SUBLINGUAL FORMULATION OF RILUZOLE

REFERENCE TO RELATED APPLICATIONS

The present application is a continuation-in-part of United States Provisional Application Serial No. 62/083,094, filed November 21, 2014, the disclosure of which is incorporated herein in its entirety.

TECHNICAL FIELD

The present invention relates to sublingual administration of riluzole and methods using a sublingual formulation of riluzole.

BACKGROUND

Riluzole (6-(trifluoromethoxy)benzothiazol-2-amine) is a pharmaceutical which has been used for treatment of amyotrophic lateral sclerosis (ALS). Recently, riluzole has been shown to have other clinical benefits. For example, orally administered riluzole dosed twice a day at a total dose of 100 mg may relieve or treat neuropsychiatric symptoms and disorders, such as mood, anxiety disorder, refractory depression, obsessive-compulsive anxiety and the like.

However, such therapeutic neuropsychiatric effects via current oral dosing are not evident until multiple days after administration, or up to weeks, and at doses of 100mg/day. The current oral administration is currently limited by poor solubility, variable absorption, undesirable tolerability including increased liver function abnormalities and extensive first past metabolism requiring high doses. Despite being approved for ALS, extensively researched in neuropsychiatric disorders and commercially available for over 20 years, the clinically undesirable effects of riluzole have not been overcome and have limited its use. The intrinsic property of the drug itself teaches away from the sublingual administration of riluzole. Riluzole has a very low solubility in water, poor oral palatability, pH dependent chemical stability, and intense as well as persistent numbness or burning sensation throughout the oral cavity. Techniques aimed at reducing these undesirable effects, such as use of chelating agents, would only facilitate the oral swallowing and gastric absorption

rather than resulting in sublingual absorption. Novel administration of riluzole and effects thereof have not been addressed for improving therapeutic use, particularly in neuropsychiatric treatment, or to attenuate undesirable adverse effects. Further teaching away from the use of sublingual riluzole, sublingual routes of administration have been limited to delivering doses from the microgram range up to 10 mg.

As such, an alternative route for administrating riluzole for extended therapeutic and clinical use is desired.

SUMMARY OF THE INVENTION

The present invention provides: 1) a novel method of sublingual administration of riluzole to a subject, particularly to a human, in need thereof, 2) unexpected low doses of riluzole that possess therapeutic effects across disease indications including desirable neuropsychiatric effects, and 3) the ability to provide a larger than expect dose of riluzole in a sublingual formulation.

The sublingual formulation as provided in the present invention comprises an effective amount of riluzole or a pharmaceutically acceptable salts, solvate, anomers, enantiomers, hydrate or prodrugs thereof. The formulation provides sufficient solubility for riluzole to be incorporated into the sublingual formulation at relatively large doses and sublingually delivered. The formulation is preferably a modified oral disintegrating formulation of riluzole. The excipients, including mannitol and gelatin, are blended, solubilized with water and deaerated before being mixed with the active pharmaceutical ingredient (or "API"), riluzole, which has been milled separately. Particle size of the API (D_{50})is less than about 2 microns. The mixture is lyophilized by flash freezing and then freeze-dried. The formulation has good oral palatability.

In another aspect, a method of treating a disease of a subject by administering the sublingual formulation is provided. The method comprises providing a sublingual formulation made using the process described herein having an effective amount of riluzole or a pharmaceutically acceptable salts, solvate, anomers, enantiomers, hydrate or prodrugs thereof, and administering the formulation to a subject to treat the disease state. The riluzole is preferably delivered in a once per day format but if needed, two or more doses per day may be used.

The subject may be a human.

The disease may be a neuropsychiatric disorder or symptom. In particular, the neuropsychiatric disorder may be anxiety disorders, generalized anxiety disorder, panic disorder, social anxiety, mood disorders, cognitive disorders, schizophrenia, dementia, agitation, apathy, anxiety, psychoses, post-traumatic stress disorders, irritability, disinhibition, learning disorders, memory loss, personality disorders, bipolar disorders, obsessive-compulsive disorders, autism, Rett syndrome, eating disorders, conduct disorders in DSM-5 and or combinations thereof. The disease state may also include neurodegenerative disorders, pain disorders, ALS, cerebellar ataxia, other ataxia, Huntington's disease, Parkinson's disease, supranuclear palsy, frontotemporal dementia, frontotemporal lobar degeneration, delirium, Alzheimer's disease, mild cognitive impairment, mild cognitive impairment due to Alzheimer's disease, drug addiction, tinnitus, and mental retardation.

In addition, the neuropsychiatric symptom may be anxiety, depression, stress, fatigue, feelings of panic, fear, uneasiness, problems in sleeping, cold or sweaty hands and/or feet, mood liability, mania, impaired concentration or attention, cognitive problems, obsessions, compulsions, repetitive behaviors, aggression, social phobias or impairments, stage fright, shortness of breath, heart palpitations, an inability to be still and calm, dry mouth, numbness or tingling in the hands or feet, nausea, muscle tension, dizziness apathy, elation, disinhibition, irritability, wandering, irritable bowel, belly pain, belly discomfort, diarrhea, change in bowel habits, abdominal bloating, abdominal gas, abdominal bloating, constipation or combinations thereof.

The effective amount of riluzole for the sublingual formulation of the present invention to achieve a lower therapeutic dose may be less than that of orally administered riluzole. Moreover, effective dose of the sublingual formulation of the riluzole may be about 1 to 95 % of that of the orally administered riluzole.

The sublingual formulation of riluzole may produce a rapid therapeutic onset of action within minutes or an onset that is quicker than the orally swallowed dose. Further, the sublingual formulation of riluzole is associated with minimal or no oral numbness. The palatability is also good while still resulting in sublingual absorption.

According to the present invention, the method of treating the disease of the subject by administering the sublingual formulation may reduce side effects of riluzole including attenuates liver function abnormalities, which is associated with the orally administered riluzole. According to the present invention, the method of treating the disease of the subject by administering the sublingual formulation may reduce the total drug load necessary to result in a therapeutic effect. A lower sublingual dose of the formulation may deliver similar effects compared to a higher oral dose or even enhanced effects compared to a higher oral dose.

The sublingual formulation for treating neuropsychiatric disorders or symptoms may be dosed at or below about 200 mg/day, at or below about 150 mg/day, at or below about 100 mg/day, at or below about 70 mg/day, at or below about 60 mg/day, at or below about 50 mg/day, at or below about 42.5 mg/day, at or below about 37.5 mg/day at or below about 35 mg/day, at or below about 20 mg/day, at or below about 17.5 mg/day, at or below about 15 mg/day, at or below about 10 mg/day, at or below about 5 mg/day, or at or below about 1 mg/day.

According to the method of the present invention, a therapeutic effect may begin within about 30 min after administration, within about 20 min after administration, within about 15 min after administration, within within about 10 min after administration. within within about 5 min after administration, within within about 4 min after administration, within within about 3 min after administration, within within about 2 min after administration, or within within about 1 min after administration.

The method of treating a disease of a subject by administering a sublingual formulation may further comprise using the sublingual formulation including a riluzole prodrug, which may help to minimize parethesias or numbness associated with the riluzole.

In still another aspect, a method of relieving or reducing oral pain of a subject is provided. The method may comprise administering an effective amount of riluzole or a pharmaceutically acceptable salts, solvate, anomers, hydrate or prodrugs thereof in the oral cavity. Alternatively, a method of relieving or reducing oral pain of a subject by administering a sublingual formulation comprising an effective amount of riluzole or a pharmaceutically acceptable salts, solvate, anomers, hydrate or prodrugs thereof.

Although the sublingual formulation may cause numbness or parathesias, the effect is normally nominal and well tolerated.

A treatment area of oral pain may be throughout an oral cavity including the upper surface of the tongue, lips, buccal area, back of throat, entire oral cavity or combinations thereof. In addition, the oral pain for treatment is caused by infection, inflammation, burn, cut, toothache, sore gums, canker sores, braces, minor dental procedures, denture irritation, oral surgery, neurologic disorders, disorders of the mucosa, oral ulcers, chemotherapy agents or combinations thereof.

A therapeutic effect begins within within about 30 min after administration, within 20 min after administration, within within about 15 minute after administration, within within about 10 min after administration, within about 5 min after administration, within within about 4 min after administration, within about 3 min after administration, within within about 2 min after administration, or within within about 1 min after administration.

The sublingual formulation for treating oral pain may be dosed at or below about 200 mg/day, at or below about 100 mg/day, at or below about 70 mg/day, at or below about 50 mg/day, at or below about 42.5 mg/day, at or below about 37.5 mg mg/day, at or below about 35 mg/day, at or below about 20 mg/day, at or below about 15 mg/day, at or below about 10 mg/day, or at or below about 5 mg/day.

According to various exemplary embodiments, the sublingual formulation may have a greater C_{max} or greater dose normalized C_{max} than the orally administered riluzole to provide a therapeutically beneficial effect. Moreover, the sublingual formulation of the present invention may have a lesser or earlier T_{max} than orally administered riluzole to provide a therapeutically beneficial effect. In addition, the sublingual formulation may have a greater AUC per milligram of the riluzole than the orally administered riluzole. The greater AUC per milligram may be measured in partial $AUC_{0\text{-}0.5h}$, $AUC_{0\text{-}1h}$, $AUC_{0\text{-}2h}$, $AUC_{0\text{-}12h}$, $AUC_{0\text{-}t}$ or $AUC_{0\text{-}inf}$.

The present invention also provides a sublingual or sustained release formulation which may comprise an effective amount of riluzole or a pharmaceutically acceptable salts, solvate, anomers, enantiomers, hydrate or prodrugs thereof to treat irritable bowel syndrome. The present invention also provides a sublingual or sustained release formulation which may

comprise an effective amount of riluzole or a pharmaceutically acceptable salts, solvate, anomers, enantiomers, hydrate or prodrugs thereof to treat cancers such as gliomas, glioblastoma or melanoma. The present invention also provides a sublingual or sustained release formulation which may comprise an effective amount of riluzole or a pharmaceutically acceptable salts, solvate, anomers, enantiomers, hydrate or prodrugs thereof to treat cancers in combination with immunotherapies (including alone or in combination with vaccines, anti-PD1, anti-PDL1, anti-CTLA4 or other immunotherapy or checkpoint inhibitor targets including: CTLA4, cytotoxic T-lymphocyte-associated antigen 4; Ig, immunoglobulin; LAG3, lymphocyte activation gene 3; mAbs, monoclonal antibodies; PD1, programmed cell death protein 1; PDL, PD1 ligand; TIM3, T cell membrane protein 3, CD40L, A2aR, adenosine A2a receptor; B7RP1, B7-related protein 1; BTLA, B and T lymphocyte attenuator; GAL9, galectin 9; HVEM, herpesvirus entry mediator; ICOS, inducible T cell co-stimulator; IL, interleukin; KIR, killer cell immunoglobulin-like receptor; LAG3, lymphocyte activation gene 3; PD1, programmed cell death protein 1; PDL, PD1 ligand; TGFβ, transforming growth factor-β; TIM3, T cell membrane protein 3; CD27).

Other aspects of the invention are disclosed herein.

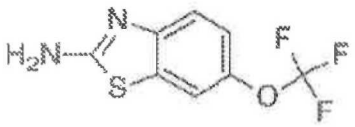
DETAILED DESCRIPTION OF THE INVENTION

The following is a detailed description provided to aid those skilled in the art in practicing the present invention. Those of ordinary skill in the art may make modifications and variations in the embodiments described herein without departing from the spirit or scope of the present disclosure. Unless otherwise defined, 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 disclosure belongs. The terminology used in the description is for describing particular embodiments only and is not intended to be limiting. All publications, patent applications, patents, figures and other references mentioned herein are expressly incorporated by reference in their entirety.

The following terms are used to describe the present invention. In instances where a term is not specifically defined herein, that term is given an art-recognized meaning by those of ordinary skill applying that term in context to its use in describing the present invention.

The articles "a" and "an" as used herein and in the appended claims are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article unless the context clearly indicates otherwise. By way of example, "an element" means one element or more than one element.

The term "riluzole", as used herein, refers to a drug having a chemical structure as follows. It is currently available in the market as RILUTEK®. The term "riluzole" also refers to all prodrugs, enantiomers, or derivatives and its pharmaceutically acceptable salts.



6-(trifluoromethoxy)benzothiazol-2-amine

The term "sublingual administration", as used herein, refers to a route of administrating a chemical agent or a drug by placing thereof under a tongue of a subject.

The term "prodrug" as used herein, is a precursor of a drug which may be administered in an altered or less active form. The prodrug may be converted into the active drug form in physiological environments by hydrolysis or other metabolic pathways.

