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(57) Abstract

Methods for the prevention, treatment, or management of apnea, apnea disorders, bulimia nervosa, irritable bowel syndrome, urinary incontinence, bradycardia, bradyarrhythmia, syncope, other disorders, or symptoms thereof using (–) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

USE OF OPTICALLY PURE (-) NORCISAPRIDE IN THE TREATMENT OF APNEA, BULIMIA, AND OTHER DISORDERS

1. FIELD OF THE INVENTION

The invention relates to methods of prevention, treatment, or management, of apnea, apnea disorders, bulimia, other disorders, or symptoms thereof.

2. BACKGROUND OF THE INVENTION

Apnea is defined in *Stedman's Medical Dictionary*, 26th Edition, Williams and Wilkins (1995), as the absence of breathing. There are a number of disorders associated with apnea, which are characterized by interrupted breathing in which a person stops breathing long enough to decrease the amount of oxygen and increase the amount of carbon dioxide in the blood and brain. Each type of apnea involves the absence of airflow at the nose or the mouth, typically for at least 10 seconds.

Various apnea disorders exist, including: central apnea, which results from medullary depression and inhibits respiratory movement; deglutition apnea, which is the inhibition of breathing during swallowing; obstructive or peripheral apnea, which is either a result of obstruction of air passages or inadequate respiratory muscle activity; sleep apnea, which is central and/or obstructive apnea during sleep; and sleep induced apnea, which results from failure of the respiratory center to stimulate adequate respiration during sleep.

Obstructive apneas usually occur in obese men and are much less common in women. The obesity, perhaps in combination with aging body tissues and other factors, leads to narrowing of the upper airways. Tobacco smoking, excessive alcohol use, and lung diseases, such as emphysema, increase the risk of developing obstructive apneas.

For those suffering from sleep apnea, quitting smoking, avoiding excessive use of alcohol, and losing weight are commonly the first behavioral steps for treating the disorder. In order to inhibit or avoid apnea, heavy snorers and people who often choke in their sleep should not take tranquilizers, sleep aids, or other sedating drugs.

Sleep apnea is one of the most common forms of apnea. Rarely, a person who has severe sleep apnea needs a tracheostomy, a surgical procedure that creates a permanent opening into the windpipe through the neck. Sometimes other surgical procedures are performed to widen the upper airway and alleviate the problem. However, such extreme measures are seldom needed and never desired.

Apnea can also be treated by non-invasive means by administering to a patient a therapeutic agent. U.S. Patent No. 5,075,290 discloses the medical treatment of obstructive sleep apnea and associated symptoms, such as snoring, by the administration of the nucleoside uptake blocker, dipyridamole, during sleep. U.S. Patent Nos. 5,502,067 and 5,407,953 disclose a method of treating sleep apnea, hyponea and snoring in a human patient by administering a pilocarpine compound. U.S. Patent No. 5,422,374 discloses a method of treating sleep apnea by the administration of ubidecarenone to a patient. U.S. Patent No. 5,356,934 discloses a method of employing (R)-fluoxetine to treat sleep apnea.

Bulimia nervosa, or bulimia, is a disorder described in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, American Psychiatric Association, 1996 ("DSM-IV"), which is characterized in part by recurrent episodes of binge eating during which the patient experiences a loss of control resulting in over eating and self-induced vomiting. The disorder primarily afflicts females of upper and middle socioeconomic status, especially college-age women.

Currently, two approaches for treating bulimia are used: cognitive-behavioral and pharmacological. Traditional pharmacological treatments involved antidepressants. More recent research into the fundamental causes of bulimia, however, has suggested other pharmacological treatments. In particular, some researchers have argued that the pathophysiological characteristics driving the behaviors characteristic of bulimia involve an increase in the basal tone of the vagal nerve, and have suggested that racemic ondansetron may be useful for the treatment of bulimia. Faris, P. L. *et al., Biol. Psychiatry,* 32:462-466 (1992); Dumuis *et al., N.S. Arch. Pharmacol.*, 340:403-410 (1989).

