hydrochloride, girisopam, glaspimod, glaucocalyxin A, Glemanserin, Gliamilide, Glibornuride, Glicetanile Sodium, Gliflumide, Glimepiride, Glipizide, Gloximonam, Glucagon, glutapyrone, glutathione inhibitors, Glutethimide, Glyburide, glycopine, glycopril, Glycopyrrolate, Glyhexamide, Glymidine Sodium, Glyoctamide, Glyparamide, Gold Au 198, Gonadoctrinins, Gonadorelin, Gonadotropins, Goserelin, Gramicidin, Granisetron, grepafloxacin, Griseofulvin, Guaiapate, Guaithylline, Guanabenz, Guanabenz Acetate, Guanadrel Sulfate, Guancydine, Guanethidine Monosulfate, Guanfacine Hydrochloride, Guanisoquin Sulfate, Guanoclor Sulfate, Guanoctine Hydrochloride, Guanoxabenz, Guanoxan Sulfate, Guanoxyfen Sulfate, Gusperimus Trihydrochloride, Halazepam, Halcinonide, halichondrin B,

Halobetasol Propionate, halofantrine, Halofantrine Hydrochloride, Halofenate, Halofuginone Hydrobromide, halomon, Halopemide, Haloperidol, halopredone, Haloprogesterone, Haloprogin, Halothane, Halquinols, Hamycin, Han memopausal gonadotropins, hatomamicin, hatomarubigin A, hatomarubigin B, hatomarubigin C, hatomarubigin D, Heparin Sodium, hepsulfam, heregulin, Hetacillin, Heteronium Bromide, Hexachlorophene:Hydrogen Peroxide, Hexafluorenium Bromide, hexamethylene bisacetamide, Hexedine, Hexobendine, Hexoprenaline Sulfate, Hexylresorcinol, Histamine Phosphate, Histidine, Histoplasmin, Histrelin, Homatropine Hydrobromide, Hoquizil Hydrochloride, Human chorionic gonadotropin, Hycanthone, Hydralazine Hydrochloride, Hydralazine Polistirex, Hydrochlorothiazide, Hydrocodone Bitartrate, Hydrocortisone, Hydroflumethiazide, Hydromorphone Hydrochloride, Hydroxyamphetamine Hydrobromide, Hydroxychloroquine Sulfate, Hydroxyphenamate, Hydroxyprogesterone Caproate, Hydroxyurca, Hydroxyzine Hydrochloride, Hymecromone, Hyoscyamine, hypericin, Ibafloxacin, ibandronic acid, ibogaine, Ibopamine, ibudilast, Ibufenac, Ibuprofen, Ibutilide Fumarate, Icatibant Acetate, Ichthammol, Icotidine, idarubicin, idoxifene, Idoxuridine, idramantone, Iemefloxacin, Iesopitron, Ifetroban, Ifosfamide, Ilepeimide, illimaquinone, ilmofosine, ilomastat, Ilonidap, iloperidone, iloprost, Imafen Hydrochloride, Imazodan Hydrochloride, imidapril, imidazenil, imidazoacridones, Imidecyl Iodine, Imidocarb Hydrochloride, Imidoline Hydrochloride, Imidurea, Imiloxan Hydrochloride, Imipenem, Imipramine Hydrochloride, imiquimod, immunostimulant peptides, Impromidine Hydrochloride, Indacrinone, Indapamide, Indecainide Hydrochloride, Indeloxazine Hydrochloride, Indigotindisulfonate Sodium, indinavir, Indocyanine Green, Indolapril Hydrochloride, Indolidan, indometacin, Indomethacin Sodium, Indoprofen, indoramin, Indorenate Hydrochloride, Indoxole, Indriline Hydrochloride, inocoterone, inogatran, inolimomab, Inositol Niacinate, Insulin, interferons, interleukins, Intrazole, Intriptyline Hydrochloride, iobenguane, Iobenzamic Acid, iobitridol, Iocarmate Meglumine, Iocarmic Acid, Iocetamic Acid, Iodamide, Iodine, Iodipamide Meglumine, Iodixanol, iodoamiloride, Iodoantipyrine I 131, Iodocholesterol I 131, iododoxorubicin, Iodohippurate Sodium I 131, Iodopyracet I 125, Iodoquinol, Iodoxamate Meglumine, Iodoxamie Acid, Ioglicic Acid, Iofetamine Hydrochloride I 123, iofratol, Ioglucol, Ioglucomide, Ioglycamic Acid, Iogulamide, Iohexol, iomeprol, Iomethin I 125, Iopamidol, Iopanoic Acid, iopentol, Iophendylate, Ioprocemic Acid, iopromide, Iopronic Acid, Iopydol,

Iopydone, iopyrol, Iosefamic Acid, Ioseric Acid, Iosulamide Meglumine, Iosumetic Acid, Iotasul, Iotetric Acid, Iothalamate Sodium, Iothalamic Acid, iotriside, Iotrolan, Iotroxic Acid, Iotyrosine I 131, Ioversol, Ioxagiate Sodium, Ioxaglate Meglumine, Ioxaglic Acid, ioxilan, Ioxotrizoic Acid, ipazilide, ipenoxazone, ipidacrine, Ipodate Calcium, ipomeanol, 4-, Ipratropium Bromide, ipriflavone, Iprindole, Iprofenin, Ipronidazole, Iproplatin, Iproxamine Hydrochloride, ipsapirone, irbesartan, irinotecan, irloxacin, iroplact, irsogladine, Irtemazole, isalsteine, Isamoxole, isbogrel, Isepamicin, isobengazole, Isobutamben, Isocarboxazid, Isoconazole, Isoetharine, isofloxythepin, Isoflupredone Acetate, Isoflurane, Isoflurophate, isohomohalicondrin B, Isoleucine, Isomazole Hydrochloride, Isomylamine Hydrochloride, Isoniazid, Isopropamide Iodide, Isopropyl Alcohol, isopropyl unoprostone, Isoproterenol Hydrochloride, Isosorbide, Isosorbide Mononitrate, Isotiquimide, Isotretinoin, Isoxepac, Isoxicam, Isoxsuprine Hydrochloride, isradipine, itameline, itasetron, Itazigrel, itopride, Itraconazole, Ivermectin, jasplakinolide, Josamycin, kahalalide F, Kalafungin, Kanamycin Sulfate, Ketamine Hydrochloride, Ketanserin, Ketazocine, Ketazolam, Kethoxal, Ketipramine Fumarate, Ketoconazole, Ketoprofen, Ketorfanol, ketorolac, Ketotifen Fumarate, Kitasamycin, Labetalol Hydrochloride, Lacidipine, lacidipine, lactitol, lactivicin, laennec, lafutidine, lamellarin-N triacetate, lamifiban, Lamivudine, Lamotrigine, lanoconazole, Lanoxin, lanperisone, lanreotide, Lansoprazole, latanoprost, lateritin, laurocapram, Lauryl Isoquinolinium Bromide, Lavoltidine Succinate, lazabemide, Lecimibide, leinamycin, lemildipine, leminoprazole, lenercept, Leniquinsin, lenograstim, Lenperone, lentinan sulfate, leptin, leptolstatin, lercanidipine, Lergotrile, lerisetron, Letimide Hydrochloride, letrazuril, letrozole, Leucine, leucomyzin, Leuprolide Acetate, leuprolide+estrogen+progesterone, leuprorelin, Levamfetamine Succinate, levamisole, Levdobutamine Lactobionate, Leveromakalim, levetiracetam, Leveycloserine, levobetaxolol, levobunolol, levobupivacaine, levocabastine, levocarnitine, Levodopa, levodropropizine, levofloxacin, Levofuraltadone, Levoleucovorin Calcium, Levomethadyl Acetate, Levomethadyl Acetate Hydrochloride, levomoprolol, Levonantradol Hydrochloride, Levonordefrin, Levonorgestrel, Levopropoxyphene Napsylate, Levopropylcillin Potassium, levormeloxifene, Levorphanol Tartrate, levosimendan, levosulpiride, Levothyroxine Sodium, Levoxadrol Hydrochloride, Lexipafant, Lexithromycin, liarozole, Libenzapril, Lidamidine Hydrochloride, Lidocaine, Lidofenin, Lidoflazine, Lifarizine, Lifibrate, Lifibrol, Linarotene, Lincomycin, linear polyamine analogue, Linogliride, Linopirdine,

linotroban, linsidomine, lintitript, lintopride, Liothyronine I 125, liothyronine sodium, Liotrix, lirexapride, lisinopril, lissoclinamide 7, Lixazinone Sulfate, lobaplatin, Lobenzarit Sodium, Lobucavir, Lodelaben, lodoxamide, Lofemizole Hydrochloride, Lofentanil Oxalate, Lofepramine Hydrochloride, Lofexidine Hydrochloride, lombricine, Lomefloxacin, lomerizine, Lometraline Hydrochloride, lometrexol, Lomofungin, Lomoxicam, Lomustine, Lonapalene, lonazolac, lonidamine, Loperamide Hydrochloride, loracarbef, Lorajmine Hydrochloride, loratadine, Lorazepam, Lorbamate, Lorcainide Hydrochloride, Loreclezole, Loreinadol, lorglumide, Lormetazepam, Lornoxicam, lornoxicam, Lortalamine, Lorzafone, losartan, losigamone, losoxantrone, Losulazine Hydrochloride, loteprednol, lovastatin, loviride, Loxapine, Loxoribine, lubeluzole, Lucanthone Hydrochloride, Lufironil, Lurosetron Mesylate, lurtotecan, luteinizing hormone, lutetium, Lutrelin Acetate, luzindole, Lyapolate Sodium, Lycetamine, lydicamycin, Lydimycin, Lynestrenol, Lypressin, Lysine, lysofylline, lysostaphin, lytic peptides, Maduramicin, Mafenide, magainin 2 amide, Magnesium Salicylate, Magnesium Sulfate, magnolol, maitansine, Malethamer, mallotochromene, mallotojaponin, Malotilate, malotilate, mangafodipir, manidipine, maniwamycin A, Mannitol, mannostatin A, manumycin E, manumycin F, mapinastine, Maprotiline, marimastat, Martek 8708, Martek 92211, Masoprocol, maspin, massetolide, matrilysin inhibitors, Maytansine, Mazapertine Succiniate, Mazindol, Mebendazole, Mebeverine Hydrochloride, Mebrofenin, Mebutamate, Mecamylamine Hydrochloride, Mechlorethamine Hydrochloride, Meclocycline, Meclofenamate Sodium, Mecloqualone, Meclorisone Dibutyrate, Medazepam Hydrochloride, Medorinone, Medrogestone, Medroxalol, Medroxyprogesterone, Medrysone, Meelizine Hydrochloride, Mefenamic Acid, Mefenidil, Mefenorex Hydrochloride, Mefexamide, Mefloquine Hydrochloride, Mefruside, Megalomicin Potassium Phosphate, Megestrol Acetate, Meglumine, Meglutol, Melengestrol Acetate, Melitracen Hydrochloride, Melphalan, Memotine Hydrochloride, Menabitan Hydrochloride, Menoctone, menogaril, Menotropins, Meobentine Sulfate, Mepartricin, Mepenzolate Bromide, Meperidine Hydrochloride, Mephentermine Sulfate, Mephenyloin, Mephobarbital, Mepivacaine Hydrochloride, Meprobamate, Meptazinol Hydrochloride, Mequidox, Meralein Sodium, merbarone, Mercaptopurine, Mercufenol Chloride, Mercury, Ammoniated, Merisoprol Hg 197, Meropenem, Mesalamine, Meseclazone, Mesoridazine, Mesterolone, Mestranol, Mesuprine Hydrochloride, Metalol Hydrochloride,