The term "riluzole prodrug" refers to a compound which is a derivative from riluzole with modification therein. A riluzole prodrug may also refer to a compound that is metabolized into an active form of riluzole by the body.

The term "ALS", as used herein, means Amyotrophic Lateral Sclerosis.

The term "neuropsychiatric disorder", as used herein, is a mental or neurologic disorder which is associated with the nervous system. For example, the neuropsychiatric disorder may include anxiety disorders, mood disorders, neurodegenerative disorders, neurodevelopmental disorders, autism, pervasive developmental disorder, pain disorders, neuropathic pain, ALS, cognitive disorders, Huntington's disease, Parkinson's disease, supranuclear palsy, frontotemporal dementia, frontotemporal lobar degeneration, delirium, Alzheimer's disease, mild cognitive impairment, mild cognitive impairment due to Alzheimer's disease, depression, mania, attention deficit disorders, drug addiction, dementia, agitation, apathy, anxiety, psychoses, post-traumatic stress disorders, irritability, and disinhibition, learning disorders, memory loss, mental retardation, dementia, personality

disorders, bipolar disorders, bipolar depression, generalized anxiety disorder, panic disorder, obsessive-compulsive disorders, trichotillomania, eating disorders, and the like. More specifically, neuropsychiatric disorders includes those listed in the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 5th Edition): Neurodevelopmental disorders, Intellectual disabilities, Intellectual disability (intellectual developmental disorder), Global developmental delay, Unspecified intellectual disability (Intellectual developmental disorder), Communication disorders, Language disorder, Speech sound disorder, Childhood-onset fluency disorder (stuttering), Social (pragmatic) communication disorder, Unspecified communication disorder, Autism spectrum disorder, Rett Syndrome, Attention deficit hyperactivity disorder (ADHD), Unspecified attention-deficit/Hyperactivity disorder, Specific learning disorder, Motor disorders, Developmental coordination disorder, Stereotypic movement disorder, Tic disorders, Tourette's disorder, Persistent (Chronic) motor or vocal tic disorder, Provisional tic disorder, Other specified tic disorder, Unspecified tic disorder, Other neurodevelopmental disorders, Unspecified neurodevelopmental disorder, Schizophrenia spectrum and other psychotic disorders, Delusional disorder, Brief psychotic disorder, Schizophreniform disorder, Schizophrenia, Schizoaffective disorder, Major depressive or manic mood disorder concurrent with primary symptoms of schizophrenia, Substance/Medication-induced psychotic disorder, Psychotic disorder due to another medical condition, Catatonia, Other specified schizophrenia spectrum and other psychotic disorder, Unspecified schizophrenia spectrum and other psychotic disorder, Bipolar and related disorders, Anxiety disorders, Obsessive-compulsive and related disorders, Trauma- and stressor-related disorders, Reactive attachment disorder, Disinhibited social engagement disorder, Posttraumatic stress disorder, Acute stress disorder, Adjustment disorder, Other specified Trauma- and stressor-related disorder, Unspecified trauma- and stressor-related disorder, Dissociative disorders. Dissociative identity disorder, Dissociative amnesia, Depersonalization/Derealization disorder, Somatic symptom disorders, Encopresis, other elimination disorder, Disruptive, impulse-control and conduct disorders in DSM-5, Oppositional defiant disorder, Intermittent explosive disorder, Conduct disorder, Other specified disruptive, conduct disorder, unspecified disruptive, and conduct disorder, Substance-Related and Addictive Disorders, Substance-Related Disorders, Alcohol-Related Disorders, Alcohol Use Disorder, Alcohol Withdrawal, Cannabis-Related Disorders, Cannabis Use Disorder, Gambling Disorder, Cluster A personality disorders, Paranoid personality disorder, Schizoid personality disorder, Schizotypal personality disorder, Cluster

B personality disorders, Antisocial personality disorder, Borderline personality disorder, Histrionic personality disorder, Narcissistic personality disorder, Cluster C personality disorders, Avoidant personality disorder, Dependent personality disorder, Obsessive-compulsive personality disorder, Paraphilic disorders.

The term "DSM" refers to a Diagnostic and Statistical Manual of Mental Disorders as provided by American Psychiatric Association's (APA) classification and diagnostic tool. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5 or DSM-V) is updated in 2013 and exemplary disorders in DSM-V are listed in Appendix A. In addition, the DSM-V has a structure that includes broad categories and subdiagnoses indicating disorders, conditions and problems.

"Neuropsychiatric disorders" could also include neurodegenerative or neurologic disorders including: Alzheimer's disease, dementia, vascular dementia, mixed dementia, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis (ALS), pseudobulbar affect, agitation in Alzheimer's disease, cerebellar ataxia, hereditary ataxias, multiple sclerosis, Progressive Supranuclear Palsy, pain disorders, neuropathic pain, neuropathies, stroke, seizure, Fragile X, tinnitus, and similar conditions.

The neuropsychiatric symptoms may include anxiety, depression, stress, fatigue, feelings of panic, fear, uneasiness, problems in sleeping, cold or sweaty hands and/or feet, shortness of breath, heart palpitations, social phobia, fear of public speaking, an inability to be still and calm, dry mouth, numbness or tingling in the hands or feet, nausea, muscle tension, dizziness apathy, elation, disinhibition, irritability, wandering, and the like. Additionally, neuropsychiatric symptoms could include: delusions, hallucinations, disorganized thinking or speech, derailment of focal topic or loose associations, incoherence, grossly disorganized or abnormal motor behavior (including catatonia), negative symptoms - reduced emotional expression, avolition, alogia, anhedonia, associality, dyskinesias (including tardive dyskinesia), anhedonia and dysphoria, anger and aggression, or symptoms of dissociation, or some combination of these.

Other disorders treated could include cancer (including Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), Adrenocortical Carcinoma, Childhood cancers, AIDS-Related Cancers, Kaposi Sarcoma, AIDS-Related Lymphoma, Primary CNS Lymphoma, Anal Cancer, Astrocytomas, Atypical Teratoid/Rhabdoid Tumor, Basal Cell

Carcinoma, Skin Cancer (Nonmelanoma), Bile Duct Cancer, Bladder Cancer, Bone Cancer, Ewing Sarcoma Family of Tumors, Osteosarcoma and Malignant Fibrous Histiocytoma, Brain Stem Glioma, Atypical Teratoid/Rhabdoid Tumor, Embryonal Tumors, Germ Cell Tumors, Craniopharyngioma, Ependymoma, Breast Cancer, Bronchial Tumors, Burkitt Lymphoma, Non-Hodgkin Lymphoma, Carcinoid Tumor, Gastrointestinal Carcinoma, Cardiac (Heart) Tumors, Primary Lymphoma, Cervical Cancer, Cholangiocarcinoma, Chordoma, Chronic Lymphocytic Leukemia (CLL), Chronic Myelogenous Leukemia (CML), Chronic Myeloproliferative Neoplasms, Colon Cancer, Colorectal Cancer, Craniopharyngioma, Cutaneous T-Cell Lymphoma, Mycosis Fungoides and Sézary Syndrome, Ductal Carcinoma In Situ (DCIS), Embryonal Tumors, Endometrial Cancer, Ependymoma, Esophageal Cancer, Esthesioneuroblastoma, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Eye Cancer, Intraocular Melanoma, Retinoblastoma, Fallopian Tube Cancer, Fibrous Histiocytoma of Bone, Malignant, and Osteosarcoma, Gallbladder Cancer, Gastric (Stomach) Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Stromal Tumors (GIST), Germ Cell Tumor, Ovarian, Testicular, Gestational Trophoblastic Disease, Glioma, Hairy Cell Leukemia, Head and Neck Cancer, Hepatocellular (Liver) Cancer, Histiocytosis, Langerhans Cell, Hodgkin Lymphoma, Hypopharyngeal Cancer, Islet Cell Tumors, Pancreatic Neuroendocrine Tumors, Kaposi Sarcoma, Kidney, Renal Cell, Wilms Tumor, Langerhans Cell Histiocytosis, Laryngeal Cancer, Leukemia, Acute Lymphoblastic (ALL), Acute Myeloid (AML), Chronic Lymphocytic (CLL), Chronic Myelogenous (CML), Hairy Cell, Lip and Oral Cavity Cancer, Liver Cancer (Primary), Lung Cancer, Non-Small Cell, Small Cell, Lymphoma, Hodgkin, Non-Hodgkin, Macroglobulinemia, Waldenström, Male Breast Cancer, Melanoma, Merkel Cell Carcinoma, Mesothelioma,Metastatic Squamous Neck Cancer with Occult Primary, Midline Tract Carcinoma Involving NUT Gene, Mouth Cancer, Multiple Endocrine Neoplasia Syndromes, Multiple Myeloma/Plasma Cell Neoplasm, Mycosis Fungoides, Myelodysplastic Syndromes, Myelodysplastic/Myeloproliferative Neoplasms, Myelogenous Leukemia, Chronic (CML), Myeloid Leukemia, Acute (AML) Myeloma, Multiple, Myeloproliferative Neoplasms, Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin Lymphoma, Non-Small Cell Lung Cancer, Oral Cancer, Oral Cavity Cancer, Lip and Oropharyngeal Cancer, Osteosarcoma and Malignant Fibrous Histiocytoma of Bone, Ovarian Cancer, Low Malignant Potential Tumor, Pancreatic Cancer, Pancreatic Neuroendocrine Tumors (Islet Cell Tumors), Papillomatosis, Paraganglioma, Paranasal Sinus and Nasal

Cavity Cancer, Parathyroid Cancer, Penile Cancer, Pharyngeal Cancer, Pheochromocytoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Pleuropulmonary Blastoma, Pregnancy and Breast Cancer, Primary Central Nervous System (CNS) Lymphoma, Primary Peritoneal Cancer, Prostate Cancer, Rectal Cancer, Renal Cell (Kidney) Cancer, Renal Pelvis and Ureter, Transitional Cell Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Rhabdomyosarcoma, Uterine, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Cell Carcinoma, Squamous Neck Cancer with Occult Primary, Metastatic, Ttomach (Gastric) Cancer, T-Cell Lymphoma, Testicular Cancer, Throat Cancer, Thymoma and Thymic Carcinoma. Thyroid Cancer. Transitional Cell Cancer of the Renal Pelvis and Ureter, Unknown Primary, Ureter and Renal Pelvis, Transitional Cell Cancer, Urethral Cancer, Uterine Cancer, Endometrial, Uterine Sarcoma, Vaginal Cancer, Vulvar Cancer, Waldenström Macroglobulinemia, Wilms Tumor.

The term "treatment" as used herein includes any treatment of a condition or disease in a subject, or particularly a human, and may include: (i) preventing the disease or condition from occurring in the subject which may be predisposed to the disease but has not yet been diagnosed as having it; (ii) inhibiting the disease or condition, i.e., arresting its development; relieving the disease or condition, i.e., causing regression of the condition; or (iii) ameliorating or relieving the conditions caused by the disease, i.e., symptoms of the disease. "Treatment," as used herein, could be used in combination with other standard therapies or alone.

The term "effective" is used to describe an amount of a compound, composition or component which, when used within the context of its intended use, effects an intended result.

The term "effective amount" refers to that amount which is sufficient to effect treatment, as defined herein, when administered to a subject in need of such treatment. The effective amount will vary depending on the subject and disease state being treated, the severity of the affliction and the manner of administration, and may be determined routinely by one of ordinary skill in the art.

The term "pharmaceutically acceptable salt" is used throughout the specification to describe, where applicable, a salt form of one or more of the compounds or prodrugs described herein which are presented to increase the solubility of the compound in the gastric

or gastroenteric juices of the patient's gastrointestinal tract in order to promote dissolution and the bioavailability of the compounds. Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic or organic bases and acids, where applicable. Suitable salts include those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium, magnesium and ammonium salts, among numerous other acids and bases well known in the pharmaceutical art. Sodium and potassium salts are particularly preferred as neutralization salts of the phosphates according to the present invention. In a preferred embodiment, the description provides pharmaceutically acceptable salts of the modified peptides as described herein, which retain the biological effectiveness and properties of the parent compounds and which are not biologically or otherwise harmful as the dosage administered. The compounds of this invention are capable of forming both acid and base salts by virtue of the presence of amino and carboxy groups respectively.

The term "C_{max}", as used herein, refers to a maximum concentration of a drug in blood, serum, a specified compartment or test area of a subject between administration of a first dose and administration of a second dose. The term C_{max} could also refer to dose normalized ratios if specified.

The term "T_{max}", as used herein, refers to a time or period after administration of a drug when the maximum concentration (C_{max}) is reached in blood, serum, a specified compartment or test area of a subject.