Cisapride, chemically named *cis*-4-amino-5-chloro-N-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide, is a benzamide derivative, the parent compound being metoclopramide. Schapira *et al., Acta Gastroenterolog. Belg.*, LIII:446-457 (1990). Benzamide derivatives have several prominent pharmacological actions due to their effects on neuronal systems modulated by the neurotransmitter serotonin.

Because of their modulation of the serotonin neuronal system in the gastrointestinal tract, many benzamide derivatives are effective antiemetic agents and are commonly used to control vomiting during cancer chemotherapy or radiotherapy. Costall *et al., Neuropharmacology*, 26:1321-1326 (1987). This action is almost certainly the result of an ability to block serotonin at specific sites, particularly type-3 5-hydroxytryptamine

($5\text{-}HT_3$) receptors. Clarke *et al.*, *Trends in Pharmacological Sciences*, 10:385-386 (1989). In theory, chemotherapy and radiation therapy can induce nausea and vomiting by damaging enterochromaffin cells in the gastrointestinal tract. As a result, the neurotransmitter serotonin is released and stimulates both afferent vagal nerve fibers (thus initiating the vomiting reflex) and serotonin receptors in the chemoreceptor trigger zone of the area postrema region of the brain. The anatomical site for this action of the benzamide derivatives, and whether such action is central (CNS), peripheral, or a combination thereof, remains unresolved. Barnes *et al.*, *J. Pharm. Pharmacol.*, 40:586-588 (1988).

Racemic cisapride is used primarily to treat gastroesophageal reflux disease ("GERD"), which is characterized as the backward flow of the stomach contents into the esophagus. Cisapride is commercially available as the racemic mixture of the *cis* diastereomeric enantiomers of cisapride known as PROPULSID®.

The co-administration of racemic cisapride with other therapeutic agents causes inhibitory problems with the metabolism of cisapride by the liver. For example, ketoconazole has a pronounced effect on cisapride kinetics resulting from the inhibition of the metabolic elimination of cisapride and leads to an 8-fold increase of the steady-state plasma levels. *Physician's Desk Reference®*, 52nd Edition, Medical Economics Co., Inc., 1998. Interaction of racemic cisapride and other therapeutic agents can also potentiate cardiovascular side effects, such as cardiotoxicity. This potentiation occurs when other drugs present in the patient's system interfere with the metabolism of cisapride, thereby building up racemic cisapride in the body.

These interactions are a significant drawback to the use of racemic cisapride; in particular, because racemic cisapride is often used before, with or immediately after another therapeutic agent. In addition, administration of racemic cisapride to a human has been found to cause adverse effects such as cardiac arrhythmia, including ventricular tachycardia, ventricular fibrillation, Q_T prolongation, and torsades de pointes, central nervous system ("CNS") effects, increased systolic pressure, interactions with other drugs, diarrhea, abdominal cramping and cardiac depression.

Racemic cisapride is almost completely absorbed after oral administration to humans, but bioavailability of cisapride is only 40-50% due to rapid first-pass metabolism in the liver. Van Peer *et al.*, in *Progress in the Treatment of Gastrointestinal Motility Disorders: The Role of Cisapride,* Proceedings of a Symposium in Frankfurt, Germany, November 1986, *Excerpta Medica*, A.G. Johnson and G Lux Eds., Amsterdam, pp. 23-29

(1988). More than 90% of a dose of racemic cisapride in humans is metabolized mainly by oxidative N-dealkylation of the piperidine nitrogen or by aromatic hydroxylation occurring on either the 4-fluorophenoxy or benzamide rings. Meuldermans *et al.*, *Drug Metab. Dispos.*, 16(3):410-419 (1988); and Meuldermans *et al.*, *Drug Metab. Dispos.*, 16(3):403-409 (1988). Norcisapride, chemically named 4-amino-5-chloro-N-(3-methoxy-4-piperidinyl)-2-methoxybenzamide, is a metabolite of cisapride.