Metaproterenol Polistirex, Metaraminol Bitartrate, Metaxalone, Meteneprost, meterelin, Metformin, Methacholine Chloride, Methacycline, Methadone Hydrochloride, Methadyl Acetate, Methalthiazide, Methamphetamine Hydrochloride, Methaqualone, Methazolamide, Methdilazine, Methenamine, Methenolone Acetate, Methetoin, Methicillin Sodium, Methimazole, methioninase, Methionine, Methisazone, Methixene Hydrochloride, Methocarbamol, Methohexital Sodium, Methopholine, Methotrexate, Methotrimeprazine, methoxatone, Methoxyflurane, Methsuximide, Methyclothiazide, Methyl Palmoxirate, Methylatropine Nitrate, Methylbenzethonium Chloride, Methyldopa, Methyldopate Hydrochloride, Methylene Blue, Methylergonovine Maleate, methylhistamine, R-alpha, methylinosine monophosphate, Methylphenidate Hydrochloride, Methylprednisolone, Methyltestosterone, Methynodiol Diacelate, Methysergide, Methysergide Maleate, Metiamide, Metiapine, Metioprim, metipamide, Metipranolol, Metizoline Hydrochloride, Metkephamid Acetate, metoclopramide, Metocurine Iodide, Metogest, Metolazone, Metopimazine, Metoprine, Metoprolol, Metoquizine, metrifonate, Metrizamide, Metrizoate Sodium, Metronidazole, Meturedepa, Metyrapone, Metyrosine, Mexiletine Hydrochloride, Mexrenoate Potassium, Mezlocillin, mfonelic Acid, Mianserin Hydrochloride, mibefradil, Mibefradil Dihydrochloride, Mibolerone, michellamine B, Miconazole, microcolin A, Midaflur, Midazolam Hydrochloride, midodrine, mifepristone, Mifobate, miglitol, milacemide, milameline, mildronate, Milenperone, Milipertine, milnacipran, Milrinone, miltefosine, Mimbane Hydrochloride, minaprine, Minaxolone, Minocromil, Minocycline, Minoxidil, Mioflazine Hydrochloride, miokamycin, mipragoside, mirfentanil, mirimostim, Mirincamycin Hydrochloride, Mirisetron Maleate, Mirtazapine, mismatched double stranded RNA, Misonidazole, Misoprostol, Mitindomide, Mitocarcin, Mitocromin, Mitogillin, mitoguazone, mitolactol, Mitomalcin, Mitomycin, mitonafide, Mitosper, Mitotane, mitoxantrone, mivacurium chloride, mivazerol, mixanpril, Mixidine, mizolastine, mizoribine, Moclobemide, modafinil, Modaline Sulfate, Modecainide, moexipril, mofarotene, Mofegiline Hydrochloride, mofezolac, molgramostim, Molinazone, Molindone Hydrochloride, Molsidomine, mometasone, Monatepil Maleate, Monensin, Monoctanoin, Montelukast Sodium, montirelin, mopidamol, moracizine, Morantel Tartrate, Moricizine, Morniflumate, Morphine Sulfate, Morrhuate Sodium, mosapramine, mosapride, motilide, Motretinide, Moxalactam Disodium, Moxazocine, moxiraprine, Moxnidazole,

moxonidine, Mumps Skin Test Antigen, mustard anticancer agent, Muzolimine, mycaperoxide B, Mycophenolic Acid, myriaporone, Nabazenil, Nabilone, Nabitan Hydrochloride, Naboctate Hydrochloride, Nabumetone, N-acetyldinaline, Nadide, nadifloxacin, Nadolol, nadroparin calcium, nafadotride, nafamostat, nafarelin, Nafcillin Sodium, Nafenopin, Nafimidone Hydrochloride, Naflocort, Nafomine Malate, Nafoxidine Hydrochloride, Nafronyl Oxalate, Naftifine Hydrochloride, naftopidil, naglivan, nagrestip, Nalbuphine Hydrochloride, Nalidixate Sodium, Nalidixic Acid, nalmefene, Nalmexone Hydrochloride, naloxone+pentazocine, Naltrexone, Namoxyrate, Nandrolone Phenpropionate, Nantradol Hydrochloride, Napactadine Hydrochloride, napadisilate, Napamezole Hydrochloride, napaviin, Naphazoline Hydrochloride, naphterpin, Naproxen, Naproxol, napsagatran, Naranol Hydrochloride, Narasin, naratriptan, nartograstim, nasaruplase, Natamycin, nateplase, Naxagolide Hydrochloride, Nebivolol, Nebramycin, nedaplatin, Nedocromil, Nefazodone Hydrochloride, Neflumozide Hydrochloride, Nefopam Hydrochloride, Nelezaprine Maleate, Nemazoline Hydrochloride, nemorubicin, Neomycin Palmitate, Neostigmine Bromide, neridronic acid, Netilmicin Sulfate, neutral endopeptidase, Neutramycin, Nevirapine, Nexeridine Hydrochloride, Niacin, Nibroxane, Nicardipine Hydrochloride, Nicergoline, Niclosamide, Nicorandil, Nicotinyl Alcohol, Nifedipine, Nifirmerone, Nifluridide, Nifuradene, Nifuraldezone, Nifuratel, Nifuratrone, Nifurdazil, Nifurimide, Nifurpirinol, Nifurquinazol, Nifurthiazole, nilutamide, Nilvadipine, Nimazone, Nimodipine, niperotidine, niravoline, Niridazole, nisamycin, Nisbuterol Mesylate, nisin, Nisobamate, Nisoldipine, Nisoxetine, Nisterime Acetate, Nitarsone, nitazoxanide, nitecapone, Nitrafudam Hydrochloride, Nitralamine Hydrochloride, Nitramisole Hydrochloride, Nitrazepam, Nitrendipine, Nitrocycline, Nitrodan, Nitrofurantoin, Nitrofurazone, Nitroglycerin, Nitromersol, Nitromide, Nitromifene Citrate, Nitrous Oxide, nitroxide antioxidant, nitrullyn, Nivazol, Nivimedone Sodium, Nizatidine, Noberastine, Nocodazole, Nogalamycin, Nolinium Bromide, Nomifensine Maleate, Noracymethadol Hydrochloride, Norbolethone, Norepinephrine Bitartrate, Norethindrone, Norethynodrel, Norfloxacin, Norflurane, Norgestimate, Norgestomet, Norgestrel, Nortriptyline Hydrochloride, Noscapine, Novobiocin Sodium, N-substituted benzaimides, Nufenoxole, Nylestriol, Nystatin, O6-benzylguanine, Obidoxime Chloride, Ocaperidone, Ocfentanil Hydrochloride, Ocinaplon, Octanoic Acid, Octazamide, Octenidine Hydrochloride, Octodrine, Octreotide, Octriptyline Phosphate, Ofloxacin, Oformine, okicenone,

Olanzapine, oligonucleotides, olopatadine, olprinone, olsalazine, Olsalazine Sodium, Olvanil, omeprazole, onapristone, ondansetron, Ontazolast, Oocyte maturation inhibitor, Opipramol Hydrochloride, oracin, Orconazole Nitrate, Orgotein, Orlislat, Ormaplatin, Ormetoprim, Ornidazole, Orpanoxin, Orphenadrine Citrate, osaterone, otenzepad, Oxacillin Sodium, Oxagrelate, oxaliplatin, Oxamarin Hydrochloride, oxamisole, Oxamniquine, oxandrolone, Oxantel Pamoate, Oxaprotiline Hydrochloride, Oxaprozin, Oxarbazole, Oxatomide, oxaunomycin, Oxazepam, oxcarbazepine, Oxendolone, Oxethazaine, Oxetorone Fumarate, Oxfendazole, Oxfenicine, Oxibendazole, oxiconazole, Oxidopamine, Oxidronic Acid, Oxifungin Hydrochloride, Oxilorphan, Oximonam, Oximonam Sodium, Oxiperomide, oxiracetam, Oxiramide, Oxisuran, Oxmetidine Hydrochloride, oxodipine, Oxogestone Phenpropionate, Oxolinic Acid, Oxprenolol Hydrochloride, Oxtriphylline, Oxybutynin Chloride, Oxychlorosene, Oxycodone, Oxymetazoline Hydrochloride, Oxymetholone, Oxymorphone Hydrochloride, Oxypertine, Oxyphenbutazone, Oxypurinol, Oxytetracycline, Oxytocin, ozagrel, Ozolinone, Paclitaxel, palauamine, Paldimycin, palinavir, palmitoylrhizoxin, Palmoxirate Sodium, pamaqueside, Pamatolol Sulfate, pamicogrel, Pamidronate Disodium, pamidronic acid, Panadiplon, panamesine, panaxytriol, Pancopride, Pancuronium Bromide, panipenem, pannorin, panomifene, pantethine, pantoprazole, Papaverine Hydrochloride, parabactin, Parachlorophenol, Paraldehyde, Paramethasone Acetate, Paranyline Hydrochloride, Parapenzolate Bromide, Pararosaniline Pamoate, Parbendazole, Parconazole Hydrochloride, Paregoric, Pareptide Sulfate, Pargyline Hydrochloride, parnaparin sodium, Paromomycin Sulfate, Paroxetine, parthenolide, Partricin, Paulomycin, pazelliptine, Pazinaclone, Pazoxide, pazufloxacin, pefloxacin, pegaspargase, Pegorgotein, Pelanserin Hydrochloride, peldesine, Peliomycin, Pelretin, Pelrinone Hydrochloride, Pemedolac, Pemerid Nitrate, pemirolast, Pemoline, Penamecillin, Penbutolol Sulfate, Penciclovir, Penfluridol, Penicillin G Benzathine, Penicillin G Potassium, Penicillin G Procaine, Penicillin G Sodium, Penicillin V, Penicillin V Benzathine, Penicillin V Hydrabamine, Penicillin V Potassium, Pentabamate, Pentaerythritol Tetranitrate, pentafuside, pentamidine, pentamorphone, Pentamustine, Pentapiperium Methylsulfate, Pentazocine, Pentetic Acid, Pentiapine Maleate, pentigetide, Pentisomicin, Pentizidone Sodium, Pentobarbital, Pentomone, Pentopril, pentosan, pentostatin, Pentoxifylline, Pentrinitrol, pentrozole, Peplomycin Sulfate, Pepstatin, perflubron, perfofamide, Perfosfamide, pergolide, Perhexiline Maleate, perillyl