The term "AUC" (area under the curve), as used herein, refers to a total amount of drug absorbed or exposed to a subject. Generally, AUC may be obtained from mathematical method in a plot of drug concentration in the subject over time until the concentration is negligible. The term "AUC" (area under the curve) could also refer to partial AUC at specified time intervals (as may be the case with sublingual absorption which would increase AUC at earlier time intervals).

SUBLINGUAL FORMULATION OF RILUZOLE

The invention relates to a sublingual formulation of riluzole. The sublingual formulation may be administered in an effective amount to a subject in need thereof. The subject may be an animal or human.

According to the current invention, the riluzole or its pharmaceutically acceptable salts thereof may be formulated in a pharmaceutical composition suitable for sublingual administration.

Riluzole and the pharmaceutically acceptable salts thereof can be formulated using pharmaceutically acceptable carriers well known in the art into dosages suitable for sublingual or buccal administration. Such carriers enable the riluzole for sublingual administration to be formulated in dosage forms such as tablets, powders, pills, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for sublingual absorption by a subject to be treated. These carriers may be, but not limited to, selected from sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulphate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffered solutions, emulsifiers, isotonic saline, pyrogen-free water and combinations thereof. In particular, any form of substance may be accepted to sublingual administration if it dissolves easily in saliva.

The sublingually administered chemical agent or the drug can diffuse into capillaries through mucous membrane under the tongue, and then enter venous circulation of the subject. As such, sublingual administration may have advantages over oral administration as allowing for direct or faster entry to venous circulation, without risks of degradation in gastrointestinal tract, alteration by drug metabolism in liver and the like. Various drugs in the market are designed for sublingual administration. Riluzole is generally used to treat amyotrophic lateral sclerosis (ALS). However, other uses have been found, and in particular, riluzole or prodrugs of riluzole or pharmaceutically acceptable salts thereof is subjected to a sublingual administration for the treatment of neuropsychiatric disorders. The sublingual administration may also be used for other neuropsychiatric disorders or relieving or reducing pain. In some instances, the preferred effect is on oral pain.

The pharmaceutical composition may include an approved pharmaceutical ingredient, i.e., riluzole, in an effective amount to achieve their intended purpose. For example, the dose of the riluzole administered sublingually to the subject should be sufficient to provide a beneficial response in the subject over time such as reduction in symptoms.

The quantity of the riluzole to be administered may depend on the subject to be treated inclusive of the age, sex, weight and general health condition thereof. In this regard, precise amounts of the agent(s) for administration will depend on the judgement of the practitioner. In determining the effective amount of the riluzole to be administered in the treatment or reducing of the conditions associated with the neuropsychiatric symptoms and disorders, the physician may evaluate clinical factors including symptoms severity or progression of the disorder. In some conditions, a rapid absorption of riluzole may be desirable. In any event, those of skill in the art may readily determine suitable dosages of the chemical agents of the invention.

The pharmaceutical composition also includes other pharmaceutically acceptable carriers and/or excipients such as binders, lubricants, diluents, coatings, disintegrants, barrier layer components, glidants, colouring agents, solubility enhancers, gelling agents, fillers, proteins, co-factors, emulsifiers, solubilising agents, suspending agents and mixtures thereof. A skilled artisan in the art would know what other pharmaceutically acceptable carriers and/or excipients could be included in the formulations according to the invention. The choice of excipients would depend on the characteristics of the compositions and on the nature of other pharmacologically active compounds in the formulation. Appropriate excipients are known to those skilled in the art (see Handbook Of Pharmaceutical Excipients, fifth edition, 2005 edited by Rowe et al., McGraw Hill) and have been utilized to yield a novel sublingual formulation with unexpected properties.

In addition, the pharmaceutical composition for sublingual use can be obtained by combining the approved pharmaceutical ingredient, i.e., riluzole, with further excipients, with optionally processing to obtain dosage forms such as tablets, powders, pills, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for sublingual absorption by a subject to be treated. Suitable excipients may be, but not limited to, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropyl methyl-cellulose, sodium carboxymethylcellulose, and/or polyvinyl-pyrrolidone (PVP). If desired, disintegrating agents may be combined as well, and exemplary disintegrating agents may be, but not limited to, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. The compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association one or more

chemical agents as described above with the carrier which constitutes one or more necessary ingredients. In general, the pharmaceutical compositions of the present invention may be manufactured in conventional methods known in the art, for example, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, lyophilising processes and the like.

The sublingual formulation of the invention may be prepared in a form of an orally dissolving or disintegrating tablet (ODT). The ODT as used herein may be prepared by mixing the riluzole with water-soluble diluents and compressed in a tablet. A suspension comprising riluzole may be prepared with appropriate excipients and the riluzole suspension may be dispensed into blister packs and freeze-dried. An exemplary freeze-dried preparation platform that could be used for the riluzole ODT is the ZYDIS® (Catalent, Somerset, NJ, USA) formulation. In particular, the excipients, including water, are blended and the riluzole is separately milled to size and mixed with the excipients. The suspension then undergoes lyophilisation by flash freezing and freeze drying. Other methods of preparing ODTs may be used without limitation, and detailed description of general methods thereof have been disclosed, for example, in U.S. Pat. No 5,631,023; 5,837,287; 6 ,149,938; 6,212,791; 6,284,270; 6,316,029; 6,465,010; 6,471,992; 6,471,992; 6,509,040; 6,814,978; 6,908,626; 6,908,626; 6,982,251; 7,282,217; 7,425,341; 7,939,105; 7.993,674; 8,048,449; 8,127,516; 8,158,152; 8,221,480; 8,256,233; and 8,313,768, each of which is incorporated herein by reference in its entirety.

The sublingual formulation of the invention may comprise riluzole or an effective amount of a riluzole prodrug. The riluzole prodrug may be similar or less active form of riluzole. The riluzole prodrug may have improved physiochemical, physiological pharmacokinetic or therapeutical characteristics when administered sublingually. The riluzole prodrug may reduce side effects when orally or sublingually administered. In particular, the numbness or parethesias that can occur when riluzole is administered orally or sublingually may be reduced or eliminated by using the riluzole prodrug instead of riluzole.

The clinical or therapeutic effect of the riluzole sublingually formulated may have an improved pharmacokinetic profile for the pharmaceutical agent as measured by standard testing parameters. When the riluzole is administered sublingually, the T_{max}, C_{max} and AUC of the drug may be improved compared to the same dose of the orally administered riluzole. For example, the sublingual formulation of the riluzole may have a greater C_{max} than the

orally administered riluzole to provide a therapeutically beneficial effect. The sublingual formulation of the riluzole may have an earlier or lesser T_{max} than the orally administered riluzole to provide a therapeutically beneficial effect and in some instances, a more rapid therapeutic effect. Alternatively, the sublingual formulation of the riluzole may have a greater AUC per milligram of the riluzole than the orally administered riluzole.

METHOD OF TREATING A DISEASE

The invention also provides a method of treating a disease. The method comprises administering sublingually an effective amount of riluzole or pharmaceutically acceptable salts thereof to a subject in need thereof.

Identifying the subject in need of such treatment can be in the judgment of the subject or a health care professional and can be subjective (e.g., opinion) or objective (e.g., measurable by a test or diagnostic method). The identified subject may be an animal or human in need thereof, particularly a human. Such treatment will be suitably administered to subjects, particularly humans, suffering from the disease.

The disease from which the subject may be suffered may be a neuropsychiatric disorder or symptom. Exemplary neuropsychiatric disorder may be anxiety disorders, mood disorders, neurodegenerative disorders, pain disorders, ALS, cognitive disorders, Huntington's disease, Parkinson's disease, supranuclear palsy, frontotemporal dementia, frontotemporal lobar degeneration, delirium, Alzheimer's disease, mild cognitive impairment, mild cognitive impairment due to Alzheimer's disease, depression, mania, attention deficit disorders, drug addiction, dementia, agitation, apathy, anxiety, psychoses, post-traumatic stress disorders, irritability, and disinhibition, learning disorders, memory loss, mental retardation, dementia, personality disorders, bipolar disorders, obsessive-compulsive disorders, eating disorders, and the like. Exemplary neuropsychiatric symptoms may be anxiety, depression, stress, fatigue, feelings of panic, fear, uneasiness, problems in sleeping, cold or sweaty hands and/or feet, shortness of breath, heart palpitations, an inability to be still and calm, dry mouth, numbness or tingling in the hands or feet, nausea, muscle tension, dizziness apathy, elation, disinhibition, irritability, wandering, or combinations thereof.

The effective amount of the riluzole may be determined by the degree of a therapeutic effect, such as anxiolytic, antidepressant, mood stabilizing, stress resilient or stress relieving,

anti-pain, or combinations thereof. Further, the effect of sublingual administration of riluzole may be also be indicated by unexpected and novel properties including, but not limited to: a) an attenuated or improved side effect or tolerability profile compared to oral dosing; b) rapid onset of therapeutic action; c) decreased liver function abnormalities; d) a unique pharmacokinetic profile compared to oral administration; e) a lower therapeutic dose compared that typical oral dosing; f) once daily dosing; and g) minimized or absent oral parenthesis or numbing.

The effective amount will vary depending on the subject and disease state being treated, the severity of the affliction and the manner of administration, and may be determined routinely by one of ordinary skill in the art.

The therapeutic effect of the riluzole may be evident to occur within about a few minutes to about an hour after sublingual administration thereof. In particular, the therapeutic effect may begin within about 1 minute, within about 2 minutes, within about 3 minutes, within about 4 minutes, within about 5 minutes, within about 6 minutes, within about 7 minutes, within about 8 minutes, within about 9 minutes, within about 10 minutes, within about 11 minutes, within about 12 minutes, within about 13 minutes, within about 14 minutes, within about 15 minutes, within about 16 minutes, within about 17 minutes, within about 18 minutes, within about 20 minutes, within about 60 minutes, or within about 90 minutes after administration.

The effects of the riluzole may be maintained for about 1 hour, for about 2 hours, for about 3 hours, for about 4 hours, for about 5 hours, for about 6 hours m for about 7 hours, for about 8 hours, for about 9 hours, for about 10 hours, for about 12 hours, for about 14 hours, for about 16 hours, for about 18 hours, for about 20 hours, for about 22 hours, for about 24 hours, for about 2 days, or for about 3 days or more after sublingual administration thereof.

The effective amount or dose of riluzole for sublingual administration may be less than that of orally administered riluzole. In particular, the effective dose in sublingual administration of riluzole may be of about 1-95 % of the dose of the orally administered riluzole.

The effective amount of the riluzole or pharmaceutically acceptable salts thereof in sublingual administration for treatment of neuropsychiatric disorders may be dosed at or less than about 200 mg/day, at or below about 150 mg/day, at or less than about 100 mg/day, at or

less than about 90 mg/day, at or less than about 80 mg/day, at or less than about 70 mg/day, at or less than about 60 mg/day, at or less than about 50 mg/day, at or less than about 40 mg/day, at or less than about 37.5 mg/day, at or less than about 35 mg/day, at or less than about 30 mg/day, at or less than about 20 mg/day, at or less than about 17.5 mg/day, at or less than about 15 mg/day, at or less than about 10 mg/day, at or less than about 9 mg/day, at or less than about 8 mg/day, at or less than about 7 mg/day, at or less than about 6 mg/day, at or less than about 5 mg/day, at or less than about 4 mg/day, at or less than about 3 mg/day, at or less than about 2 mg/day, or at or less than about 1 mg/day.

Optional dosage frequencies include once a day, twice a day, three times a day, four times a day, once every other day, once a week, twice a week, three times a week, four times a week, once every two weeks, once or twice monthly, and the like.

The clinical or therapeutic effect of the riluzole sublingually formulated and administered for neuropsychiatric disorders or symptoms may have an improved pharmacokinetic profile for the pharmaceutical agent as measured by standard testing parameters. When the riluzole is administered sublingually, the T_{max}, C_{max} or AUC of the drug may be improved compared to the same dose of the orally administered riluzole. For example, the sublingual administration of the riluzole may have a greater C_{max} than the orally administered riluzole to provide a therapeutically beneficial effect. The sublingual administration of the riluzole has a less T_{max} than the orally administered riluzole to provide a therapeutically beneficial effect. Alternatively, the sublingual administration of the riluzole may have a greater AUC per milligram of the riluzole than the orally administered riluzole.

In some embodiments, the orally disintegrating formulation would be a prodrug that could be sublingually administered or even orally dispersed then swallowed with enhanced pharmacokinetic properties.

SUBLINGUAL FORMULATION FOR ORAL PAIN

The current invention further includes a method of sublingually administering the riluzole to the subject to produce other desired effects.

A method is provided of relieving or reducing oral pain by sublingual administration of riluzole. The method comprises administering a sublingual formulation having an

effective amount of riluzole to a subject in need thereof. In certain embodiments, the subject may be an animal or human.