Recently, investigators have reported that the optically pure (-) stereoisomer of the cisapride metabolite norcisapride exhibits many of the useful characteristics, but without certain of the attendant side effects of racemic cisapride. U.S. Patent No. 5,712,293 discloses methods of treating gastroesophageal reflux disease, and other conditions, including emesis, dyspepsia, constipation, gastroparesis, intestinal pseudo-obstruction, and post-operative ileus using (-) norcisapride.

It is desirable to provide safe and effective methods of preventing, treating, or managing apnea, apnea disorders, bulimia nervosa and related disorders, or symptoms thereof, particularly a treatment that allows the patient to undergo other related therapies without adverse effects or drug-drug interactions.

3. SUMMARY OF THE INVENTION

The present invention encompasses the use of the optically pure (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, in preventing, treating, or managing apnea, apnea disorders, bulimia, irritable bowel syndrome, asthma, urinary incontinence, syncope, bradycardia, bradyarrhythmia, or symptoms thereof. It should be understood that the invention encompasses any combination of preventing, treating, or managing each disorder or multiple disorders.

This invention also relates to pharmaceutical compositions adapted for the prevention, treatment, or management of a patient suffering from a vagal nerve mediated disorder or symptoms thereof, which comprises a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

This invention also relates to pharmaceutical compositions adapted for the prevention, treatment, or management of a patient suffering from apnea, apnea disorders, or symptoms thereof, which comprises a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

This invention further relates to pharmaceutical compositions adapted for the prevention, treatment, or management of bulimia, irritable bowel syndrome, asthma, urinary incontinence, bradycardia, bradyarrhythmia, syncope, related disorders, and symptoms thereof in a mammal, which comprises a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate symptoms of said conditions while reducing or avoiding adverse effects associated with administration of racemic cisapride.

The invention also encompasses single unit dosage forms of optically pure (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, which comprise from about 0.5 mg to about 500 mg of active ingredient in a compressed tablet. This dosage form is particularly suitable for the prevention, treatment, or management of apnea, apnea disorders, bulimia, irritable bowel syndrome, asthma, urinary incontinence, bradycardia, bradyarrhythmia, syncope, related disorders, or symptoms thereof.

4. DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses the use of optically pure (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, in preventing, treating, or managing disorders, including, but not limited to, apnea, apnea disorders, bulimia, irritable bowel syndrome, asthma, urinary incontinence, bradycardia, bradyarrhythmia, syncope, and related disorders, or symptoms thereof. Apnea or apnea disorders include, but are not limited to, central apnea, deglutition apnea, obstructive or peripheral apnea, sleep apnea, and sleep induced apnea, or a combination thereof.

The present invention also encompasses the use of optically pure (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, in preventing, treating, or managing apnea, apnea disorders, bulimia, irritable bowel syndrome, asthma, urinary incontinence, bradycardia, bradyarrhythmia, syncope, and related disorders, or symptoms thereof, preferably while reducing or avoiding adverse effects associated with administration of racemic cisapride.

In one embodiment, the present invention relates to a method of preventing, treating, or managing bulimia comprising administering to a patient a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

In another embodiment, the present invention relates to a method of preventing, treating, or managing apnea or apnea disorders comprising administering to a patient a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

In another embodiment, the present invention relates to a method for preventing, treating, or managing conditions mediated by vagal activity in a patient comprising administering a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

The present invention also encompasses a method of preventing, treating, or managing irritable bowel syndrome comprising administering to a patient a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

In another embodiment, the present invention relates to methods of preventing, treating, or managing syncope, and in particular vasovagal syncope and cardiac or carotid sinus syncope, which comprises administering to a patient a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

The present invention further encompasses methods of preventing, treating, or managing bradycardia or bradyarrhythmia, which comprises administering to a patient a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

In another embodiment, the present invention relates to a method of preventing, treating, or managing asthma or asthma symptoms, which comprises administering to a patient a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

The present invention also encompasses a method of preventing, treating, or managing urinary incontinence, which comprises administering to a patient a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

In another embodiment, this invention encompasses single unit dosage forms of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, which comprise from about 0.5 mg to about 500 mg of active ingredient in a compressed tablet. This dosage form is particularly suitable for the prevention, treatment,

or management of apnea, apnea disorders, bulimia, irritable bowel syndrome, asthma, urinary incontinence, bradycardia, bradyarrhythmia, syncope, related disorders, or symptoms thereof.