alcohol, Perindopril, perindoprilat, Perlapine, Permethrin, perospirone, Perphenazine, Phenacemide, phenaridine, phenazinomycin, Phenazopyridine Hydrochloride, Phenbutazone Sodium Glycerate, Phencarbamide, Phencyclidine Hydrochloride, Phendimetrazine Tartrate, Phenelzine Sulfate, Phenmetrazine Hydrochloride, Phenobarbital, Phenoxybenzamine Hydrochloride, Phenprocoumon, phenserine, phensuccinal, Phensuximide, Phentermine, Phentermine Hydrochloride, phentolamine mesilate, Phentoxifylline, Phenyl Aminosalicylate, phenylacetate, Phenylalanine, phenylalanyl ketoconazole, Phenylbutazone, Phenylephrine Hydrochloride, Phenylpropanolamine Hydrochloride, Phenylpropanolamine Polistirex, Phenyramidol Hydrochloride, Phenyloin, phosphatase inhibitors, Physostigmine, picenadol, picibanil, Picotrin Diolamine, picroliv, picumeterol, pidotimod, Pifamine, Pilocarpine, pilsicainide, pimagedine, Pimetine Hydrochloride, pimilprost, Pimobendan, Pimozide, Pinacidil, Pinadoline, Pindolol, pinnenol, pinocebrin, Pinoxepin Hydrochloride, pioglitazone, Pipamperone, Pipazethate, pipecuronium bromide, Piperacetazine, Piperacillin Sodium, Piperamide Maleate, piperazine, Pipobroman, Piposulfan, Pipotiazine Palmitate, Pipoxolan Hydrochloride, Piprozolin, Piquindone Hydrochloride, Piquizil Hydrochloride, Piracetam, Pirandamine Hydrochloride, pirarubicin, Pirazmonam Sodium, Pirazolac, Pirbenicillin Sodium, Pirbuterol Acetate, Pirenperone, Pirenzepine Hydrochloride, piretanide, Pirfenidone, Piridicillin Sodium, Piridronate Sodium, Piriprost, piritrexim, Pirlimycin Hydrochloride, pirlindole, pirmagrel, Pirmenol Hydrochloride, Pirnabine, Piroctone, Pirodavir, pirodomast, Pirogliride Tartrate, Pirolate, Pirolazamide, Piroxantrone Hydrochloride, Piroxicam, Piroximone, Pirprofen, Pirquinozol, Pirsidomine, Prenylamine, Pituitary, Posterior, Pivampicillin Hydrochloride, Pivopril, Pizotyline, placetin A, platinum compounds, platinum-triamine complex, Plicamycin, Plomestane, Pobilukast Edamine, Podofilox, Poisonoak Extract, Poldine Methylsulfate, Poliglusam, Polignate Sodium, Polymyxin B Sulfate, Polythiazide, Ponalrestat, Porfimer Sodium, Porfiromycin, Potassium Chloride, Potassium Iodide, Potassium Permanganate, Povidone-Iodine, Practolol, Pralidoxime Chloride, Pramiracetam Hydrochloride, Pramoxine Hydrochloride, Pranolium Chloride, Pravadoline Maleate, Pravastatin (Pravachol), Prazepam, Prazosin, Prazosin Hydrochloride, Prednazate, Prednicarbate, Prednimustine, Prednisolone, Prednisone, Prednival, Pregnenolone Succiniate, Prenalterol Hydrochloride, Pridefine Hydrochloride, Prifelone, Prilocalne Hydrochloride, Prilosec, Primaquine Phosphate, Primidolol, Primidone, Prinivil,

Prinomide Tromethamine, Prinoxodan, Prizidilol Hydrochloride, Proadifen Hydrochloride, Probenecid, Probicromil Calcium, Probucol, Procainamide Hydrochloride, Procaine Hydrochloride, Procarbazine Hydrochloride, Procaterol Hydrochloride, Prochlorperazine, Procinonide, Proclonol, Procyclidine Hydrochloride, Prodilidine Hydrochloride, Prodolic Acid, Profadol Hydrochloride, Progabide, Progesterone, Proglumide, Proinsulin Human, Proline, Prolintane Hydrochloride, Promazine Hydrochloride, Promethazine Hydrochloride, Propafenone Hydrochloride, propagermanium, Propanidid, Propantheline Bromide, Proparacaine Hydrochloride, Propatyl Nitrate, propentofylline, Propenzolate Hydrochloride, Propikacin, Propiomazine, Propionic Acid, propionylcarnitine, L-, propiram, propiram+paracetamol, propiverine, Propofol, Propoxycaine Hydrochloride, Propoxyphene Hydrochloride, Propranolol Hydrochloride, Propulsid, propyl bis-acridone, Propylhexedrine, Propyliodone, Propylthiouracil, Proquazone, Prorenoate Potassium, Proroxan Hydrochloride, Proscillaridin, Prostalene, prostratin, Protamine Sulfate, protegrin, Protirelin, protosufloxacin, Protriptyline Hydrochloride, Proxazole, Proxazole Citrate, Proxicromil, Proxorphan Tartrate, prulifloxacin, Pseudoephedrine Hydrochloride, Puromycin, purpurins, Pyrabrom, Pyrantel Pamoate, Pyrazinamide, Pyrazofurin, pyrazoloacridine, Pyridostigmine Bromide, Pyrilamine Maleate, Pyrimethamine, Pyrinoline, Pyrithione Sodium, Pyrithione Zinc, Pyrovalerone Hydrochloride, Pyroxamine Maleate, Pyrrocaine, Pyrroliphene Hydrochloride, PyrroInitrin, Pyrvinium Pamoate, Quadazocine Mesylate, Quazepam, Quazinone, Quazodine, Quazolast, quetiapine, quiflapon, quinagolide, Quinaldine Blue, quinapril, Quinaprilat, Quinazosin Hydrochloride, Quinbolone, Quinctolate, Quindecamine Acetate, Quindonium Bromide, Quinelorane Hydrochloride, Quinestrol, Quinfamide, Quingestanol Acetate, Quingestrone, Quinidine Gluconate, Quinielorane Hydrochloride, Quinine Sulfate, Quinpirole Hydrochloride, Quinterenol Sulfate, Quinuclium Bromide, Quinupristin, Quipazine Maleate, Rabeprazole Sodium, Racephenicol, Racepinephrine, raf antagonists, Rafoxanide, Ralitoline, raloxifene, raltitrexed, ramatroban, Ramipril, Ramoplanin, ramosetron, ranelic acid, Ranimycin, Ranitidine, ranolazine, Rauwolfia Serpentina, recainam, Recainam Hydrochloride, Reclazepam, regavirumab, Regramostim, Relaxin, Relomycin, Remacemide Hydrochloride, Remifentanil Hydrochloride, Remiprostol, Remoxipride, Repirinast, Repromicin, Reproterol Hydrochloride, Reserpine, resinferatoxin, Resorcinol, retelliptine demethylated, reticulon, reviparin sodium, revizinone, rhenium Re 186 etidronate, rhizoxin, Ribaminol,