In certain embodiments, the sublingual formulation may induce numbness from the deposition site thereof. The numbness may be effective to reduce or relieve oral pain and spread throughout the mucosal contacts. A level of numbness may be in a tolerable range to the subject.

A treatment area of oral pain may be, but not limited to, throughout an oral cavity including the upper surface of the tongue, lips, buccal area, back of throat, entire oral cavity and the like. The oral pain for treatment may be caused by infection, viruses, inflammation, burn, cut, toothache, sore gums, canker sores, braces, minor dental procedures, denture irritation, oral surgery, neurologic disorders, disorders of the mucosa or caused by other drugs known to induce painful oral ulcers (such as chemotherapy agents).

The effects of reducing oral pain may occur within a minute or about a few minutes to about an hour. In particular, the numbness may begin within about 1 minute, within about 2 minutes, within about 3 minutes, within about 4 minutes, within about 5 minutes, within about 6 minutes, within about 7 minutes, within about 8 minutes, within about 9 minutes, within about 10 minutes, within about 11 minutes, within about 12 minutes, within about 13 minutes, within about 14 minutes, within about 15 minutes, within about 16 minutes, within about 17 minutes, or within about 18 minutes, within about 19 minutes, or within about 20 minutes after administration.

The effects of relieving or reducing oral pain may be maintained for about 1 hour, for about 2 hours, for about 3 hours, for about 4 hours, for about 5 hours , for about 6 hours m for about 7 hours, for about 8 hours, for about 9 hours, for about 10 hours, for about 12 hours, for about 14 hours, for about 16 hours, for about 18 hours, for about 20 hours, for about 22 hours, for about 24 hours, for about 2 days, or for about 3 days after sublingual administration thereof.

The sublingual administration of riluzole for relieving or reducing oral pain may be dosed at or less than about 200 mg/day, at or less than about 150 mg/day, at or less than about 100 mg/day, at or less than about 90 mg/day, at or less than about 80 mg/day, at or less than about 70 mg/day, at or less than about 60 mg/day, at or less than about 50 mg/day, at or less than about 40 mg/day, at or less than about 35 mg/day, at or less than about 30 mg/day, at or

less than about 20 mg/day, at or less than about 17.5 mg/day, at or less than about 10 mg/day, at or less than about 9 mg/day, at or less than about 8 mg/day, at or less than about 7 mg/day, at or less than about 6 mg/day, at or less than about 5 mg/day, at or less than about 4 mg/day, at or less than about 3 mg/day, at or less than about 2 mg/day, or at or less than about 1 mg/day.

Optional dosage frequencies include once a day, twice a day, three times a day, four times a day, once a week, twice a week, three times a week, four times a week, once every two weeks, once or twice monthly, and the like.

The formulation for relieving or reducing oral pain may comprise an effective amount of riluzole and a pharmaceutically acceptable carrier thereof. The pharmaceutical composition can be formulated as tablets, powders, pills, capsules, liquids, gels, ointments, syrups, slurries, suspensions, and the like, to provide substantial absorption rate at the treated area. An additional bioactive agent or other drugs may be added to a pharmaceutical composition for effective and elevated effects of pain relief. In some embodiments the formulation may be administered topically in the oral cavity or buccal mucosa.

EXAMPLES

The following examples illustrate the invention and are not intended to limit the scope of the invention.

EXAMPLE 1

A 51 year-old male was administrated with riluzole on four occasions.

(1) An oral administration of riluzole was used as a comparator. A standard 50 mg riluzole tablet (a tablet not of the present invention) was pulverized and administered into the mouth cavity for 40 seconds to allow for transmucosal and/or oral absorption. This was not sublingual or buccal administration. There were no acute or chronic effects on neuropsychiatric domains. More specifically, there were no effects on mood, anxiety or behavior. Prominent oral numbness was noted. Within the first minute, a sensation of numbness spread throughout the oral cavity including the upper surface of the tongue and

lips, resulting in circumoral paresthesias. The effects were moderate and peaked within 4 minutes. The effects lasted for up to 80 minutes. The effects started subsiding after 15 minutes and were considered mild after 40 minutes and minimal after 80 minutes. All effects were limited to local mouth-related sensations described above.

(2) Separately, a first sublingual administration of a formulation of the invention was performed. About 70 mg of the sublingual formulation of riluzole was placed under the tongue of the subject and held firmly in place. Unexpectedly, the subject experienced acute psychotropic effects shortly after the sublingual administration. Within approximately 40 minutes from the sublingual administration, the subject experienced a sense of enhanced or improved mood. The subject noted a sense of well-being and conveyed a sense of optimism that represented a change from the baseline mood state. The mood state change was estimated to last at least four hours.

Within one minute of sublingual administration, tongue numbness developed, and, after 4 minutes, numbness spread over the lips as well as the back of the throat. The numbness reached to a moderate level in 16 minutes, lessened to a mild level by 20 minutes, and fully dissipated over the next hour. The numbness associated with the sublingual administration was significantly attenuated compared to the diffuse oral pulverized administration described previously. The sublingual formulation yielded a mild and not bothersome numbness that was localized (versus the pulverized riluzole tablet that was more intense, bothersome and generalized).

(3) A second sublingual administration occurred on another day. About 70 mg of a sublingual formulation of riluzole was placed under the tongue of the subject for about 95 seconds until fully dissolved. Again, the subject experienced a similar improvement in mood. The subject reported a sense of optimism and well-being. These feelings peaked by 40 minutes. After 25 minutes, the subject reported feeling relaxed (less anxious) and with an increased level of alertness. The subject reported improved sleep condition and vivid dreams that evening.

Tongue and lip numbness was noted after about 4 minutes, peaked after 6 minutes with a moderate level of numbness and waned thereafter to a mild level by about 24 minutes. The mouth numbness was considered very mild to minimal at this time point. Again, the oral numbness was attenuated compared to the diffuse oral administration of the pulverized standard riluzole tablet. No sedation was recognized.

(4) A third sublingual administration was tried with a lower dose of the sublingual formulation. About 30 mg of a sublingual formulation of riluzole was placed under the tongue of the subject. Once again, acute effects (within 25 minutes) of the sublingual riluzole administration were observed and included the subject feeling relaxed, having a feeling of wellbeing, optimism, and alertness. Similar oral numbness to the previous sublingual administrations was reported but attenuated compared to the oral administration.

EXAMPLE 2

A 43 year old male administered with riluzole on two occasions.

(1) An oral administration: About 50 mg of an unpulverized riluzole tablet (a formulation not of the invention) was placed on a tongue of the subject. No psychoactive effect was reported but immediately upon application, the subject reported numbness in the local area of application that spread quickly throughout the entire oral cavity. Numbness lasted past 20 minutes. No mood or behavioral sensation was reported. The numbness was intense and bothersome.

(2) A sublingual administration: About 20 mg of a sublingual formulation of riluzole was place under the tongue of the subject for about 30 seconds. Within about 20 minutes, the subject reported the onset of beneficial psychoactive effects including feeling relaxed, calm and less anxious. The subject also reported the sensation of feeling alert. These psychoactive effects or feelings persisted for about 90 minutes. The subject noted that his stomach and gut felt "calm" and previous upset stomach was lessened. The subject reported improved sleep condition that evening.

Within a minute of application, the subject reported that numbness in tongue and mouth reached a peak by about 7 minutes with moderate effect. The numbness started waning significantly after about 18 minutes to very mild by about 24 minutes. The numbness associated with the sublingual administration was noted to be attenuated compared to the oral administration in this subject. Overall, the numbness was very mild and not bothersome with good mouth palatability compared to the pulverized standard riluzole (which was intense, bothersome, generalized and with poor mouth palatability).

EXAMPLE 3

A 50 year old male was administered with a sublingual formulation of riluzole.

About 5 mg sublingual formulation of riluzole was placed under the tongue of the subject for about 20 seconds until the formulation was fully dissolved. Again, as in the other subjects who received the sublingual administration, there were previously unexpected psychotropic effects soon after administration. Within 20 to 30 minutes, the subject reported the onset of beneficial psychoactive effects and he reported a feeling of relaxation and calm.

After about 7 minutes of administration, the subject reported numbness on the roof of his mouth and tongue that peaked around about 7 minutes, and then was completely gone after about 21 minutes.

EXAMPLE 4

A 57 year old male was administered with a sublingual formulation of riluzole.

About 70 mg sublingual formulation of riluzole was placed under the tongue of the subject for about 74 seconds. Within about 24 minutes, the subject reported psychoactive effects that were characterized by a feeling of being relaxed and alert that endured through about an hour. The subject reported that he felt so relaxed that he took a restful nap. The subject also reported that his stomach felt relaxed.

After 2 minutes of administration, the subject reported feelings of numbness on the tongue. Peak of mouth numbness occurred after about 4 minutes and numbness waned to mild level after about 15 minutes. Again, compared to the subjects who received oral administration of riluzole, the sublingual administration was associated with an attenuated oral numbness and parathesias.

Example 5

A number of different but related formulations of riluzole for sublingual administration were made. Formulations of 10 mg, 17.5 mg and 35 mg were all made and proved effective at providing the psychoactive effects. The formulations were related in that the same materials were used but the proportions were slightly different.

Each of the formulations included a tablet binder, preferably gelatin; a bulking agent such as mannitol or sorbitol; a solubilizing agent such as docusate sodium; a flavoring agent providing a flavoring such as mint, spearmint, orange, cherry or the like; a sweetener such as sucralose; and purified or distilled water as a solvent. The flavoring agent and the sweetener a merely for taste purposes and can be omitted. To process the tablets, the tablet binder,

bulking agent, solubilizing agent, and any sweetener and flavoring are mixed together and solubilized with purified water. The tablet binder should be about 1-10% of the weight of the mixture (including the riluzole and water), preferably 3-5%, most preferably 4-4.5%; the bulking agent should be about 2-4%, preferably about 3% of the mixture; the solubilizing agent should be about 0.01-0.5 % of the mixture, preferably about 0.1-0.2% of the mixture; the flavoring agent (if used) should be about 0.1-1.0%, preferably about 0.3-0.5% of the mixture; and the sweetener (if used) should be about 0.1-1.0% of the mixture, preferably about 0.5% of the mixture. The riluzole should be about 5-25% of the mixture, preferably about 5-20%, more preferably 7-18% of the mixture. The riluzole is milled separately so that the D_{50} particle size is preferably below 2 microns, then it is added to the other solubilized materials. The amount of riluzole is normally a lower percentage for smaller doses than in the higher doses. The remainder of the mixture is purified or deionized water. All of the weights are before lyophillization, where most of the water is removed. Lyophillization is carried out by flash freezing then freeze drying the resulting mixture in tablet form.

Example 6

In this example, the three sublingual formulations of riluzole described in Example 5 were tested for pharmokinetic properties against a commercially available 50 mg riluzole tablet. Partial AUC values, $AUC_{0-0.5}$, AUC_{0-1}, AUC_{0-}, and AUC_{0-12} (being AUC values measured for 0.5 hours, 1 hour, 2 hours and 12 hours after the dose was given) were measured and the ratios of the values for the test materials to the 50 mg oral dose were determined. As can be seen from the Table, the values from the sublingual formulation were higher than a weight adjusted value of the oral dosage for all the doses, particularly at the earlier times. The predicted ratios (assuming that the sublingual and oral formulation reached the circulation at the same rate) would be 20% for the 10 mg version, 35% for the 17.5 mg version, and 70% for the 35 mg version.

Parameter	Treatment Comparison	Ratio
$AUC_{0-0.5}$		
	10 mg sublingual v. 50 mg oral	36.19%

	17.5 mg sublingual v. 50 mg oral	82.16%
	35 mg sublingual v. 50 mg oral	180.84%
AUC_{0-1}		
	10 mg sublingual v. 50 mg oral	29.93%
	17.5 mg sublingual v. 50 mg oral	65.26%
	35 mg sublingual v. 50 mg oral	136.20%
AUC_{0-2}		
	10 mg sublingual v. 50 mg oral	26.28%
	17.5 mg sublingual v. 50 mg oral	53.91%
	35 mg sublingual v. 50 mg oral	110.28%
AUC_{0-12}		
	10 mg sublingual v. 50 mg oral	22.47%
	17.5 mg sublingual v. 50 mg oral	43.38%
	35 mg sublingual v. 50 mg oral	89.89%

As is evident from the Table, the sublingual formulations achieved a much higher AUC value than predicted at the earlier times and it is only at 12 hours that the values are near (but still higher) that the weight percent ratios. This shows that the sublingual formulation is being adsorbed and not merely swallowed.

The entire contents of all patents, published patent applications and other references cited herein are hereby expressly incorporated herein in their entireties by reference.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the following claims.