The vagus nerve is the largest nerve of the cranial nerves. There are two main branches of the vagus nerve, each of which act to provide both motor and sensory functions. The vagus nerves contain efferent fibers, which carry impulses from the nerve's origin in the medulla obligata of the brain to a tissue or visceral organ, and afferent fibers, which carry impulses from the organ back to the brain. It is present in a large portion of the body, extending from the brain stem to the organs of the neck, chest, and abdomen. Vagal stimulation occurs in a number of organs, including the heart, lungs, bronchia, trachea, esophagus, stomach, pancreas, small intestine, large intestine, colon, liver, gall bladder, and portions of the urinary tract.

Without being limited by theory, it is believed that symptoms of bulimia, irritable bowel syndrome, urinary incontinence, bradycardia, bradyarrhythmia, asthma, and syncope, particularly vasovagal syncope and cardiac or carotid sinus syncope, are affected by the basal tone of the vagus, or vagal, nerve.

Without being limited by theory, it is further believed that by blocking 5-HT-induced depolarization in the vagus, or vagal, nerve, (-) norcisapride lessens or inhibits symptoms of these disorders. Therefore, in one embodiment, the present invention relates to the use of optically pure (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, in preventing, treating, or managing bulimia, irritable bowel syndrome, asthma, urinary incontinence, bradycardia, bradyarrhythmia, syncope, and related disorders, or symptoms thereof.

Additionally, the invention includes the use of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, in combination with other therapeutic agents. Examples of other therapeutic agents include, but are not limited to, fluoxetine or the R or S stereoisomer thereof; descarboethoxyloratidine; ondansetron or the R or S stereoisomer thereof, preferably R ondansetron; ubidecarenone; dipyridamole; pilocarpine or the stereoisomers thereof; primidone or the R or S stereoisomer thereof; orphenadrine citrate; and the like, as well as any active metabolites thereof. Administration of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, in combination with these other therapeutic agents for the prevention, treatment, or management of apnea, apnea

disorders, bulimia, irritable bowel syndrome, urinary incontinence, bradycardia, bradyarrhythmia, asthma, syncope, or symptoms thereof in the methods of the present invention, may be made either concurrently or sequentially, *i.e.*, (-) norcisapride and at least one other therapeutic agent may be administered as a combination, concurrently but separately, or by sequential administration. The compositions administered in each of these methods may be concurrent, sequential, or in any combination of concurrent or sequential.

The methods and compositions of this invention also include the benefit of reducing or avoiding adverse effects associated with administration of racemic cisapride. The invention also allows the concurrent or sequential use of antidepressant drugs, such as tricyclic antidepressants, fluoxetine or its R or S stereoisomer, Zoloft®, and the like, and other drugs, such as anti-anxiety drugs.

The term "patient" as used herein refers to mammals, particularly humans.

The methods of the present invention for the prevention, treatment, or management of bulimia are particularly useful in adolescents and young adults. In a preferred embodiment, the method of preventing, treating, or managing bulimia is directed to females from the ages of 13 to 25. It should be recognized that the methods of the present invention can be used to prevent, treat, or manage bulimia in males and females. including children and adults, notwithstanding the preferences mentioned above.

The methods of the present invention for the prevention, treatment, or management of apnea or apnea disorders are particularly useful in obese men. In a preferred embodiment, the methods are directed to the prevention, treatment, or management of obstructive apnea in obese men. It should be recognized that the methods can be used to prevent, treat, or manage apnea or apnea disorders in males and females, including children and adults, notwithstanding the preferences mentioned above.

As used herein, the terms "adverse effects" and "adverse side effects" include, but are not limited to, cardiac arrhythmia, cardiac conduction disturbances, appetite stimulation, weight gain, sedation, gastrointestinal distress, headache, dry mouth, constipation, diarrhea, and drug-drug interactions. See, for example, *Physician's Desk Reference*®, 52nd Edition, Medical Economics Co., Inc., pp. 1308-1309, 1998. The term "cardiac arrhythmia" includes, but is not limited to, ventricular tachyrhythmia, torsades de pointes, Q_T prolongation, and ventricular fibrillation.