Ribavirin, Riboprine, ribozymes, ricasetron, Ridogrel, Rifabutin, Rifametane, Rifamexil, Rifamide, Rifampin, Rifapentine, Rifaximin, RII retinamide, rilopirox, Riluzole, rimantadine, Rimcazole Hydrochloride, Rimexolone, Rimiterol Hydrobromide, rimoprogin, riodipine, Rioprostil, Ripazepam, ripisartan, Risedronate Sodium, risedronic acid, Risocaine, Risotilide Hydrochloride, rispenzepine, Risperdal, Risperidone, Ritanserin, ritipenem, Ritodrine, Ritolukast, ritonavir, rizatriptan benzoate, Rocastine Hydrochloride, Rocuronium Bromide, Rodocaine, Roflurane, Rogletimide, rohitukine, rokitamycin, Roletamicide, Rolgamidine, Rolicyprine, Rolipram, Rolitetracycline, Rolodine, Romazarit, romurtide, Ronidazole, ropinirole, Ropitoin Hydrochloride, ropivacaine, Ropizine, roquinimex, Rosaramicin, Rosoxacin, Rotoxamine, roxaitidine, Roxarsone, roxindole, roxithromycin, rubiginone B1, ruboxyl, rufloxacin, rupatidine, Rutamycin, ruzadolane, Sabeluzole, safingol, safironil, saintopin, salbutamol, R-, Salcolex, Salethamide Maleate, Salicyl Alcohol, Salicylamide, Salicylate Meglumine, Salicylic Acid, Salmeterol, Salnacediin, Salsalate, sameridine, sampatrilat, Sancycline, sanfetrinem, Sanguinarium Chloride, Saperconazole, saprisartan, sapropterin, saquinavir, Sarafloxacin Hydrochloride, Saralasin Acetate, SarCNU, sarcophytol A, sargramostim, Sarmoxicillin, Sarpicillin, sarpogrelate, saruplase, saterinone, satigrel, satumomab pendetide, Schick Test Control, Scopafungin, Scopolamine Hydrobromide, Scrazaipine Hydrochloride, Sdi 1 mimetics, Secalciferol, Secobarbital, Seelzone, Seglitide Acetate, selegiline, Selegiline Hydrochloride, Selenium Sulfide, Selenomethionine Se 75, Selfotel, sematilide, semduramicin, semotiadil, semustine, sense oligonucleotides, Sepazonium Chloride, Seperidol Hydrochloride, Seprilose, Seproxetine Hydrochloride, Seractide Acetate, Sergolexole Maleate, Serine, Sermetacin, Sermorelin Acetate, sertaconazole, sertindole, sertraline, setiptiline, Setoperone, sevirumab, sevoflurane, sezolamide, Sibopirdine, Sibutramine Hydrochloride, signal transduction inhibitors, Silandrone, silipide, silteplase, Silver Nitrate, simendan, Simtrazene, Simvastatin, Sincalide, Sinefungin, sinitrodil, sinnabidol, sipatrigine, sirolimus, Sisomicin, Sitogluside, sizofiran, sobuzoxane, Sodium Amylosulfate, Sodium Iodide I 123, Sodium Nitroprusside, Sodium Oxybate, sodium phenylacetate, Sodium Salicylate, solverol, Solypertine Tartrate, Somalapor, Somantadine Hydrochloride, somatomedin B, somatomedin C, somatrem, somatropin, Somenopor, Somidobove, sonermin, Sorbinil, Sorivudine, sotalol, Soterenol Hydrochloride, Sparfloxacin, Sparfosate Sodium, sparfosic acid, Sparsomycin, Sparteine Sulfate,

Spectinomycin Hydrochloride, spicamycin D, Spiperone, Spiradoline Mesylate, Spiramycin, Spirapril Hydrochloride, Spiraprilat, Spirogermanium Hydrochloride, Spiromustine, Spironolactone, Spiroplatin, Spiroxasone, splenopentin, spongistatin 1, Sprodiamide, squalamine, Stallimycin Hydrochloride, Stannous Pyrophosphate, Stannous Sulfur Colloid, Stanozolol, Statolon, staurosporine, stavudine, Steffimycin, Stenbolone Acetate, stepronin, Stilbazium Iodide, Stilonium Iodide, stipiamide, Stiripentol, stobadine, Streptomycin Sulfate, Streptonicozid, Streptonigrin, Streptozocin, stromelysin inhibitors, Strontium Chloride Sr 89, succibun, Succimer, Succinylcholine Chloride, Sucralfate, Sucrosofate Potassium, Sudoxicam, Sufentanil, Sufotidine, Sulazepam, Sulbactam Pivoxil, Sulconazole Nitrate, Sulfabenz, Sulfabenzamide, Sulfacetamide, Sulfacytine, Sulfadiazine, Sulfadoxine, Sulfalene, Sulfamerazine, Sulfameter, Sulfamethazine, Sulfamethizole, Sulfamethoxazole, Sulfamonomethoxine, Sulfamoxole, Sulfanilate Zinc, Sulfanitran, sulfasalazine, Sulfasomizole, Sulfazamet, Sulfinalol Hydrochloride, sulfinosine, Sulfinpyrazone, Sulfisoxazole, Sulfomyxin, Sulfonterol Hydrochloride, sulfoxamine, Sulindac, Sulmarin, Sulnidazole, Suloctidil, Sulofenur, sulopenem, Suloxifen Oxalate, Sulpiride, Sulprostone, sultamicillin, Sulthiame, sultopride, sulukast, Sumarotene, sumatriptan, Suncillin Sodium, Suproclone, Suprofen, suradista, suramin, Surfomer, Suricainide Maleate, Suritozole, Suronacrine Maleate, Suxemerid Sulfate, swainsonine, symakalim, Symclosene, Symetine Hydrochloride, synthetic glycosaminoglycans, Taciamine Hydrochloride, Tacrine Hydrochloride, Tacrolimus, Talampicillin Hydrochloride, Taleranol, Talisomycin, tallimustine, Talmetacin, Talniflumate, Talopram Hydrochloride, Talosalate, Tametraline Hydrochloride, Tamoxifen, Tampramine Fumarate, Tamsulosin Hydrochloride, Tandamine Hydrochloride, tandospirone, tapgen, taprostene, Tasosartan, tauromustine, Taxane, Taxoid, Tazadolene Succinate, tazanolast, tazarotene, Tazifylline Hydrochloride, Tazobactam, Tazofelone, Tazolol Hydrochloride, Tebufelone, Tebuquine, Technetium Tc 99 m Bicisate, Teclozan, Tecogalan Sodium, Teecleukin, Teflurane, Tegafur, Tegretol, Teicoplanin, telenzepine, tellurapyrylium, telmesteine, telmisartan, telomerase inhibitors, Teloxantrone Hydrochloride, Teludipine Hydrochloride, Temafloxacin Hydrochloride, Tematropium Methyl sulfate, Temazepam, Temelastine, temocapril, Temocillin, temoporfin, temozolomide, Tenidap, Teniposide, tenosal, tenoxicam, tepirindole, Tepoxalin, Teprotide, terazosin, Terbinafine, Terbutaline Sulfate, Terconazole, terfenadine, terflavoxate, terguride, Teriparatide Acetate, terlakiren, terlipressin,

terodiline, Teroxalene Hydrochloride, Teroxirone, tertatolol, Tesicam, Tesimide, Testolactone, Testosterone, Tetracaine, tetrachlorodecaoxide, Tetracycline, Tetrahydrozoline Hydrochloride, Tetramisole Hydrochloride, Tetrazolast Meglumine, tetrazomine, Tetrofosmin, Tetroquinone, Tetroxoprim, Tetrydamine, thaliblastine, Thalidomide, Theofibrate, Theophylline, Thiabendazole, Thiamiprine, Thiamphenicol, Thiamylal, Thiazesim Hydrochloride, Thiazinamium Chloride, Thiethylperazine, Thimerfonate Sodium, Thimerosal, thiocoraline, thiofedrine, Thioguanine, thiomarinol, Thiopental Sodium, thioperamide, Thioridazine, Thiotepa, Thiothixene, Thiphenamil Hydrochloride, Thiphencillin Potassium, Thiram, Thozalinone, Threonine, Thrombin, thrombopoietin, thrombopoietin mimetic, thymalfasin, thymopoietin receptor agonist, thymotrinan, Thyromedan Hydrochloride, Thyroxine I 125, Thyroxine I 131, Tiacrilast, Tiacrilast Sodium, tiagabine, Tiamenidine, tianeptine, tiapafant, Tiapamil Hydrochloride, Tiaramide Hydrochloride, Tiazofurin, Tibenelast Sodium, Tibolone, Tibric Acid, Ticabesone Propionate, Ticarbodine, Ticarcillin Cresyl Sodium, Ticlatone, ticlopidine, Ticrynafen, tienoxolol, Tifurac Sodium, Tigemonam Dicholine, Tigestol, Tiletamine Hydrochloride, Tilidine Hydrochloride, tilisolol, tilnoprofen arbamel, Tilorone Hydrochloride, Tiludronate Disodium, tiludronic acid, Timefurone, Timobesone Acetate, Timolol, tin ethyl etiopurpurin, Tinabinol, Tinidazole, Tinzaparin Sodium, Tioconazole, Tiodazosin, Tiodonium Chloride, Tioperidone Hydrochloride, Tiopinac, Tiospirone Hydrochloride, Tiotidine, tiotropium bromide, Tioxidazole, Tipentosin Hydrochloride, Tipredane, Tiprenolol Hydrochloride, Tiprinast Meglumine, Tipropidil Hydrochloride, Tiqueside, Tiquinamide Hydrochloride, tirandalydigin, Tirapazamine, tirilazad, tirofiban, tiropramide, titanocene dichloride, Tixanox, Tixocortol Pivalate, Tizanidine Hydrochloride, Tobramycin, Tocainide, Tocamphyl, Tofenacin Hydrochloride, Tolamolol, Tolazamide, Tolazoline Hydrochloride, Tolbutamide, Tolcapone, Tolciclate, Tolfamide, Tolgabide, lamotrigine, Tolimidone, Tolindate, Tolmetin, Tolnaftate, Tolpovidone I 131, Tolpyrramide, Tolrestat, Tomelukast, Tomoxetine Hydrochloride, Tonazocine Mesylate, Topiramate, topotecan, Topotecan Hydrochloride, topsentin, Topterone, Toquizine, torasemide, toremifene, Torsemide, Tosifen, Tosufloxacin, totipotent stem cell factor, Tracazolate, trafermin, Tralonide, Tramadol Hydrochloride, Tramazoline Hydrochloride, trandolapril, Tranexamic Acid, Tranilast, Transcainide, translation inhibitors, traxanox, Trazodone Hydrochloride, Trazodone-HCL, Trebenzomine Hydrochloride, Trefentanil