APPENDIX A

ICD-9-CM	ICD-10-CM	Disorder, condition, or problem
V62.3	Z55.9	Academic or educational problem
V62.4	Z60.3	Acculturation difficulty
308.3	F43.0	Acute stress disorder
		Adjustment disorders
309.24	F43.22	With anxiety
309.0	F43.21	With depressed mood
309.3	F43.24	With disturbance of conduct
309.28	F43.23	With mixed anxiety and depressed mood
309.4	F43.25	With mixed disturbance of emotions and conduct
309.9	F43.20	Unspecified
V71.01	Z72.811	Adult antisocial behavior
307.0	F98.5	Adult-onset fluency disorder
		Adult physical abuse by nonspouse or nonpartner, Confirmed
995.81	T74.11XA	Initial encounter
995.81	T74.11XD	Subsequent encounter
		Adult physical abuse by nonspouse or nonpartner, Suspected
995.81	T76.11XA	Initial encounter
995.81	T76.11XD	Subsequent encounter
		Adult psychological abuse by nonspouse or nonpartner, Confirmed
995.82	T74.31XA	Initial encounter
995.82	T74.31XD	Subsequent encounter
		Adult psychological abuse by nonspouse or nonpartner, Suspected
995.82	T76.31XA	Initial encounter
995.82	T76.31XD	Subsequent encounter
		Adult sexual abuse by nonspouse or nonpartner, Confirmed
995.83	T74.21XA	Initial encounter
995.83	T74.21XD	Subsequent encounter
		Adult sexual abuse by nonspouse or nonpartner, Suspected
995.83	T76.21XA	Initial encounter
995.83	T76.21XD	Subsequent encounter
300.22	F40.00	Agoraphobia
291.89		Alcohol-induced anxiety disorder
	F10.180	With mild use disorder
	F10.280	With moderate or severe use disorder
	F10.980	Without use disorder
291.89		Alcohol-induced bipolar and related disorder
	F10.14	With mild use disorder
	F10.24	With moderate or severe use disorder

	F10.94	Without use disorder
291.89		Alcohol-induced depressive disorder
	F10.14	With mild use disorder
	F10.24	With moderate or severe use disorder
	F10.94	Without use disorder
291.1		Alcohol-induced major neurocognitive disorder, Amnestic confabulatory type
	F10.26	With moderate or severe use disorder
	F10.96	Without use disorder
291.2		Alcohol-induced major neurocognitive disorder, Nonamnestic confabulatory type
	F10.27	With moderate or severe use disorder
	F10.97	Without use disorder
291.89		Alcohol-induced mild neurocognitive disorder
	F10.288	With moderate or severe use disorder
	F10.988	Without use disorder
291.9		Alcohol-induced psychotic disorder
	F10.159	With mild use disorder
	F10.259	With moderate or severe use disorder
	F10.959	Without use disorder
291.89		Alcohol-induced sexual dysfunction
	F10.181	With mild use disorder
	F10.281	With moderate or severe use disorder
	F10.981	Without use disorder
291.82		Alcohol-induced sleep disorder
	F10.182	With mild use disorder
	F10.282	With moderate or severe use disorder
	F10.982	Without use disorder
303.00		Alcohol intoxication
	F10.129	With mild use disorder
	F10.229	With moderate or severe use disorder
	F10.929	Without use disorder
291.0		Alcohol intoxication delirium
	F10.121	With mild use disorder
	F10.221	With moderate or severe use disorder
	F10.921	Without use disorder
		Alcohol use disorder
305.00	F10.10	Mild
303.90	F10.20	Moderate
303.90	F10.20	Severe
291.81		Alcohol withdrawal
	F10.232	With perceptual disturbances
	F10.239	Without perceptual disturbances
291.0	F10.231	Alcohol withdrawal delirium
292.89		Amphetamine (or other stimulant)–induced anxiety disorder
	F15.180	With mild use disorder

	F15.280	With moderate or severe use disorder
	F15.980	Without use disorder
292.84		Amphetamine (or other stimulant)-induced bipolar and related disorder
	F15.14	With mild use disorder
	F15.24	With moderate or severe use disorder
	F15.94	Without use disorder
	F15.921	Amphetamine (or other stimulant)-induced delirium
292.84		Amphetamine (or other stimulant)-induced depressive disorder
	F15.14	With mild use disorder
	F15.24	With moderate or severe use disorder
	F15.94	Without use disorder
292.89		Amphetamine (or other stimulant)-induced obsessive-compulsive and related disorder
	F15.188	With mild use disorder
	F15.288	With moderate or severe use disorder
	F15.988	Without use disorder
292.9		Amphetamine (or other stimulant)-induced psychotic disorder
	F15.159	With mild use disorder
	F15.259	With moderate or severe use disorder
	F15.959	Without use disorder
292.89		Amphetamine (or other stimulant)-induced sexual dysfunction
	F15.181	With mild use disorder
	F15.281	With moderate or severe use disorder
	F15.981	Without use disorder
292.85		Amphetamine (or other stimulant)-induced sleep disorder
	F15.182	With mild use disorder
	F15.282	With moderate or severe use disorder
	F15.982	Without use disorder
292.89		Amphetamine or other stimulant intoxication
		Amphetamine or other stimulant intoxication, With perceptual disturbances
	F15.122	With mild use disorder
	F15.222	With moderate or severe use disorder
	F15.922	Without use disorder
		Amphetamine or other stimulant intoxication, Without perceptual disturbances
	F15.129	With mild use disorder
	F15.229	With moderate or severe use disorder
	F15.929	Without use disorder
292.81		Amphetamine (or other stimulant) intoxication delirium
	F15.121	With mild use disorder
	F15.221	With moderate or severe use disorder
	F15.921	Without use disorder

292.0	F15.23	Amphetamine or other stimulant withdrawal
		Amphetamine-type substance use disorder
305.70	F15.10	Mild
304.40	F15.20	Moderate
304.40	F15.20	Severe
307.1		Anorexia nervosa
	F50.02	Binge-eating/purging type
	F50.01	Restricting type
		Antidepressant discontinuation syndrome
995.29	T43.205A	Initial encounter
995.29	T43.205S	Sequelae
995.29	T43.205D	Subsequent encounter
301.7	F60.2	Antisocial personality disorder
293.84	F06.4	Anxiety disorder due to another medical condition
		Attention-deficit/hyperactivity disorder
314.01	F90.2	Combined presentation
314.01	F90.1	Predominantly hyperactive/impulsive presentation
314.00	F90.0	Predominantly inattentive presentation
299.00	F84.0	Autism spectrum disorder
301.82	F60.6	Avoidant personality disorder
307.59	F50.8	Avoidant/restrictive food intake disorder
307.51	F50.8	Binge-eating disorder
		Bipolar I disorder, Current or most recent episode depressed
296.56	F31.76	In full remission
296.55	F31.75	In partial remission
296.51	F31.31	Mild
296.52	F31.32	Moderate
296.53	F31.4	Severe
296.54	F31.5	With psychotic features
296.50	F31.9	Unspecified
296.40	F31.0	Bipolar I disorder, Current or most recent episode hypomanic
296.46	F31.72	In full remission
296.45	F31.71	In partial remission
296.40	F31.9	Unspecified
		Bipolar I disorder, Current or most recent episode manic
296.46	F31.74	In full remission
296.45	F31.73	In partial remission
296.41	F31.11	Mild
296.42	F31.12	Moderate
296.43	F31.13	Severe
296.44	F31.2	With psychotic features
296.40	F31.9	Unspecified
296.7	F31.9	Bipolar I disorder, Current or most recent episode unspecified
296.89	F31.81	Bipolar II disorder

293.83		Bipolar and related disorder due to another medical condition
	F06.33	With manic features
	F06.33	With manic- or hypomanic-like episodes
	F06.34	With mixed features
300.7	F45.22	Body dysmorphic disorder
V62.89	R41.83	Borderline intellectual functioning
301.83	F60.3	Borderline personality disorder
298.8	F23	Brief psychotic disorder
307.51	F50.2	Bulimia nervosa
292.89		Caffeine-induced anxiety disorder
	F15.180	With mild use disorder
	F15.280	With moderate or severe use disorder
	F15.980	Without use disorder
292.85		Caffeine-induced sleep disorder
	F15.182	With mild use disorder
	F15.282	With moderate or severe use disorder
	F15.982	Without use disorder
305.90	F15.929	Caffeine intoxication
292.0	F15.93	Caffeine withdrawal
292.89		Cannabis-induced anxiety disorder
	F12.180	With mild use disorder
	F12.280	With moderate or severe use disorder
	F12.980	Without use disorder
292.9		Cannabis-induced psychotic disorder
	F12.159	With mild use disorder
	F12.259	With moderate or severe use disorder
	F12.959	Without use disorder
292.85		Cannabis-induced sleep disorder
	F12.188	With mild use disorder
	F12.288	With moderate or severe use disorder
	F12.988	Without use disorder
292.89		Cannabis intoxication
		Cannabis intoxication, With perceptual disturbances
	F12.122	With mild use disorder
	F12.222	With moderate or severe use disorder
	F12.922	Without use disorder
		Cannabis intoxication, Without perceptual disturbances
	F12.129	With mild use disorder
	F12.229	With moderate or severe use disorder
	F12.929	Without use disorder
292.81		Cannabis intoxication delirium
	F12.121	With mild use disorder
	F12.221	With moderate or severe use disorder
	F12.921	Without use disorder
		Cannabis use disorder
305.20	F12.10	Mild

304.30	F12.20	Moderate
304.30	F12.20	Severe
292.0	F12.288	Cannabis withdrawal
293.89	F06.1	Catatonia associated with another mental disorder (catatonia specifier)
293.89	F06.1	Catatonic disorder due to another medical condition
		Central sleep apnea
780.57	G47.37	Central sleep apnea comorbid with opioid use
786.04	R06.3	Cheyne-Stokes breathing
327.21	G47.31	Idiopathic central sleep apnea
V61.29	Z62.898	Child affected by parental relationship distress
		Child neglect, Confirmed
995.52	T74.02XA	Initial encounter
995.52	T74.02XD	Subsequent encounter
		Child neglect, Suspected
995.52	T76.02XA	Initial encounter
995.52	T76.02XD	Subsequent encounter
V71.02	Z72.810	Child or adolescent antisocial behavior
		Child physical abuse, Confirmed
995.54	T74.12XA	Initial encounter
995.54	T74.12XD	Subsequent encounter
		Child physical abuse, Suspected
995.54	T76.12XA	Initial encounter
995.54	T76.12XD	Subsequent encounter
		Child psychological abuse, Confirmed
995.51	T74.32XA	Initial encounter
995.51	T74.32XD	Subsequent encounter
		Child psychological abuse, Suspected
995.51	T76.32XA	Initial encounter
995.51	T76.32XD	Subsequent encounter
		Child sexual abuse, Confirmed
995.53	T74.22XA	Initial encounter
995.53	T74.22XD	Subsequent encounter
		Child sexual abuse, Suspected
995.53	T76.22XA	Initial encounter
995.53	T76.22XD	Subsequent encounter
315.35	F80.81	Childhood-onset fluency disorder (stuttering)
		Circadian rhythm sleep-wake disorders
307.45	G47.22	Advanced sleep phase type
307.45	G47.21	Delayed sleep phase type
307.45	G47.23	Irregular sleep-wake type
307.45	G47.24	Non-24-hour sleep-wake type
307.45	G47.26	Shift work type
307.45	G47.20	Unspecified type
292.89		Cocaine-induced anxiety disorder
	F14.180	With mild use disorder
	F14.280	With moderate or severe use disorder

	F14.980	Without use disorder
292.84		Cocaine-induced bipolar and related disorder
	F14.14	With mild use disorder
	F14.24	With moderate or severe use disorder
	F14.94	Without use disorder
292.84		Cocaine-induced depressive disorder
	F14.14	With mild use disorder
	F14.24	With moderate or severe use disorder
	F14.94	Without use disorder
292.89		Cocaine-induced obsessive-compulsive and related disorder
	F14.188	With mild use disorder
	F14.288	With moderate or severe use disorder
	F14.988	Without use disorder
292.9		Cocaine-induced psychotic disorder
	F14.159	With mild use disorder
	F14.259	With moderate or severe use disorder
	F14.959	Without use disorder
292.89		Cocaine-induced sexual dysfunction
	F14.181	With mild use disorder
	F14.281	With moderate or severe use disorder
	F14.981	Without use disorder
292.85		Cocaine-induced sleep disorder
	F14.182	With mild use disorder
	F14.282	With moderate or severe use disorder
	F14.982	Without use disorder
292.89		Cocaine intoxication
		Cocaine intoxication, With perceptual disturbances
	F14.122	With mild use disorder
	F14.222	With moderate or severe use disorder
	F14.922	Without use disorder
		Cocaine intoxication, Without perceptual disturbances
	F14.129	With mild use disorder
	F14.229	With moderate or severe use disorder
	F14.929	Without use disorder
292.81		Cocaine intoxication delirium
	F14.121	With mild use disorder
	F14.221	With moderate or severe use disorder
	F14.921	Without use disorder
		Cocaine use disorder
305.60	F14.10	Mild
304.20	F14.20	Moderate
304.20	F14.20	Severe
292.0	F14.23	Cocaine withdrawal
		Conduct disorder
312.82	F91.2	Adolescent-onset type
312.81	F91.1	Childhood-onset type