The term "racemic" as used herein means a mixture of the (-) and (+) enantiomers of a compound wherein the (-) and (+) enantiomers are present in approximately a 1:1 ratio.

The terms "substantially optically pure," "optically pure," and "optically pure enantiomers," as used herein, mean that the composition contains greater than about 90% of the (-) norcisapride stereoisomer by weight, preferably greater than about 95% of the desired enantiomer by weight, and more preferably greater than about 99% of the desired enantiomer by weight, based upon the total weight of norcisapride. In other words, the term "substantially free" means less than about 10 weight percent, preferably less than about 5 weight percent, and more preferably less than about 1 weight percent of (+) norcisapride is present according to the invention.

The terms "5-hydroxytryptamine receptor antagonist," "serotonin receptor antagonist," and "5-HT_3 receptor antagonist," as used herein, mean a compound capable of binding reversibly to a 5-hydroxytryptamine receptor, whether on the vagal nerve or elsewhere in a mammal.

The phrases "bulimia" and "bulimia nervosa" are used herein consistently with the definition according to *DSM-IV*.

The terms "apnea" and "apnea disorder," as used herein, include, but are not limited to, a disorder characterized by interrupted breathing, in which a person stops breathing long enough to decrease the amount of oxygen and increase the amount of carbon dioxide in the blood and brain.

The term "asthma," as used herein, is defined as a disorder characterized by increased responsiveness of the trachea and bronchi to various stimuli, which results in symptoms that include, but are not limited to, wheezing, cough, shortness of breath, dyspnea, and the like. Asthma includes, for example, allergic asthma.

The term "syncope," as used herein, is defined as a disorder characterized by loss of consciousness and postural tone caused by diminished cerebral blood flow. Syncope includes, for example, Adams-Stokes syncope, cardiac syncope, carotid sinus syncope, hysterical syncope, laryngeal syncope, local syncope, micturition syncope, orthostatic syncope, postural syncope, swallow syncope, syncope due to seizures, syncope due to pulmonary embolism, syncope of gradual onset, tussive syncope, vasodepressor syncope, or vasovagal syncope.

The phrase "therapeutically effective amount of (-) norcisapride," as used herein, means that amount of substantially optically pure (-) norcisapride, or a pharmaceutically acceptable salt thereof, which, alone or in combination with other drugs, provides a therapeutic benefit in the prevention, treatment, or management, or of apnea, apnea disorders, bulimia, irritable bowel syndrome, urinary incontinence, bradycardia, bradyarrhythmia, asthma, syncope, or one or more symptoms thereof. Different therapeutically effective amounts may be applicable for each disorder, as will be readily known by those of ordinary skill in the art.

Substantially pure (-) norcisapride may be obtained from a racemic mixture of cisapride, the chemical synthesis of which can be performed according to the method described in European Patent Application No. 0,076,530 A2 published April 13, 1983, U.S. Patent Nos. 4,962,115, 5,057,525, 5,137,896 , the disclosures of which are each hereby incorporated herein by express reference thereto. *See also*, and Van Daele, *et al.*, *Drug Development Res.*, 8:225-232 (1986) The metabolism of cisapride to norcisapride is described in Meuldermans, W., *et al.*, *Drug Metab. Dispos.*, 16(3):410-419 (1988) and Meuldermans, W., *et al.*, *Drug Metab. Dispos.*, 16(3):403-409 (1988). The preparation of racemic norcisapride is also known to those of ordinary skill in the art, particularly in view of EP 0,076,530 A2 and U.S. Patent No. 5,137,896 to Van Daele, the disclosures of which are hereby incorporated herein by express reference thereto.

Optically pure (-) norcisapride may also be obtained from racemic norcisapride by HPLC separation or resolution of the enantiomers using conventional means, for example, from an optically active resolving acid. The resolution of racemic norcisapride is also known to those of ordinary skill in the art, particularly from Jacques, J., *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S. H., *et al.*, *Tetrahedron*, 33:2725 (1977); Eliel, E. L. *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); Wilen, S. H. *Tables of Resolving Agents and Optical Resolutions*, p. 268 (E.L. Eliel, Ed. Univ. of Notre Dame Press, Notre Dame, IN, 1972).