Hydrochloride, Treloxinate, Trepipam Maleate, Trestolone Acetate, tretinoin, Triacetin, triacetyluridine, Triafungin, Triamcinolone, Triampyzine Sulfate, Triamterene, Triazolam, Tribenoside, tricaprilin, Tricetamide, Trichlormethiazide, trichohyalin, triciribine, Tricitrates, Triclofenol piperazine, Triclofos Sodium, Triclonide, trientine, Trifenagrel, triflavin, Triflocin, Triflubazam, Triflumidate, Trifluoperazine Hydrochloride, Trifluperidol, Triflupromazine, Triflupromazine Hydrochloride, Trifluridine, Trihexyphenidyl Hydrochloride, Trilostane, Trimazosin Hydrochloride, trimegestone, Trimeprazine Tartrate, Trimethadione, Trimethaphan Camsylate, Trimethobenzamide Hydrochloride, Trimethoprim, Trimetozine, Trimetrexate, Trimipramine, Trimoprostil, Trimoxamine Hydrochloride, Triolein I 125, Triolein I 131, Trioxifene Mesylate, Tripamide, Tripelennamine Hydrochloride, Triprolidine Hydrochloride, Triptorelin, Trisulfapyrimidines, Troclosene Potassium, troglitazone, Trolamine, Troleandomycin, trombodipine, trometamol, Tropanserin Hydrochloride, Tropicamide, tropine ester, tropisetron, trospectomycin, trovafloxacin, trovirdine, Tryptophan, Tuberculin, Tubocurarine Chloride, Tubulozole Hydrochloride, tucarcsol, tulobuterol, turosteride, Tybamate, tylogenin, Tyropanoate Sodium, Tyrosine, Tyrothricin, tyrphostins, ubenimex, Uldazepam, Undecylenic Acid, Uracil Mustard, urapidil, Urea, Uredepa, uridine triphosphate, Urofollitropin, Urokinase, Ursodiol, valaciclovir, Valine, Valnoctamide, Valproate Sodium, Valproic Acid, valsartan, vamicamide, vanadeine, Vancomycin, vaninolol, Vapiprost Hydrochloride, Vapreotide, variolin B, Vasopressin, Vecuronium Bromide, velaresol, Velnacrine Maleate, venlafaxine, Veradoline Hydrochloride, veramine, Verapamil Hydrochloride, verdins, Verilopam Hydrochloride, Verlukast, Verofylline, veroxan, verteporfin, Vesnarinone, vexibinol, Vidarabine, vigabatrin, Viloxazine Hydrochloride, Vinblastine Sulfate, vinburnine citrate, Vincofos, vinconate, Vincristine Sulfate, Vindesine, Vindesine Sulfate, Vinepidine Sulfate, Vinglycinate Sulfate, Vinleurosine Sulfate, vinorelbine, vinpocetine, vintoperol, vinxaltine, Vinzolidine Sulfate, Viprostol, Virginiamycin, Viridofulvin, Viroxime, vitaxin, Volazocine, voriconazole, vorozole, voxergolide, Warfarin Sodium, Xamoterol, Xanomeline, Xanoxate Sodium, Xanthinol Niacinate, xemilofiban, Xenalipin, Xenbucin, Xilobam, ximoprofen, Xipamide, Xorphanol Mesylate, Xylamidine Tosylate, Xylazine Hydrochloride, Xylometazoline Hydrochloride, Xylose, yangambin, zabicipril, zacopride, zafirlukast, Zalcitabine, zaleplon, zalospirone, Zaltidine Hydrochloride, zaltoprofen, zanamivir, zankiren, zanoterone, Zantac, Zarirlukast,

zatebradine, zatosetron, Zatosetron Maleate, zenarestat, Zenazocine Mesylate, Zeniplatin, Zeranol, Zidometacin, Zidovudine, zifrosilone, Zilantel, zilascorb, zileuton, Zimeldine Hydrochloride, Zinc Undecylenate, Zindotrine, Zinoconazole Hydrochloride, Zinostatin, Zinterol Hydrochloride, Zinviroxime, ziprasidone, Zobolt, Zofenopril Calcium, Zofenoprilat, Zolamine Hydrochloride, Zolazepam Hydrochloride, zoledronie acid, Zolertine Hydrochloride, zolmitriptan, zolpidem, Zomepirac Sodium, Zometapine, Zoniclezole Hydrochloride, Zonisamide, zopiclone, Zopolrestat, Zorbamyciin, Zorubicin Hydrochloride, zotepine, Zucapsaicin or its pharmaceutically acceptable salts thereof.

As indicated the pharmaceutical formulations as disclosed herein may comprise auxiliary excipients such as for example diluents, binders, lubricants, surfactants, disintegrants, plasticisers, anti-tack agents, opacifying agents, pigments, and such like. As will be appreciated by those skilled in the art, the exact choice of excipient and their relative amounts will depend to some extent on the final oral dosage form.

Pharmaceutical Compositions

According to certain embodiments described herein, pharmaceutical composition or transdermal formulation of contains active agents such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds. More preferably transdermal formulation may include active agents such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds.

One embodiment of the present disclosure can be a transdermal drug delivery system which may include without any limitation to transdermal formulation, transdermal patches, topical formulation, microneedles, iontophoresis, metered dose transdermal spray, film forming formulation, transdermal aerosols.

Transdermal formulation which includes liquids for example without any limitation like solutions, suspensions, dispersions, emulsion. Transdermal formulation includes semisolids for example without any limitations like gels, ointments, emulsions, creams, suspension, paste, lotion, balm. Liquid formulation and/or gel formulation incorporated in transdermal patch is preferred. Transdermal matrix formulations which includes matrix patches without any

limitations like adhesive matrix patch, non-adhesive matrix patch, A transdermal matrix formulation as drug-in-adhesive matrix patch is preferred.

Without any limitation, transdermal patch may include all transdermal drug delivery systems stated in art preferably but not limited to reservoir patch, matrix patch, bilayer matrix patch, multilayer matrix patch, microreservoir patch, adhesive systems, transdermally applicable tape and other.

In certain embodiments of the present disclosure, a transdermal patch comprises transdermal formulation containing active agents such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds contained in a reservoir or a matrix, and an adhesive which allows the transdermal patch to adhere to the skin, allowing the passage of the active agents such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds from the transdermal patch through the skin of the patient. The transdermal delivery system can be occlusive, semi-occlusive or non-occlusive, and can be adhesive or non-adhesive.

The transdermal formulation comprising active agents such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds can be incorporated within the patch and patch can be applied topically to the skin surface. The patch can be left on the subject for any suitable period of time.

In some embodiments, the transdermal patches provide for a constant rate of delivery of the active components of the transdermal patch over a predetermined time period. In some embodiments, the predetermined time period is 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

In yet further embodiments, the transdermal patches described herein provide a steady absorption rate of the active components of the transdermal patches by the patient over a predetermined time. In some embodiments, the predetermined time period is 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

In yet further embodiments, the transdermal patches described herein provide a constant blood serum level of the active components of the transdermal patches in a patient over a predetermined time. In some embodiments, the predetermined time period is 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

In yet further embodiments, the transdermal patches described herein provide a plasma concentration of the active components of the transdermal patches in a therapeutic range in a patient over a predetermined time. In some embodiments, the predetermined time period is 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

In yet further embodiments, the transdermal patches described herein allow for reduced variability in dosage of active components in a patient over a predetermined time. In some embodiments, the predetermined time period is 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

In yet further embodiments, the transdermal patches described herein provide a plasma concentration of the active components of the transdermal patches in a therapeutic range in a patient over a predetermined time. In exemplary embodiments as disclosed herein, the transdermal patch provides a blood serum level of active agent of, for example, about 0.01 ng/mL, about 0.02 ng/mL, about 0.05 ng/mL, about 0.1 ng/mL, about 0.2 ng/mL, about 0.5 ng/mL, about 1 ng/mL, about 2 ng/mL, about 5 ng/mL, about 10 ng/mL, about 20 ng/mL, about 50 ng/mL, about 100 ng/mL, about 200 ng/mL, about 500 ng/mL, about 1 μg/mL, about 2 μg/mL, about 5 μg/mL, about 10 μg/mL, about 20 μg/mL, about 50 μg/mL, , and ranges thereof.

The topical formulation stated in the art which include, for example without any limitation, semisolids such as ointment, cream, emulsion, micro emulsion, nano emulsion, paste, balms, gels, lotions, mousses. Liquids such as solutions, suspensions, micro suspension, nano suspension, dispersions, nano dispersion etc. Sprays, aerosols, magma, etc. The topical formulation comprising such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds can be topically applied to the skin surface for

transdermal delivery of such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds.

The transdermal formulation and/or topical formulation of some embodiments of the present disclosure may include carriers or ingredients in effective amount either alone or in combinations thereof without any limitation to the following carriers or ingredients such as solvents, gelling agents, polymers, biodegradable polymers, adhesive polymers, pressure sensitive adhesive polymers, penetration enhancers, emollients, skin irritation reducing agents, buffering agents, pH stabilizers, solubilizers, suspending agents, dispersing agents, stabilizers, plasticizers, tackifiers, surfactants, volatile chemicals, antioxidants, oxidants, chelating agents, complexing agents, diluents, excipients, material to prepare patch, material to prepare matrix patch, material to prepare reservoir patch etc.

Active agents may be dissolved, suspended, dispersed or uniformly mixed in the above stated single carrier, mixture of carriers and combinations of carrier. Any combination of two or more drugs such as such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds may be dissolved, suspended, dispersed or uniformly mixed in the above stated single carrier, mixture of carriers and combinations of carrier.

The desired optimum transdermal and/or topical formulation of such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds alone or in combinations thereof may comprise without any limitation to following carriers as stated from example 1 to example 11 either alone or in combinations thereof.

According to certain embodiments, transdermal compositions described herein are for the treatment and/or prevention and/or control of severe depression (treatment resistant), major depressive disorder, obsessive-compulsive disorder, quitting smoking, alcohol addiction, cocaine addiction, opioid addiction, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress.