312.89	F91.9	Unspecified onset
300.11		Conversion disorder (functional neurological symptom disorder)
	F44.4	With abnormal movement
	F44.6	With anesthesia or sensory loss
	F44.5	With attacks or seizures
	F44.7	With mixed symptoms
	F44.6	With special sensory symptoms
	F44.4	With speech symptoms
	F44.4	With swallowing symptoms
	F44.4	With weakness/paralysis
V62.5	Z65.0	Conviction in civil or criminal proceedings without imprisonment
301.13	F34.0	Cyclothymic disorder
302.74	F52.32	Delayed ejaculation
		Delirium
293.0	F05	Delirium due to another medical condition
293.0	F05	Delirium due to multiple etiologies
292.81		Medication-induced delirium *(for ICD-10-CM codes, see specific substances)*
		Substance intoxication delirium *(see specific substances for codes)*
		Substance withdrawal delirium *(see specific substances for codes)*
297.1	F22	Delusional disorder
301.6	F60.7	Dependent personality disorder
300.6	F48.1	Depersonalization/derealization disorder
293.83		Depressive disorder due to another medical condition
	F06.31	With depressive features
	F06.32	With major depressive-like episode
	F06.34	With mixed features
315.4	F82	Developmental coordination disorder
V60.89	Z59.2	Discord with neighbor, lodger, or landlord
V62.89	Z64.4	Discord with social service provider, including probation officer, case manager, or social services worker
313.89	F94.2	Disinhibited social engagement disorder
V61.03	Z63.5	Disruption of family by separation or divorce
296.99	F34.8	Disruptive mood dysregulation disorder
300.12	F44.0	Dissociative amnesia
300.13	F44.1	Dissociative amnesia, with dissociative fugue
300.14	F44.81	Dissociative identity disorder
307.7	F98.1	Encopresis
307.6	F98.0	Enuresis
302.72	F52.21	Erectile disorder
698.4	L98.1	Excoriation (skin-picking) disorder
302.4	F65.2	Exhibitionistic disorder
V62.22	Z65.5	Exposure to disaster, war, or other hostilities

V60.2	Z59.5	Extreme poverty
300.19	F68.10	Factitious disorder
302.73	F52.31	Female orgasmic disorder
302.72	F52.22	Female sexual interest/arousal disorder
302.81	F65.0	Fetishistic disorder
302.89	F65.81	Frotteuristic disorder
312.31	F63.0	Gambling disorder
302.85	F64.1	Gender dysphoria in adolescents and adults
302.6	F64.2	Gender dysphoria in children
300.02	F41.1	Generalized anxiety disorder
302.76	F52.6	Genito-pelvic pain/penetration disorder
315.8	F88	Global developmental delay
292.89	F16.983	Hallucinogen persisting perception disorder
V61.8	Z63.8	High expressed emotion level within family
301.50	F60.4	Histrionic personality disorder
300.3	F42	Hoarding disorder
V60.0	Z59.0	Homelessness
307.44	F51.11	Hypersomnolence disorder
300.7	F45.21	Illness anxiety disorder
V62.5	Z65.1	Imprisonment or other incarceration
V60.1	Z59.1	Inadequate housing
292.89		Inhalant-induced anxiety disorder
	F18.180	With mild use disorder
	F18.280	With moderate or severe use disorder
	F18.980	Without use disorder
292.84		Inhalant-induced depressive disorder
	F18.14	With mild use disorder
	F18.24	With moderate or severe use disorder
	F18.94	Without use disorder
292.82		Inhalant-induced major neurocognitive disorder
	F18.17	With mild use disorder
	F18.27	With moderate or severe use disorder
	F18.97	Without use disorder
292.89		Inhalant-induced mild neurocognitive disorder
	F18.188	With mild use disorder
	F18.288	With moderate or severe use disorder
	F18.988	Without use disorder
292.9		Inhalant-induced psychotic disorder
	F18.159	With mild use disorder
	F18.259	With moderate or severe use disorder
	F18.959	Without use disorder
292.89		Inhalant intoxication
	F18.129	With mild use disorder
	F18.229	With moderate or severe use disorder
	F18.929	Without use disorder
292.81		Inhalant intoxication delirium
	F18.121	With mild use disorder

	F18.221	With moderate or severe use disorder
	F18.921	Without use disorder
		Inhalant use disorder
305.90	F18.10	Mild
304.60	F18.20	Moderate
304.60	F18.20	Severe
307.42	F51.01	Insomnia disorder
V60.2	Z59.7	Insufficient social insurance or welfare support
		Intellectual disability (intellectual developmental disorder)
317	F70	Mild
318.0	F71	Moderate
318.1	F72	Severe
318.2	F73	Profound
312.34	F63.81	Intermittent explosive disorder
312.32	F63.2	Kleptomania
V60.2	Z59.4	Lack of adequate food or safe drinking water
315.32	F80.2	Language disorder
V60.2	Z59.6	Low income
		Major depressive disorder, Recurrent episode
296.36	F33.42	In full remission
296.35	F33.41	In partial remission
296.31	F33.0	Mild
296.32	F33.1	Moderate
296.33	F33.2	Severe
296.34	F33.3	With psychotic features
296.30	F33.9	Unspecified
		Major depressive disorder, Single episode
296.26	F32.5	In full remission
296.25	F32.4	In partial remission
296.21	F32.0	Mild
296.22	F32.1	Moderate
296.23	F32.2	Severe
296.24	F32.3	With psychotic features
296.20	F32.9	Unspecifed
331.9	G31.9	Major frontotemporal neurocognitive disorder, Possible
		Major frontotemporal neurocognitive disorder, Probable (*code first* 331.19 [G31.09] frontotemporal disease)
294.11	F02.81	With behavioral disturbance
294.10	F02.80	Without behavioral disturbance
331.9	G31.9	Major neurocognitive disorder due to Alzheimer's disease, Possible
		Major neurocognitive disorder due to Alzheimer's disease, Probable (*code first* 331.0 [G30.9] Alzheimer's disease)
294.11	F02.81	With behavioral disturbance
294.10	F02.80	Without behavioral disturbance
		Major neurocognitive disorder due to another medical condition

294.11	F02.81	With behavioral disturbance
294.10	F02.80	Without behavioral disturbance
		Major neurocognitive disorder due to HIV infection (*code first* 042 [B20] HIV infection)
294.11	F02.81	With behavioral disturbance
294.10	F02.80	Without behavioral disturbance
		Major neurocognitive disorder due to Huntington's disease (*code first* 333.4 [G10] Huntington's disease)
294.11	F02.81	With behavioral disturbance
294.10	F02.80	Without behavioral disturbance
331.9	G31.9	Major neurocognitive disorder with Lewy bodies, Possible
		Major neurocognitive disorder with Lewy bodies, Probable (*code first* 331.82 [G31.83] Lewy body disease)
294.11	F02.81	With behavioral disturbance
294.10	F02.80	Without behavioral disturbance
		Major neurocognitive disorder due to multiple etiologies
294.11	F02.81	With behavioral disturbance
294.10	F02.80	Without behavioral disturbance
331.9	G31.9	Major neurocognitive disorder due to Parkinson's disease, Possible
		Major neurocognitive disorder due to Parkinson's disease, Probable (*code first* 332.0 [G20] Parkinson's disease)
294.11	F02.81	With behavioral disturbance
294.10	F02.80	Without behavioral disturbance
		Major neurocognitive disorder due to prion disease (*code first* 046.79 [A81.9] prion disease)
294.11	F02.81	With behavioral disturbance
294.10	F02.80	Without behavioral disturbance
		Major neurocognitive disorder due to traumatic brain injury (*code first* 907.0 late effect of intracranial injury without skull fracture [S06.2X9S diffuse traumatic brain injury with loss of consciousness of unspecified duration, sequela])
294.11	F02.81	With behavioral disturbance
294.10	F02.80	Without behavioral disturbance
331.9	G31.9	Major vascular neurocognitive disorder, Possible
		Major vascular neurocognitive disorder, Probable
290.40	F01.51	With behavioral disturbance
290.40	F01.50	Without behavioral disturbance
302.71	F52.0	Male hypoactive sexual desire disorder
V65.2	Z76.5	Malingering
333.99	G25.71	Medication-induced acute akathisia
333.72	G24.02	Medication-induced acute dystonia
292.81		Medication-induced delirium *(for ICD-10-CM codes, see specific substances)*
333.1	G25.1	Medication-induced postural tremor
331.83	G31.84	Mild frontotemporal neurocognitive disorder
331.83	G31.84	Mild neurocognitive disorder due to Alzheimer's disease

331.83	G31.84	Mild neurocognitive disorder due to another medical condition
331.83	G31.84	Mild neurocognitive disorder due to HIV infection
331.83	G31.84	Mild neurocognitive disorder due to Huntington's disease
331.83	G31.84	Mild neurocognitive disorder due to multiple etiologies
331.83	G31.84	Mild neurocognitive disorder due to Parkinson's disease
331.83	G31.84	Mild neurocognitive disorder due to prion disease
331.83	G31.84	Mild neurocognitive disorder due to traumatic brain injury
331.83	G31.84	Mild neurocognitive disorder with Lewy bodies
331.83	G31.84	Mild vascular neurocognitive disorder
301.81	F60.81	Narcissistic personality disorder
		Narcolepsy
347.00	G47.419	Autosomal dominant cerebellar ataxia, deafness, and narcolepsy
347.00	G47.419	Autosomal dominant narcolepsy, obesity, and type 2 diabetes
347.10	G47.429	Narcolepsy secondary to another medical condition
347.01	G47.411	Narcolepsy with cataplexy but without hypocretin deficiency
347.00	G47.419	Narcolepsy without cataplexy but with hypocretin deficiency
332.1	G21.11	Neuroleptic-induced parkinsonism
333.92	G21.0	Neuroleptic malignant syndrome
307.47	F51.5	Nightmare disorder
V15.81	Z91.19	Nonadherence to medical treatment
		Non–rapid eye movement sleep arousal disorders
307.46	F51.4	Sleep terror type
307.46	F51.3	Sleepwalking type
300.3	F42	Obsessive-compulsive disorder
301.4	F60.5	Obsessive-compulsive personality disorder
294.8	F06.8	Obsessive-compulsive and related disorder due to another medical condition
327.23	G47.33	Obstructive sleep apnea hypopnea
292.89		Opioid-induced anxiety disorder
	F11.188	With mild use disorder
	F11.288	With moderate or severe use disorder
	F11.988	Without use disorder
	F11.921	Opioid-induced delirium
292.84		Opioid-induced depressive disorder
	F11.14	With mild use disorder
	F11.24	With moderate or severe use disorder
	F11.94	Without use disorder
292.89		Opioid-induced sexual dysfunction
	F11.181	With mild use disorder
	F11.281	With moderate or severe use disorder
	F11.981	Without use disorder
292.85		Opioid-induced sleep disorder