In addition to separation techniques, such as those described above, (-) norcisapride may be synthesized by stereospecific synthesis using methodology well known to those of ordinary skill in the art. Chiral synthesis can result in products of high enantiomeric purity. However, in some cases, the enantiomeric purity of the product is not sufficiently high. The skilled artisan will appreciate that the separation methods described

above may be used to further enhance the enantiomeric purity of (-) norcisapride obtained by chiral synthesis.

Optically pure (-) norcisapride may also be prepared from the racemic mixture by enzymatic biocatalytic resolution. See, for example, U.S. Patent Nos. 5,057,427 and 5,077,217, the disclosures of which are incorporated herein by express reference thereto.

The magnitude of a prophylactic or therapeutic dose of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, in the acute or chronic management of diseases and disorders described herein will vary with the severity of the condition to be prevented, treated, or managed and the route of administration. For example, oral, mucosal (including rectal), parenteral (including subcutaneous, intramuscular, bolus injection, and intravenous), sublingual, transdermal, nasal, buccal, and like may be employed. Dosage forms include tablets, troches, lozenges, dispersions, suspensions, suppositories, solutions, capsules, soft elastic gelatin capsules, patches, and the like. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. Suitable dosing regimens can be readily selected by those skilled in the art with due consideration of such factors. In general, the total daily dosage for the conditions described herein, is from about 0.5 mg to about 500 mg of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer. Preferably, a daily dose range is from about 1 mg to about 250 mg and more preferably, a daily dose range is between about 1 mg to about 100 mg. Preferably, the active ingredient is administered in single or divided doses orally from one to four times a day, or by slow intravenous injection. The most preferred route of administration for the present invention is oral. The oral dosage forms may be conveniently presented in unit dosage forms and prepared by any methods well known in the art of pharmacy.

In managing the patient, the therapy may be initiated at a lower dose, *e.g.*, from about 0.5 mg to about 10 mg, and increased up to the recommended daily dose or higher depending on the patient's global response. It is further recommended that children, patients over 65 years, and those with impaired renal or hepatic function, initially receive low doses, and that they be titrated based on individual response(s) and blood level(s). It may be necessary to use dosages outside these ranges in some cases, as will be apparent to those of ordinary skill in the art. Furthermore, it is noted that the clinician or treating

physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response.

Any suitable route of administration may be employed for providing the patient with an effective dosage of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer. The most suitable route in any given case will depend on the nature and severity of the condition being prevented, treated, or managed.

The pharmaceutical compositions for use in the present invention comprise optically pure (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, as the active ingredient, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients. As used herein, the term "pharmaceutically acceptable salt" refers to a salt prepared from pharmaceutically acceptable non-toxic acids including inorganic acids, organic acids, solvates, hydrates, or clathrates thereof. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, and phosphoric. Appropriate organic acids may be selected, for example, from aliphatic, aromatic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, camphorsulfonic, citric, fumaric, gluconic, isethionic, lactic, malic, mucic, tartaric, para-toluenesulfonic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, benzenesulfonic (besylate), stearic, sulfanilic, alginic, galacturonic, and the like. Particularly preferred acids are hydrobromic, hydrochloric, phosphoric, and sulfuric acids. In a preferred embodiment, (-) norcisapride is administered as the free base or hydrate.

In practical use, (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms and may comprise a number of components depending on the form of preparation desired for administration. The compositions of the present invention include, but are not limited to, suspensions, solutions and elixirs; aerosols; or carriers, including, but not limited to, starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like. Because of their ease of administration, tablets and capsules are preferred and represent the most advantageous oral dosage unit form, in which

case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete pharmaceutical unit dosage forms, such as capsules, cachets, soft elastic gelatin capsules, tablets, or aerosols sprays, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the pharmaceutically acceptable carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. Oral solid preparations are preferred over oral liquid preparations. One preferred oral solid preparation is capsules, but the most preferred oral solid preparation is tablets.