Further indications are cognitive disorders. The term "cognitive disorder" shall refer to anxiety disorders, delirium, dementia, amnestic disorders, dissociative disorders, eating disorders, mood disorders, schizophrenia, psychotic disorders, sexual and gender identity disorders, sleep

disorders, somatoform disorders, acute stress disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, specific phobia, social phobia, substance withdrawal delirium, Alzheimer's disease, Creutzfeldt-Jakob disease, head trauma, Huntington's disease, HIV disease, Parkinson's disease, Pick's disease, learning disorders, motor skills disorders, developmental coordination disorder, communication disorders, phonological disorder, pervasive developmental disorders, Asperger's disorder, autistic disorder, childhood disintegrative disorder, Rett's disorder, pervasive developmental disorder, attention-deficit/hyperactivity disorder (ADHD), conduct disorder, oppositional defiant disorder, pica, rumination disorder, tic disorders, chronic motor or vocal tic disorder, Tourette's disorder, elimination disorders, encopresis, enuresis, selective mutism, separation anxiety disorder, dissociative amnesia, depersonalization disorder, dissociative fugue, dissociative identity disorder, anorexia nervosa, bulimia nervosa, bipolar disorders, schizophreniform disorder, schizoaffective disorder, delusional disorder, psychotic disorder, shared psychotic disorder, delusions, hallucinations, substance-induced psychotic disorder, orgasmic disorders, sexual pain disorders, dyspareunia, vaginismus, sexual dysfunction, paraphilias, dyssomnias, breathing-related sleep disorder, circadian rhythm sleep disorder, hypersomnia, insomnia, narcolepsy, dyssomnia, parasomnias, nightmare disorder, sleep terror disorder, sleepwalking disorder, parasomnia, body dysmorphic disorder, conversion disorder, hypochondriasis, pain disorder, somatization disorder, alcohol related disorders, amphetamine related disorders, caffeine related disorders, cannabis related disorders, cocaine related disorders, hallucinogen related disorders, inhalant related disorders, nicotine related disorders, opioid related disorders, phencyclidine-related disorder, abuse, persisting amnestic disorder, intoxication, withdrawal.

The term "bipolar and clinical disorders" shall refer to adjustment disorders, anxiety disorders, delirium, dementia, amnestic and other cognitive disorders, disorders usually first diagnosed in infancy (e.g.), childhood, or adolescence, dissociative disorders (e.g. dissociative amnesia, depersonalization disorder, dissociative fugue and dissociative identity disorder), eating disorders, factitious disorders, impulse-control disorders, mental disorders due to a general medical condition, mood disorders, other conditions that may be a focus of clinical attention, personality disorders, schizophrenia and other psychotic disorders, sexual and gender identity disorders, sleep disorders, somatoform disorders, substance-related disorders, generalized anxiety

disorder (e.g. acute stress disorder, posttraumatic stress disorder), panic disorder, phobia, agoraphobia, obsessive-compulsive disorder, stress, acute stress disorder, anxiety neurosis, nervousness, phobia, posttraumatic stress disorder, posttraumatic stress disorder (PTSD), abuse, obsessive-compulsive disorder (OCD), manic depressive psychosis, specific phobias, social phobia, adjustment disorder with anxious features.

The invention will be illustrated in more detail with reference to the following Examples, but it should be understood that the present invention is not deemed to be limited thereto.

EXAMPLES

Example 1

This Example describes the preparation of a patch or semisolid formulation, which must give a blood level (±20%) bioequivalent to 10 mg oral psilocybin. Initially, a transdermal formulation will be prepared containing a dose of 20 mg psilocybin and/or 10 mg psilocin and based on the in-vitro permeability flux profile obtained from Franz-diffusion cells, the dose will be adjusted to obtain desired blood level (±20%) bioequivalent to oral 10 mg/day psilocybin. Different approaches will be implemented (e.g. change in drug loading dose, combination of solvents/enhancers etc.) to prepare a transdermal formulation which can deliver target therapeutic blood level from day 1 to day 5 or day 7.

Example 2

Below is a description of the experimental procedure, utilized for development and optimization of transdermal matrix patch or transdermal semisolid formulation containing psilocybin lone or psiloccin alone, or a combination of psilocybn and psilocin. Exemplary formualtions are set forth in Table 1:

Table 1

Excipients	PSI 1 (%w/w)	PSI 2 (%w/w)	PSI 3 (%w/w)	PSI 4 (%w/w)

Psilocybin/psilocin	0.1 – 20%	0.1 – 20%	0.1 – 20%	0.1 – 20%
Enhancers		0.1 – 20%		0.1 – 20%
Solvents			0.1 – 20%	0.1 – 20%
Adhesive/Polymers	80 – 99.9%	50 – 99.8%	50 – 99.8%	30 – 99.7%

The transdermal formulation and/or topical formulation of the disclosure may comprise **solvents** known to those skilled in the art either alone or in combinations thereof without any limitation to following like alcohol C_1-C_{20} such as but not limited to (methanol, ethanol, isopropyl alcohol, butanol, propanol etc.), polyhydric alcohols, glycols such as but not limited to (propylene glycol, polyethylene glycol, dipropylene glycol, hexylene glycol, butyene glycol, glycerine etc.), derivative of glycols, pyrrolidone such as but not limited to (N methyl 2- pyrrolidone, 2-pyrrolidone etc.), sulfoxides such as but not limited to (dimethyl sulfoxide, decymethylsulfoxide etc), dimethylisosorbide, mineral oils, vegetable oils, sesame oil water, polar solvents, semi polar solvents, non polar solvents, volatile chemicals which can be used to make matrix patch such as but not limited to (ethanol, propanol, ethyl acetate, acetone, methanol, dichloromethane, chloroform, toluene, IPA, hexane), acids such as but not limited to acetic acid, lactic acid, levulinic acid, bases and others, pentane, dimethylformamide, butane, lipids. More preferably in the range of 0.01% - 95% w/w or w/v. In exemplary embodiments, formulations of the disclosure may comprise **solvents** at a concentration of about 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80%, and about 95% of the formulation. In exemplary embodiments,

formulations of the disclosure may comprise **solvents** at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, about 63.13%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the solvents will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation.

The transdermal formulation and/or topical formulation of the disclosure may comprise **gelling agents and/or thickening and/or suspending agents and/or polymers and/or adhesive polymers and/or pressure sensitive adhesive polymers** known to those skilled in the art either alone or in combinations thereof without any limitation to following like natural polymers, polysaccharides and its derivatives such as but not limited to (agar, alginic acid and derivatives, cassia tora, collagen, gelatin, gellum gum, guar gum, pectin, potassium, or sodium carageenan, tragacanth, xantham, gum copal, chitosan, resin etc.), semisynthetic polymers and its derivatives such as without any limitation to cellulose and its derivatives (methylcellulose, ethyl cellulose, carboxymethyl cellulose, hydroxylpropyl cellulose, hydroxylpropylmethyl cellulose etc.), synthetic polymers and its derivatives such as without any limitation to carboxyvinyl polymers or carbomers (carbopol 940, carbopol 934, carbopol 971p NF), polyethylene, and its copolymers etc, clays such as but not limited to (silicates, bentonite), silicon dioxide, polyvinyl alcohol, acrylic polymers (eudragit), acrylic acid esters, polyacrylate copolymers, polyacrylamide, polyvinyl pyrrolidone homopolymer and polyvinyl pyrrolidone copolymers such as but not limited to (PVP, Kollidon 30, poloxamer), isobutylene, ethyl vinyl acetate copolymers, natural rubber, synthetic rubber, pressure sensitive adhesives such as silicone polymers such as but not limited to (bio psa 4302, bio-psa 4202 etc.,), acrylic pressure sensitive adhesives such as but not limited to (duro –tak 87-2156, duro-tak 387-2287, duro-tak 87-9301, duro-tak 387-2051 etc.), polyisobutylene such as but not limited to (polyisobutylene low molecular weight, plyisobutylene medium molecular weight, polyisobutylene 35000 mw, etc), acrylic copolymers, rubber based adhesives, hot melt adhesives, styrene-butadiene copolymers, bentonite, all water and/or organic solvent swellable polymers, etc. In exemplary embodiments, formulations of the disclosure may comprise **gelling agents and/or thickening and/or suspending agents and/or polymers and/or adhesive polymers and/or pressure sensitive adhesive polymers** at a concentration of abount 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%,

about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80%, and about 85%, and about 90% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise **gelling agents and/or thickening and/or suspending agents and/or polymers and/or adhesive polymers and/or pressure sensitive adhesive polymers** at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, about 63.13%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the gelling agents and/or thickening and/or suspending agents and/or polymers and/or adhesive polymer and/or pressure sensitive adhesive polymers will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation, and more preferably in the range of 0.1% 80% w/w or w/v.

The transdermal formulation and/or topical formulation of the disclosure may comprise **permeation enhancers** known to those skilled in the art either alone or in combination thereof without any limitation to the following, such as sulfoxides, and similar chemicals such as but not limited to (dimethylsulfoxide, dimethylacetamide, dimethylformamide, decymethylsulfoxide, dimethylisosorbide etc), azone, pyrrolidones such as but not limited to (N-methyl-2-pyrrolidone, 2-pyrrolidon etc.), esters, fatty acid esters such as but not limited to (propylene glycol monolaurate, butyl ethanoate, ethyl ethanoate, isopropyl myristate, isopropyl palmitate, methyl ethanoate,lauryl lactate, ethyl oleate decyl oleate, glycerol monooleate, glycerol monolaurate, lauryl laurate etc.), fatty acids such as but not limited to (capric acid, caprylic acid, lauric acid, oleic acid, myristic acid, linoleic acid, stearic acid, palmitic acid etc.), alcohols, fatty alcohols and glycols such as but not limited to (oleyl alcohol, nathanol, dodecanol, propylene glycol, glycerol etc.), ethers alcohol such as but not limited to (diethylene glycol monoethyl ether), urea, triglycerides such as but not limited to triacetin, polyoxyethylene fatty alcohol ethers, polyoxyethylene fatty acid esters, esters of fatty alcohols, essential oils, surfactant type enhancers

such as but not limited to (brij, sodium lauryl sulfate, tween, polysorbate), terpene, terpenoids and all penetration or permeation enhancers referred in the book "Percutaneous Penetration Enhancers" *(Eric W. Smith, Howard I. Maibach, 2005. Nov, CRC press).* In exemplary embodiments, formulations of the disclosure may comprise **permeation enhancers** at a concentration of abount 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise **permeation enhancers** at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, about 63.13%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the **permeation enhancers** will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation, and more preferably in the range of 0.01% - 95% w/w or w/v.

All of the components from Table 1, with the exception of the Psilocybin, were mixed together with stirring for 18 hours. Next, the Psilocybin was added into the excipient mixture to prepare the final transdermal formulations.

Example 3

The following steps are provided using composition PSI 1 as an example for preparing a transdermal patch. The above ingredients are blended by stirring for 18 hours and then, using a commercial benchtop spreader, the matrix is evenly spread onto an 8 x 14 inch sheet of release liner (such as 3M 9744) to a thickness of 0.5mm.