	F11.182	With mild use disorder
	F11.282	With moderate or severe use disorder
	F11.982	Without use disorder
292.89		Opioid intoxication
		Opioid intoxication, With perceptual disturbances
	F11.122	With mild use disorder
	F11.222	With moderate or severe use disorder
	F11.922	Without use disorder
		Opioid intoxication, Without perceptual disturbances
	F11.129	With mild use disorder
	F11.229	With moderate or severe use disorder
	F11.929	Without use disorder
292.81		Opioid intoxication delirium
	F11.121	With mild use disorder
	F11.221	With moderate or severe use disorder
	F11.921	Without use disorder
		Opioid use disorder
305.50	F11.10	Mild
304.00	F11.20	Moderate
304.00	F11.20	Severe
292.0	F11.23	Opioid withdrawal
292.0	F11.23	Opioid withdrawal delirium
313.81	F91.3	Oppositional defiant disorder
		Other adverse effect of medication
995.20	T50.905A	Initial encounter
995.20	T50.905S	Sequelae
995.20	T50.905D	Subsequent encounter
		Other circumstances related to adult abuse by nonspouse or nonpartner
V62.83	Z69.82	Encounter for mental health services for perpetrator of nonspousal adult abuse
V65.49	Z69.81	Encounter for mental health services for victim of nonspousal adult abuse
		Other circumstances related to child neglect
V62.83	Z69.021	Encounter for mental health services for perpetrator of nonparental child neglect
V61.22	Z69.011	Encounter for mental health services for perpetrator of parental child neglect
V61.21	Z69.010	Encounter for mental health services for victim of child neglect by parent
V61.21	Z69.020	Encounter for mental health services for victim of nonparental child neglect
V15.42	Z62.812	Personal history (past history) of neglect in childhood
		Other circumstances related to child physical abuse
V62.83	Z69.021	Encounter for mental health services for perpetrator of nonparental child abuse
V61.22	Z69.011	Encounter for mental health services for perpetrator of

		parental child abuse
V61.21	Z69.010	Encounter for mental health services for victim of child abuse by parent
V61.21	Z69.020	Encounter for mental health services for victim of nonparental child abuse
V15.41	Z62.810	Personal history (past history) of physical abuse in childhood
		Other circumstances related to child psychological abuse
V62.83	Z69.021	Encounter for mental health services for perpetrator of nonparental child psychological abuse
V61.22	Z69.011	Encounter for mental health services for perpetrator of parental child psychological abuse
V61.21	Z69.010	Encounter for mental health services for victim of child psychological abuse by parent
V61.21	Z69.020	Encounter for mental health services for victim of nonparental child psychological abuse
V15.42	Z62.811	Personal history (past history) of psychological abuse in childhood
		Other circumstances related to child sexual abuse
V62.83	Z69.021	Encounter for mental health services for perpetrator of nonparental child sexual abuse
V61.22	Z69.011	Encounter for mental health services for perpetrator of parental child sexual abuse
V61.21	Z69.010	Encounter for mental health services for victim of child sexual abuse by parent
V61.21	Z69.020	Encounter for mental health services for victim of nonparental child sexual abuse
V15.41	Z62.810	Personal history (past history) of sexual abuse in childhood
		Other circumstances related to spouse or partner abuse, Psychological
V61.12	Z69.12	Encounter for mental health services for perpetrator of spouse or partner psychological abuse
V61.11	Z69.11	Encounter for mental health services for victim of spouse or partner psychological abuse
V15.42	Z91.411	Personal history (past history) of spouse or partner psychological abuse
		Other circumstances related to spouse or partner neglect
V61.12	Z69.12	Encounter for mental health services for perpetrator of spouse or partner neglect
V61.11	Z69.11	Encounter for mental health services for victim of spouse or partner neglect
V15.42	Z91.412	Personal history (past history) of spouse or partner neglect
		Other circumstances related to spouse or partner violence, Physical
V61.12	Z69.12	Encounter for mental health services for perpetrator of spouse or partner violence, Physical
V61.11	Z69.11	Encounter for mental health services for victim of spouse or partner violence, Physical

V15.41	Z91.410	Personal history (past history) of spouse or partner violence, Physical
		Other circumstances related to spouse or partner violence, Sexual
V61.12	Z69.12	Encounter for mental health services for perpetrator of spouse or partner violence, Sexual
V61.11	Z69.81	Encounter for mental health services for victim of spouse or partner violence, Sexual
V15.41	Z91.410	Personal history (past history) of spouse or partner violence, Sexual
V65.40	Z71.9	Other counseling or consultation
292.89		Other hallucinogen–induced anxiety disorder
	F16.180	With mild use disorder
	F16.280	With moderate or severe use disorder
	F16.980	Without use disorder
292.84		Other hallucinogen–induced bipolar and related disorder
	F16.14	With mild use disorder
	F16.24	With moderate or severe use disorder
	F16.94	Without use disorder
292.84		Other hallucinogen–induced depressive disorder
	F16.14	With mild use disorder
	F16.24	With moderate or severe use disorder
	F16.94	Without use disorder
292.9		Other hallucinogen–induced psychotic disorder
	F16.159	With mild use disorder
	F16.259	With moderate or severe use disorder
	F16.959	Without use disorder
292.89		Other hallucinogen intoxication
	F16.129	With mild use disorder
	F16.229	With moderate or severe use disorder
	F16.929	Without use disorder
292.81		Other hallucinogen intoxication delirium
	F16.121	With mild use disorder
	F16.221	With moderate or severe use disorder
	F16.921	Without use disorder
		Other hallucinogen use disorder
305.30	F16.10	Mild
304.50	F16.20	Moderate
304.50	F16.20	Severe
333.99	G25.79	Other medication-induced movement disorder
332.1	G21.19	Other medication-induced parkinsonism
V15.49	Z91.49	Other personal history of psychological trauma
V15.89	Z91.89	Other personal risk factors
V62.29	Z56.9	Other problem related to employment
V62.89	Z65.8	Other problem related to psychosocial circumstances
300.09	F41.8	Other specified anxiety disorder
314.01	F90.8	Other specified attention-deficit/hyperactivity disorder

296.89	F31.89	Other specified bipolar and related disorder
780.09	R41.0	Other specified delirium
311	F32.8	Other specified depressive disorder
312.89	F91.8	Other specified disruptive, impulse-control, and conduct disorder
300.15	F44.89	Other specified dissociative disorder
		Other specified elimination disorder
787.60	R15.9	With fecal symptoms
788.39	N39.498	With urinary symptoms
307.59	F50.8	Other specified feeding or eating disorder
302.6	F64.8	Other specified gender dysphoria
780.54	G47.19	Other specified hypersomnolence disorder
780.52	G47.09	Other specified insomnia disorder
300.9	F99	Other specified mental disorder
294.8	F06.8	Other specified mental disorder due to another medical condition
315.8	F88	Other specified neurodevelopmental disorder
300.3	F42	Other specified obsessive-compulsive and related disorder
302.89	F65.89	Other specified paraphilic disorder
301.89	F60.89	Other specified personality disorder
298.8	F28	Other specified schizophrenia spectrum and other psychotic disorder
302.79	F52.8	Other specified sexual dysfunction
780.59	G47.8	Other specified sleep-wake disorder
300.89	F45.8	Other specified somatic symptom and related disorder
307.20	F95.8	Other specified tic disorder
309.89	F43.8	Other specified trauma- and stressor-related disorder
292.89		Other (or unknown) substance–induced anxiety disorder
	F19.180	With mild use disorder
	F19.280	With moderate or severe use disorder
	F19.980	Without use disorder
292.84		Other (or unknown) substance–induced bipolar and related disorder
	F19.14	With mild use disorder
	F19.24	With moderate or severe use disorder
	F19.94	Without use disorder
	F19.921	Other (or unknown) substance–induced delirium
292.84		Other (or unknown) substance–induced depressive disorder
	F19.14	With mild use disorder
	F19.24	With moderate or severe use disorder
	F19.94	Without use disorder
292.82		Other (or unknown) substance–induced major neurocognitive disorder
	F19.17	With mild use disorder
	F19.27	With moderate or severe use disorder
	F19.97	Without use disorder

292.89		Other (or unknown) substance-induced mild neurocognitive disorder
	F19.188	With mild use disorder
	F19.288	With moderate or severe use disorder
	F19.988	Without use disorder
292.89		Other (or unknown) substance-induced obsessive-compulsive and related disorder
	F19.188	With mild use disorder
	F19.288	With moderate or severe use disorder
	F19.988	Without use disorder
292.9		Other (or unknown) substance-induced psychotic disorder
	F19.159	With mild use disorder
	F19.259	With moderate or severe use disorder
	F19.959	Without use disorder
292.89		Other (or unknown) substance-induced sexual dysfunction
	F19.181	With mild use disorder
	F19.281	With moderate or severe use disorder
	F19.981	Without use disorder
292.85		Other (or unknown) substance-induced sleep disorder
	F19.182	With mild use disorder
	F19.282	With moderate or severe use disorder
	F19.982	Without use disorder
292.89		Other (or unknown) substance intoxication
	F19.129	With mild use disorder
	F19.229	With moderate or severe use disorder
	F19.929	Without use disorder
292.81		Other (or unknown) substance intoxication delirium
	F19.121	With mild use disorder
	F19.221	With moderate or severe use disorder
	F19.921	Without use disorder
		Other (or unknown) substance use disorder
305.90	F19.10	Mild
304.90	F19.20	Moderate
304.90	F19.20	Severe
292.0	F19.239	Other (or unknown) substance withdrawal
292.0	F19.231	Other (or unknown) substance withdrawal delirium
		Other or unspecified stimulant use disorder
305.70	F15.10	Mild
304.40	F15.20	Moderate
304.40	F15.20	Severe
278.00	E66.9	Overweight or obesity
		Panic attack specifier
300.01	F41.0	Panic disorder
301.0	F60.0	Paranoid personality disorder
V61.20	Z62.820	Parent-child relational problem
302.2	F65.4	Pedophilic disorder
307.22	F95.1	Persistent (chronic) motor or vocal tic disorder

300.4	F34.1	Persistent depressive disorder (dysthymia)
V62.22	Z91.82	Personal history of military deployment
V15.59	Z91.5	Personal history of self-harm
310.1	F07.0	Personality change due to another medical condition
V62.89	Z60.0	Phase of life problem
292.89		Phencyclidine-induced anxiety disorder
	F16.180	With mild use disorder
	F16.280	With moderate or severe use disorder
	F16.980	Without use disorder
292.84		Phencyclidine-induced bipolar and related disorder
	F16.14	With mild use disorder
	F16.24	With moderate or severe use disorder
	F16.94	Without use disorder
292.84		Phencyclidine-induced depressive disorder
	F16.14	With mild use disorder
	F16.24	With moderate or severe use disorder
	F16.94	Without use disorder
292.9		Phencyclidine-induced psychotic disorder
	F16.159	With mild use disorder
	F16.259	With moderate or severe use disorder
	F16.959	Without use disorder
292.89		Phencyclidine intoxication
	F16.129	With mild use disorder
	F16.229	With moderate or severe use disorder
	F16.929	Without use disorder
292.81		Phencyclidine intoxication delirium
	F16.121	With mild use disorder
	F16.221	With moderate or severe use disorder
	F16.921	Without use disorder
		Phencyclidine use disorder
305.90	F16.10	Mild
304.60	F16.20	Moderate
304.60	F16.20	Severe
307.52		Pica
	F50.8	In adults
	F98.3	In children
309.81	F43.10	Posttraumatic stress disorder
302.75	F52.4	Premature (early) ejaculation
625.4	N94.3	Premenstrual dysphoric disorder
V62.21	Z56.82	Problem related to current military deployment status
V69.9	Z72.9	Problem related to lifestyle
V60.3	Z60.2	Problem related to living alone
V60.6	Z59.3	Problem related to living in a residential institution
V61.5	Z64.1	Problems related to multiparity
V62.5	Z65.3	Problems related to other legal circumstances
V62.5	Z65.2	Problems related to release from prison
V61.7	Z64.0	Problems related to unwanted pregnancy

307.21	F95.0	Provisional tic disorder
316	F54	Psychological factors affecting other medical conditions
		Psychotic disorder due to another medical condition
293.81	F06.2	With delusions
293.82	F06.0	With hallucinations
312.33	F63.1	Pyromania
327.42	G47.52	Rapid eye movement sleep behavior disorder
313.89	F94.1	Reactive attachment disorder
V61.10	Z63.0	Relationship distress with spouse or intimate partner
V62.89	Z65.8	Religious or spiritual problem
333.94	G25.81	Restless legs syndrome
307.53	F98.21	Rumination disorder
		Schizoaffective disorder
295.70	F25.0	Bipolar type
295.70	F25.1	Depressive type
301.20	F60.1	Schizoid personality disorder
295.90	F20.9	Schizophrenia
295.40	F20.81	Schizophreniform disorder
301.22	F21	Schizotypal personality disorder
292.89		Sedative-, hypnotic-, or anxiolytic-induced anxiety disorder
	F13.180	With mild use disorder
	F13.280	With moderate or severe use disorder
	F13.980	Without use disorder
292.84		Sedative-, hypnotic-, or anxiolytic-induced bipolar and related disorder
	F13.14	With mild use disorder
	F13.24	With moderate or severe use disorder
	F13.94	Without use disorder
	F13.921	Sedative-, hypnotic-, or anxiolytic-induced delirium
292.84		Sedative-, hypnotic-, or anxiolytic-induced depressive disorder
	F13.14	With mild use disorder
	F13.24	With moderate or severe use disorder
	F13.94	Without use disorder
292.82		Sedative-, hypnotic-, or anxiolytic-induced major neurocognitive disorder
	F13.27	With moderate or severe use disorder
	F13.97	Without use disorder
292.89		Sedative-, hypnotic-, or anxiolytic-induced mild neurocognitive disorder
	F13.288	With moderate or severe use disorder
	F13.988	Without use disorder
292.9		Sedative-, hypnotic-, or anxiolytic-induced psychotic disorder
	F13.159	With mild use disorder
	F13.259	With moderate or severe use disorder