The sheet is then placed inan oven at 110°F for one hour to evaporate off the ethyl acetate adhesive solvent. An opaque backing membrane (such as 3M 9730 NR film) with low permeability to oxygen to inhibit photo and oxidative degradation is then carefully applied by hand to avoid formation of bubbles and voids. A circular die (1.5 inches diameter) is used to cut patches (7 sqcm) for subsequent studies. After drying, the drug adhesive matrix has a surface density of 5 – 30 mg/sqcm, containing psilocytbin in 0.1 – 20% w/w.

Example 4

The prepared transdermal formulations were then subjected to a flux measurement test as follows. Human cadaver skin, stored at -80°C, was thawed at room temperature in phosphate buffered saline (PBS), and visually inspected for defects before using in the study. Transdermal flux was then measured using standard Franz diffusion cells comprising a cylindrical donor compart and a separate water jacketed cylindrical receptor compartment with the volume of 13 mL. The cadaver skin was clamped between the two compartments with the dermis side facing toward the receptor compartment. The donor compartment was filled with the transdermal Psilocybin/Psilocin formulations prepared as described above. The receptor compartment was filled with receptor medium, held at constant temperature, and constantly stirred to collect the Psilocybin as it diffuses through the skin and into receptor compartment. It is important to confirm that the receptor fluid is always in contact with the skin. The receptor compartment was emptied at 24 hr intervals for assay of Psilocybin and replaced with fresh receptor solution. In order to maintain the sink condition in the receptor compartment, it is important to keep the Psilocybin concentration in the receptor compartment less than 10% of its solubility.

The transdermal formulation and/or topical formulation of the disclosure may comprise **plasticizers** known to those skilled in the art either alone or in combination thereof without any limitation to following like glycerol and its esters, phosphate esters, glycol derivatives, sugar alcohols, sebacic acid esters, citric acid esters, tartaric acid esters, adipate, phthalic acid esters, triacetin, oleic acid esters and all the plasticizers which can be used in transdermal drug delivery system referred in the book "Handbook of Plasticizers" *(George Wypych, 2004, Chem Tec Publishing).* In exemplary embodiments, formulations of the disclosure may comprise **plasticizers** at a concentration of abount 0.01%, about 0.02%, about 0.05%, about 0.1%, about

0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise **plasticizers** at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, about 63.13%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the **plasticizers** will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation. More preferably in the range of 0.01% - 95% w/w or w/v.

Example 5

The transdermal formulation and/or topical formulation of the disclosure may comprise **emollients, humectants, skin irritation reducing agents** and similar compounds or chemicals known to those skilled in the art either alone or in combinations thereof without any limitation to following like petrolatum, lanolin, mineral oil, dimethicone, zinc oxide, glycerin, propylene glycol and others. More preferably in the range of 0.01% - 95% w/w or w/v. In exemplary embodiments, formulations of the disclosure may comprise **emollients, humectants, skin irritation reducing agents** and similar compounds at a concentration of abount 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments,

formulations of the disclosure may comprise **emollients, humectants, skin irritation reducing agents** and similar compounds at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, about 63.13%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the emollients, humectants, skin irritation reducing agents and similar compounds will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation, and more preferably in the range of 0.01% - 95% w/w or w/v.

Example 6

The transdermal formulation and/or topical formulation of the disclosure may comprise **solubilizers, surfactants, emulsifying agents, dispersing agents** and similar compounds or chemicals known to those skilled in the art either alone or in combination thereof without any limitation to following like polysorbate such as but not limited to (polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80 etc.), span such as but not limited to (span 80, span 20 etc.), surfactants such as (anionic, cationic, nonionic and amphoteric), propylene glycol monocaprylate type I, propylene glycol monocaprylate type II, propylene glycol dicaprylate, medium chain triglycerides, propylene glycol monolaurate type II, linoleoyl polyoxyl-6 glycerides, oleoyl-polyoxy1-6-glycerides, lauroyl polyoxyl-6-gylcerides, polyglyceryl-3- dioleate, diethylene glycol monoethyl ether, propylene glycol monolaurate type I, polyglyceryl-3-dioleate, caprylocaproyl polyoxyl — 8 glycerides etc, cyclodextrins and others. More preferably in the range of 0.01% 95% w/w or w/v. In exemplary embodiments, formulations of the disclosure may comprise **solubilizers, surfactants, emulsifying agents, dispersing agents and similar compounds** at a concentration of abount 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%,

about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise **solubilizers, surfactants, emulsifying agents, dispersing agents and similar compounds** at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, about 63.13%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the solubilizers, surfactants, emulsifying agents, dispersing agents and similar compounds will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation, and more preferably in the range of 0.01% 95% w/w or w/v.

Example 7

Different techniques and ingredients can be used to increase the stability and/or solubility of the active agents in formulation such as without any limitation to coating, encapsulation, microencapsulation, nanoencapsulation, lyophilization, chelating agents, complexing agents, etc.

Example 8

The transdermal formulation and/or topical formulation of the disclosure may comprise auxiliary **pH buffering agents and pH stabilizers** and similar compounds known to those skilled in the art which helps to maintain the appropriate pH of formulation preferably in the range of 4.0-8.0 either alone or in combination thereof without any limitation to following such as phosphate buffer, acetate buffer, citrate buffer, etc., acids such as but not limited to (carboxylic acids, inorganic acids, sulfonic acids, vinylogous carboxylic acids and others), base such as but not limited to (sodium hydroxide, potassium hydroxide, ammonium hydroxide, triethylamine, sodium carbonate, sodium bicarbonate) etc. More preferably in the range of 0.01% - 30% w/w or w/v. In exemplary embodiments, formulations of the disclosure may comprise **pH buffering agents and pH stabilizers** and similar compounds at a concentration of abount 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%,

about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise **pH buffering agents and pH stabilizers** and similar compounds at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, about 63.13%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the **pH buffering agents and pH stabilizers** and similar compounds will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation, and more preferably in the range of 0.01% - 30% w/w or w/v.

Example 9

The transdermal formulation and/or topical formulation of the disclosure may comprise **antioxidants** such as but not limited to (sodium metabisulfite, citric acid, ascorbic acid, BHA, BHT), oxidizing agents, stabilizers, discoloring agents, preservatives and similar compounds or chemicals known to those skilled in the art which helps to get a stable formulation can be used either alone or in combination thereof without any limitation. More preferably in the range of 0.01% - 50% w/w or w/v. In exemplary embodiments, formulations of the disclosure may comprise **antioxidants** at a concentration of abount 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise **antioxidants** at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%,

about 63.13%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the **antioxidants** will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation, and more preferably in the range of 0.01% - 50% w/w or w/v.

Example 10

The transdermal formulation and/or topical formulation of the disclosure may be formulated in ointment and/or cream base and/or gel and/or film forming formulation and/or transdermal matrix formulaitn and/or drugn-in-adhesive matrix patch and/or matrix patch known to those skilled in the art.

Example 11

Materials to make the transdermal delivery system of the disclosure in patch form known to those skilled in the art, for example, such as but not limited to reservoir patch, matrix patch, drug in adhesives, film forming formulation, micro-dosing transdermal patch, transdermal films and may include, such as but are not limited to polymers, copolymers, derivatives, backing film, release membranes, release liners, etc. either alone or in combinations thereof. Pressure sensitive adhesives (such as but not limited to silicone polymers, rubber based adhesives, acrylic polymers, acrylic copolymers, polyisobutylene, acrylic acid – isooctyl acrylate copolymer, hot melt adhesives, polybutylene etc.), backing film (such as but not limited to ethylene vinyl acetate copolymers, vinyl acetate resins, polyurethane, polyvinyl chloride, metal foils, polyester, aluminized films, polyethylene, etc.), release membrane (such as but not limited to microporous polyethylene membrane, microporous polypropylene membrane, rate controlling ethylene vinyl acetate copolymer membrane etc.), release liners (such as but not limited to siliconized polyester films, fluoropolymer coated polyester film, polyester film, siliconized polyethylene terephthalate film, etc.), tapes, etc.

The transdermal formulation and/or topical formulation and/or transdermal delivery system of the disclosure may deliver at least therapeutic effective dose of active agent, such as for example, psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds, alone or in combinations thereof in human plasma required for

treating and/or preventing pain and/or inflammation. Therapeutically effective active agent such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds dosages refers to the therapeutic concentration of in human plasma required for treating and/or preventing pain and/or inflammation. Furthermore, the precise therapeutic effective dose of such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds in the transdermal formulation or topical formulation or transdermal delivery system can be determined by those skilled in the art based on factors such as but not limited to the patient's condition etc. The transdermal formulation or topical formulation or transdermal delivery system will be available in different dosage strengths and patch sizes in order to achieve optimum therapeutic outcome based on patient's requirement.

In yet another embodiment, the transdermal formulation and/or topical formulation and/or transdermal delivery system of the disclosure may deliver at least therapeutic effective dose of such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds. Therapeutically effective doses of active agents such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds refers to the therapeutic concentration of active agent in human plasma required for the treatment and/or prevention and/or control of severe depression (treatment resistant), major depressive disorder, obsessive-compulsive disorder, quitting smoking, alcohol addiction, cocaine addiction, opioid addiction, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress in a patient.

The transdermal formulation or transdermal patch of active agents such as psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, and derivatives of these compounds can be applied to the skin surface in any of the following dosage regimens such as once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in a range of from about 8 to about 13 days, once in two weeks, or once in 15 days.

Example 12

Pressure sensitive adhesive Formulaiton:

Ingredients	%W/W
Active component	0.1% - 30%
Solvent	1%-40%
Permeation Enhancers	1%-40%
Pressure sensitive adhesive	20%-90%
Polymers	2%-50%

The present formulation is not deemed to be limited thereto

While the disclosure has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

CLAIMS

WHAT IS CLAIMED IS:

1. A transdermal and/or topical pharmaceutical composition comprising:

- about 0.1 % to about 20 % of an active agent selected from the group consisting of psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, derivatives of these compounds, and combinations thereof;

- about 80% to about 99.9% of an adhesive and/or polymer;

- optionally, about 0.1 % to about 20% of a permeation enhancer;

- optionally, about 0.1% to about 20% of a solvent,

wherein said pharmaceutical composition will have no or minimal hallucinogenic effect in a patient to whom the pharmaceutical composition is applied.

2. The pharmaceutical composition of claim 1 wherein the adhesive is selected from the group consisting of pressure sensitive adhesives, silicone polymers, bio psa 4302, bio-psa 4202, acrylic pressure sensitive adhesives, duro –tak 87-2156, duro-tak 387-2287, duro-tak 87-9301, duro-tak 387-2051, polyisobutylene, polyisobutylene low molecular weight, polyisobutylene medium molecular weight, polyisobutylene 35000 mw, acrylic copolymers, rubber based adhesives, hot melt adhesives, styrene-butadiene copolymers, bentonite, all water and/or organic solvent swellable polymers and combinations thereof.

3. The pharmaceutical composition of any one of claims 1 to 2 wherein said polymer is present and is selected from the group consisting of natural polymers, polysaccharides. agar, alginic acid and derivatives, cassia tora, collagen, gelatin, gellum gum, guar gum, pectin, potassium cargeenan, sodium carageenan, tragacanth, xantham, gum copal, chitosan, resin, semisynthetic polymers, cellulose, methylcellulose, ethyl cellulose, carboxymethyl cellulose, hydroxylpropyl cellulose, hydroxylpropylmethyl cellulose, synthetic polymers, carboxyvinyl polymers, carbomers, carbopol 940, carbopol 934, carbopol 971p NF, polyethylene, clays, silicates, bentonite, silicon dioxide, polyvinyl alcohol, acrylic polymers (eudragit), acrylic

acid esters, polyacrylate copolymers, polyacrylamide, polyvinyl pyrrolidone homopolymer, polyvinyl pyrrolidone copolymers, PVP, Kollidon 30, poloxamer, isobutylene, ethyl vinyl acetate copolymers, natural rubber, synthetic rubber, and combinations thereof.

4. The pharmaceutical composition of any one of claims 1 to 3 wherein said permeation enhancer is present, and is selected from the group consisting of dimethylsulfoxide, dimethylacetamide, dimethylformamide, decymethylsulfoxide, dimethylisosorbide, azone, pyrrolidones, N-methyl-2-pyrrolidone, 2-pyrrolidon, esters, fatty acid esters, propylene glycol monolaurate, butyl ethanoate, ethyl ethanoate, isopropyl myristate, isopropyl palmitate, methyl ethanoate, lauryl lactate, ethyl oleate decyl oleate, glycerol monooleate, glycerol monolaurate, lauryl laurate, fatty acids, capric acid, caprylic acid, lauric acid, oleic acid, myristic acid, linoleic acid, stearic acid, palmitic acid, alcohols, fatty alcohols, glycols, oleyl alcohol, nathanol, dodecanol, propylene glycol, glycerol, ethers, alcohol, diethylene glycol monoethyl ether, urea, triglycerides, triacetin, polyoxyethylene fatty alcohol ethers, polyoxyethylene fatty acid esters, esters of fatty alcohols, essential oils, surfactant type enhancers, brij, sodium lauryl sulfate, tween, polysorbate, terpene, terpenoids, and combinations thereof.

5. The pharmaceutical composition of anyone of claims 1 to 4 wherein said solvent is present, and is selected from the group consisting of methanol, ethanol, isopropyl alcohol, butanol, propanol, polyhydric alcohols, glycols, propylene glycol, polyethylene glycol, dipropylene glycol, hexylene glycol, butyene glycol, glycerine, derivative of glycols, pyrrolidone, N methyl 2- pyrrolidone, 2 pyrrolidone, sulfoxides, dimethyl sulfoxide, decymethylsulfoxide, dimethylisosorbide, mineral oils, vegetable oils, sesame oil water, polar solvents, semi polar solvents, non polar solvents, volatile chemicals, ethanol, propanol, ethyl acetate, acetone, methanol, dichloromethane, chloroform, toluene, IPA, hexane, acids, acetic acid, lactic acid, levulinic acid, bases, pentane, dimethylformamide, butane, lipids, and combinations thereof.

6. The pharmaceutical composition of any one of claims 1 to 5 formulated as a liquid formulation, transdermal semisolid formulation, or transdermal polymer matrix formulation, transdermal adhesive matrix formulation, film forming gel formulation, film forming spray formulation.

7. The pharmaceutical composition of any one of claims 1 to 6 which is formulated as a transdermal patch.

8. The pharmaceutical composition of any one of claims 1 to 7 formulated as a transdermal patch, wherein the transdermal patch is selected from the group such as to reservoir patch, a microreservoir patch, a matrix patch, a pressure sensitive adhesive patch, extended release transdermal film a liquid reservoir system, a microreservoir patch, a matrix patch, a pressure sensitive adhesive patch, a film forming gel, a film forming spray, a micro-dosing patch, a mucoadhesive patch, and combinations thereof.

9. The pharmaceutical composition of any one of claims 1 to 8 further comprising carriers or ingredients in effective amount selected from the group consisting of solvents, gelling agents, polymers, pressure sensitive adhesive, penetration enhancers, emollients, skin irritation reducing agents, buffering agents, pH stabilizers, solubilizers, suspending agents, dispersing agents, stabilizers, plasticizers, tackifier, diluetns, surfactants, antioxidants, oxidants, and combinations thereof.

10. The pharmaceutical composition of any one of claims 1 to 9 indicated for the treatment and/or prevention and/or control of severe depression (treatment resistant), major depressive disorder, obsessive-compulsive disorder, post-traumatic stress disorder, quitting smoking, alcohol addiction, cocaine addiction, opioid addiction, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress in a patient.

11. The pharmaceutical composition of any one of claims 1 to 10 which is formulated as the transdermal formulation which can be administered in a dosage regimen selected from the group consisting of once daily, twice daily, three times a day, once in 1-8 hrs, once in 1-24 hrs, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in a 8 to about 13 days, once in two weeks, once in 15 days to about 30 days.

12. The pharmaceutical composition of any one of claims 1 to 11 which may be formulated as microneedles.

13. The pharmaceutical composition of any one of claims 1 to 12, wherein said psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, derivatives of these compounds, and combinations thereof is produced by a natural route or a synthetic route.

14. The pharmaceutical composition of any one of claims 1 to 13, co-administered with at least one additional active agent.

15. A method for the treatment and/or prevention and/or control of severe depression (treatment resistant), major depressive disorder, obsessive-compulsive disorder, post-traumatic stress disorder, quitting smoking, alcohol addiction, cocaine addiction, opioid addiction, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress in a patient comprising:

- selecting a patient in need of treatment and/or prevention and/or control of severe depression (treatment resistant), major depressive disorder, obsessive-compulsive disorder, quitting smoking, alcohol addiction, cocaine addiction, opioid addiction, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress;

- topically applying the transdermal pharmaceutical composition of any one of claims 1 – 14,

wherein said patent experiences no or minimal hallucinogenic effects from said transdermal pharmaceutical composition.

16. The method of claim 15 wherein the topical application of a transdermal pharmaceutical composition for the treatment and/or prevention and/or control of severe depression (treatment resistant), major depressive disorder, obsessive-compulsive disorder, post-traumatic stress disorder, quitting smoking, alcohol addiction, cocaine addiction, opioid addiction, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress in a patient, wherein the transdermal patch is applied at a time period selected from the group consisting of once in a day, once in two days, once in three

days, once in four days, once in five days, once in six days, once in a week, once in ten days, and once in fifteen days.

17. The method of any one of claims 15 to 16 further providing a constant rate of delivery of the active components of the transdermal patch over a time period selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in ten days, and once in fifteen days.

18. The method of any one of claims 15 to 17 further providing a steady absorption rates of the active components of the transdermal patch over a time period selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in ten days, and once in fifteen days.

19. The method of any one of claims 15 to 18 further achieving a constant blood serum levels of the active components of the transdermal patch over a time period selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in ten days, and once in fifteen days.

20. The method of any one of claims 15 to 19 further achieving a reduced variability in dosage of the active components of the transdermal patches over a time period selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in ten days, and once in fifteen days.

21. The method of any one of claims 15 to 20 further providing a plasma concentration of the active components of the transdermal patch in a therapeutic range over a time period selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in ten days, and once in fifteen days.

22. The method of any one of claims 15 to 21 further providing a plasma concentration of the active components of the transdermal patch in a therapeutic range of about 0.01 ng/mL to about 500 ng/mL.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/000248

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **A61K 31/675** (2006.01), ***A61K 31/4045*** (2006.01), ***A61K 31/48*** (2006.01), ***A61K 31/55*** (2006.01), ***A61K 9/00*** (2006.01), ***A61K 9/70*** (2006.01) (more IPCs on the last page)

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 31/675 (2006.01), ***A61K 31/4045*** (2006.01), ***A61K 31/48*** (2006.01), ***A61K 31/55*** (2006.01), ***A61K 9/00*** (2006.01), ***A61K 9/70*** (2006.01), ***A61P 25/00*** (2006.01), ***C07D 209/16*** (2006.01), ***C07D 457/06*** (2006.01), ***C07D 487/04*** (2006.01), ***C07F 9/572*** (2006.01)

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Databases: Canadian Patent Database, Questel Orbit, Scopus
Keywords :transdermal, topical, polymer, adhesive, psilocybin, psilobin, LSD, lysergic, ibogaine, skin, composition

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	Claim 37 Pages 23-25	10 and 15
Y	CA 2 979 049 A1 (Raz) 15 September 2016 (09-15-2016) Page 2	10 and 15

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

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"D"	document cited by the applicant in the international application	"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
"E"	earlier application or patent but published on or after the international filing date	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search 16 June 2021 (16-06-2021)	Date of mailing of the international search report 09 August 2021 (09-08-2021)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 819-953-2476	Authorized officer Pierre Tessier (819) 639-9392

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/000248

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	CA 2 934 318 A1 (Sameti et al.) 25 June 2015 (25-06-2015) Whole Document	1-22

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Information on patent family members

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A61P 25/00 (2006.01) , ***C07D 209/16*** (2006.01) , ***C07D 457/06*** (2006.01) , ***C07D 487/04*** (2006.01) , ***C07F 9/572*** (2006.01)