	F13.959	Without use disorder
292.89		Sedative-, hypnotic-, or anxiolytic-induced sexual dysfunction
	F13.181	With mild use disorder
	F13.281	With moderate or severe use disorder
	F13.981	Without use disorder
292.85		Sedative-, hypnotic-, or anxiolytic-induced sleep disorder
	F13.182	With mild use disorder
	F13.282	With moderate or severe use disorder
	F13.982	Without use disorder
292.89		Sedative, hypnotic, or anxiolytic intoxication
	F13.129	With mild use disorder
	F13.229	With moderate or severe use disorder
	F13.929	Without use disorder
292.81		Sedative, hypnotic, or anxiolytic intoxication delirium
	F13.121	With mild use disorder
	F13.221	With moderate or severe use disorder
	F13.921	Without use disorder
		Sedative, hypnotic, or anxiolytic use disorder
305.40	F13.10	Mild
304.10	F13.20	Moderate
304.10	F13.20	Severe
292.0		Sedative, hypnotic, or anxiolytic withdrawal
	F13.232	With perceptual disturbances
	F13.239	Without perceptual disturbances
292.0	F13.231	Sedative, hypnotic, or anxiolytic withdrawal delirium
313.23	F94.0	Selective mutism
309.21	F93.0	Separation anxiety disorder
V65.49	Z70.9	Sex counseling
302.83	F65.51	Sexual masochism disorder
302.84	F65.52	Sexual sadism disorder
V61.8	Z62.891	Sibling relational problem
		Sleep-related hypoventilation
327.26	G47.36	Comorbid sleep-related hypoventilation
327.25	G47.35	Congenital central alveolar hypoventilation
327.24	G47.34	Idiopathic hypoventilation
300.23	F40.10	Social anxiety disorder (social phobia)
V62.4	Z60.4	Social exclusion or rejection
315.39	F80.89	Social (pragmatic) communication disorder
300.82	F45.1	Somatic symptom disorder
		Specific learning disorder
315.1	F81.2	With impairment in mathematics
315.00	F81.0	With impairment in reading
315.2	F81.81	With impairment in written expression
		Specific phobia
300.29	F40.218	Animal
300.29		Blood-injection-injury

	F40.230	Fear of blood
	F40.231	Fear of injections and transfusions
	F40.233	Fear of injury
	F40.232	Fear of other medical care
300.29	F40.228	Natural environment
300.29	F40.298	Other
300.29	F40.248	Situational
315.39	F80.0	Speech sound disorder
		Spouse or partner abuse, Psychological, Confirmed
995.82	T74.31XA	Initial encounter
995.82	T74.31XD	Subsequent encounter
		Spouse or partner abuse, Psychological, Suspected
995.82	T76.31XA	Initial encounter
995.82	T76.31XD	Subsequent encounter
		Spouse or partner neglect, Confirmed
995.85	T74.01XA	Initial encounter
995.85	T74.01XD	Subsequent encounter
		Spouse or partner neglect, Suspected
995.85	T76.01XA	Initial encounter
995.85	T76.01XD	Subsequent encounter
		Spouse or partner violence, Physical, Confirmed
995.81	T74.11XA	Initial encounter
995.81	T74.11XD	Subsequent encounter
		Spouse or partner violence, Physical, Suspected
995.81	T76.11XA	Initial encounter
995.81	T76.11XD	Subsequent encounter
		Spouse or partner violence, Sexual, Confirmed
995.83	T74.21XA	Initial encounter
995.83	T74.21XD	Subsequent encounter
		Spouse or partner violence, Sexual, Suspected
995.83	T76.21XA	Initial encounter
995.83	T76.21XD	Subsequent encounter
307.3	F98.4	Stereotypic movement disorder
		Stimulant intoxication *(see amphetamine or cocaine intoxication for specific codes)*
		Stimulant use disorder *(see amphetamine or cocaine use disorder for specific codes)*
		Stimulant withdrawal *(see amphetamine or cocaine withdrawal for specific codes)*
		Substance intoxication delirium *(see specific substances for codes)*
		Substance withdrawal delirium *(see specific substances for codes)*
		Substance/medication-induced anxiety disorder *(see specific substances for codes)*
		Substance/medication-induced bipolar and related disorder *(see specific substances for codes)*

		Substance/medication-induced depressive disorder *(see specific substances for codes)*
		Substance/medication-induced major or mild neurocognitive disorder *(see specific substances for codes)*
		Substance/medication-induced obsessive-compulsive and related disorder *(see specific substances for codes)*
		Substance/medication-induced psychotic disorder *(see specific substances for codes)*
		Substance/medication-induced sexual dysfunction *(see specific substances for codes)*
		Substance/medication-induced sleep disorder *(see specific substances for codes)*
333.99	G25.71	Tardive akathisia
333.85	G24.01	Tardive dyskinesia
333.72	G24.09	Tardive dystonia
V62.4	Z60.5	Target of (perceived) adverse discrimination or persecution
292.85		Tobacco-induced sleep disorder
	F17.208	With moderate or severe use disorder
		Tobacco use disorder
305.1	Z72.0	Mild
305.1	F17.200	Moderate
305.1	F17.200	Severe
292.0	F17.203	Tobacco withdrawal
307.23	F95.2	Tourette's disorder
302.3	F65.1	Transvestic disorder
312.39	F63.3	Trichotillomania (hair-pulling disorder)
V63.9	Z75.3	Unavailability or inaccessibility of health care facilities
V63.8	Z75.4	Unavailability or inaccessibility of other helping agencies
V62.82	Z63.4	Uncomplicated bereavement
291.9	F10.99	Unspecified alcohol-related disorder
300.00	F41.9	Unspecified anxiety disorder
314.01	F90.9	Unspecified attention-deficit/hyperactivity disorder
296.80	F31.9	Unspecified bipolar and related disorder
292.9	F15.99	Unspecified caffeine-related disorder
292.9	F12.99	Unspecified cannabis-related disorder
293.89	F06.1	Unspecified catatonia (*code first* 781.99 [R29.818] other symptoms involving nervous and musculoskeletal systems)
307.9	F80.9	Unspecified communication disorder
780.09	R41.0	Unspecified delirium
311	F32.9	Unspecified depressive disorder
312.9	F91.9	Unspecified disruptive, impulse-control, and conduct disorder
300.15	F44.9	Unspecified dissociative disorder
		Unspecified elimination disorder
787.60	R15.9	With fecal symptoms
788.30	R32	With urinary symptoms
307.50	F50.9	Unspecified feeding or eating disorder

302.6	F64.9	Unspecified gender dysphoria
292.9	F16.99	Unspecified hallucinogen-related disorder
V60.9	Z59.9	Unspecified housing or economic problem
780.54	G47.10	Unspecified hypersomnolence disorder
292.9	F18.99	Unspecified inhalant-related disorder
780.52	G47.00	Unspecified insomnia disorder
319	F79	Unspecified intellectual disability (intellectual developmental disorder)
300.9	F99	Unspecified mental disorder
294.9	F09	Unspecified mental disorder due to another medical condition
799.59	R41.9	Unspecified neurocognitive disorder
315.9	F89	Unspecified neurodevelopmental disorder
300.3	F42	Unspecified obsessive-compulsive and related disorder
292.9	F11.99	Unspecified opioid-related disorder
292.9	F19.99	Unspecified other (or unknown) substance–related disorder
302.9	F65.9	Unspecified paraphilic disorder
301.9	F60.9	Unspecified personality disorder
292.9	F16.99	Unspecified phencyclidine-related disorder
V62.9	Z60.9	Unspecified problem related to social environment
V62.9	Z65.9	Unspecified problem related to unspecified psychosocial circumstances
298.9	F29	Unspecified schizophrenia spectrum and other psychotic disorder
292.9	F13.99	Unspecified sedative-, hypnotic-, or anxiolytic-related disorder
302.70	F52.9	Unspecified sexual dysfunction
780.59	G47.9	Unspecified sleep-wake disorder
300.82	F45.9	Unspecified somatic symptom and related disorder
292.9		Unspecified stimulant-related disorder
	F15.99	Unspecified amphetamine or other stimulant-related disorder
	F14.99	Unspecified cocaine-related disorder
307.20	F95.9	Unspecified tic disorder
292.9	F17.209	Unspecified tobacco-related disorder
309.9	F43.9	Unspecified trauma- and stressor-related disorder
V61.8	Z62.29	Upbringing away from parents
V62.89	Z65.4	Victim of crime
V62.89	Z65.4	Victim of terrorism or torture
302.82	F65.3	Voyeuristic disorder
V40.31	Z91.83	Wandering associated with a mental disorder

We claim:

1. A sublingual formulation in the form of a lyophilized pharmaceutical composition that provides sublingual adsorption of riluzole comprising a pharmaceutically effective amount of riluzole or a pharmaceutically acceptable salt, solvate, anomer, enantiomer, hydrate or prodrug thereof, said formulation further comprising a tablet binder, a sugar alcohol selected from the group consisting of mannitol and sorbitol as a bulking agent, and docusate sodium as a solubilizing agent.

2. The sublingual formulation of claim 1 further comprising a flavoring agent.

3. The sublingual formulation of claim 1 further comprising a sweetener.

4. The sublingual formulation of claim 1 wherein the formulation riluzole comprises a riluzole prodrug.

5. The sublingual formulation of claim 3 said sweetener comprises sucralose.

6. A sublingual formulation comprising an effective amount of riluzole or a pharmaceutically acceptable salt, solvate, anomer, enantiomer, hydrate or prodrug thereof, said formulation further comprising a tablet binder, a bulking agent, and a solubilizing agent, said sublingual formulation providing an AUC at a dose of 35mg of from 110% to 180% of the AUC of an oral tablet formulation at a dose of 50mg, said AUC being measured at 0.5 hours, 1 hour or 2 hours after administration.

7. Use of the sublingual formulation of any of claims 1 to 6 in the manufacture of a medicament for the treatment of a neuropsychiatric disorder or symptom.

8. The use of claim 7 wherein the neuropsychiatric disorder is anxiety disorders, mood disorders, neurodegenerative disorders, pain disorders, ALS, cognitive disorders, Huntington's disease, Parkinson's disease, supranuclear palsy, frontotemporal dementia, frontotemporal lobar degeneration, delirium, Alzheimer's disease, mild cognitive impairment, mild cognitive impairment due to Alzheimer's disease, ataxia, hereditary ataxia, depression, mania, attention deficit disorders, drug addiction, dementia, agitation, apathy, anxiety, psychoses, post-traumatic stress disorders,

irritability, and disinhibition, learning disorders, memory loss, mental retardation, Rett Syndrome, tinnitus, personality disorders, bipolar disorders, obsessive-compulsive disorders, eating disorders, conduct disorders in DSM-5 and or combinations thereof.

9. The use of claim 7 wherein the neuropsychiatric symptom is anxiety, depression, stress, fatigue, feelings of panic, fear, uneasiness, problems in sleeping, cold or sweaty hands and/or feet, mood liability, mania, impaired concentration or attention, cognitive problems, obsessions, compulsions, repetitive behaviors, aggression, social phobias or impairments, stage fright, shortness of breath, heart palpitations, an inability to be still and calm, dry mouth, numbness or tingling in the hands or feet, nausea, muscle tension, dizziness apathy, elation, disinhibition, irritability, wandering, irritable bowel, belly pain, belly discomfort, diarrhea, change in bowel habits, abdominal bloating, abdominal gas, abdominal bloating, constipation or combinations thereof.

10. The use of claim 7 which produces a rapid therapeutic onset of action within about 10 minutes after administration.

11. The use of claim 7 which is associated with minimal or no oral numbness, or said oral numbness dissipates in less than 30 minutes.

12. The use of claim 7 wherein the liver function abnormalities side effects of riluzole are attenuated relative to those which are associated with the orally administered riluzole.

13. The use of claim 7 wherein the sublingual formulation is to be dosed at or below about 50 mg/day.

14. The use of claim 7 wherein the sublingual formulation is to be dosed at or below about 35 mg/day.

15. The use sublingual formulation of any of claims 1 to 6 in the manufacture of a medicament for the treatment of oral pain.

16. The use of claim 15 wherein a treatment area of oral pain is throughout an oral cavity including the upper surface of the tongue, lips, buccal area, back of throat, entire oral cavity or combinations thereof.

17. The use of claim 15 wherein the oral pain for treatment is caused by infection, inflammation, burn, cut, toothache, sore gums, canker sores, braces, minor dental procedures, denture irritation, oral surgery, neurologic disorders, disorders of the mucosa, oral ulcers, chemotherapy agents or combinations thereof.