For example, a tablet may be prepared by compression or molding, optionally, with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, granulating agent, surface active agent, dispersing agent, or the like. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Preferably, each tablet contains from about 0.5 mg to about 500 mg of the active ingredient, more preferably from about 1 mg to about 250 mg. Preferably, each cachet or capsule contains from about 0.5 mg to about 500 mg of the active ingredient, more preferably from about 1 mg to about 250 mg. However, the amount of active ingredient found in the composition may vary depending on the amount of active ingredient to be administered to the patient.

Optically pure (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, may be formulated as a pharmaceutical composition in a soft elastic gelatin capsule unit dosage form by using conventional methods well known in the art, such as in Ebert, *Pharm. Tech*, 1(5):44-50 (1977). Soft elastic gelatin capsules have a soft, globular gelatin shell somewhat thicker than that of hard gelatin capsules, wherein a gelatin is plasticized by the addition of plasticizing agent, *e.g.*,

glycerin, sorbitol, or a similar polyol. The hardness of the capsule shell may be changed by varying the type of gelatin used and the amounts of plasticizer and water. The soft gelatin shells may contain a preservative, such as methyl- and propylparabens and sorbic acid, to prevent the growth of fungi. The active ingredient may be dissolved or suspended in a liquid vehicle or carrier, such as vegetable or mineral oils, glycols such as polyethylene glycol and propylene glycol, triglycerides, surfactants such as polysorbates, or a combination thereof.

In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release means, delivery devices, or both, as are well known to those of ordinary skill in the art, such as those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; and 5,733,566, the disclosures of which are hereby incorporated herein by express reference thereto. These pharmaceutical compositions can be used to provide slow or controlled-release of the active ingredient therein using, for example, hydropropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or the like, or a combination thereof. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, may be readily selected for use with the (-) norcisapride compositions of the invention. Thus, single unit dosage forms suitable for oral administration, such as tablets, capsules, gelcaps, caplets, and the like, that are adapted for controlled-release are encompassed by the present invention.

All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations may include: 1) extended activity of the drug; 2) reduced dosage frequency; and 3) increased patient compliance.

Most controlled-release formulations are designed to initially release an amount of drug that promptly produces the desired therapeutic effect, and gradual and continual release of other amounts of drug to maintain this level of therapeutic effect over an extended period of time. In order to maintain this constant level of drug in the body, the

drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body.

The controlled-release of the active ingredient may be stimulated by various inducers, for example pH, temperature, enzymes, water, or other physiological conditions or compounds. The term "controlled-release component" in the context of the present invention is defined herein as a compound or compounds, including polymers, polymer matrices, gels, permeable membranes, liposomes, microspheres, or the like, or a combination thereof, that facilitates the controlled-release of the active ingredient (*e.g.*, (-) norcisapride) in the pharmaceutical composition.

Optically pure (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, may also be formulated for parenteral administration by injection (subcutaneous, bolus injection, intramuscular, or intravenous), and may be dispensed in a unit dosage form, such as a multidose container or an ampule. Compositions of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, for parenteral administration may be in the form of suspensions, solutions, emulsions, or the like in aqueous or oily vehicles, and in addition to the active ingredient may contain one or more formulary agents, such as dispersing agents, suspending agents, stabilizing agents, preservatives, and the like.

In the case where an intravenous injection or infusion composition is employed, a suitable daily dosage range is, *e.g.*, from about 0.5 mg to about 500 mg total daily dose, preferably from about 1 mg to about 250 mg, more preferably from about 1 mg to about 100 mg.

Another preferred route of administration is transdermal delivery, for example, via an abdominal skin patch.

The invention is further defined by reference to the following examples, describing in detail the preparation of the compound and the compositions of the present invention, as well as their utility. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the purpose and interest of this invention.

5 EXAMPLES

5.1 EXAMPLE 1: Bioavailability

A single dose of test substance or vehicle is administered to male beagle dogs either intravenously as a bolus over one minute using a 23 gauge butterfly needle into the saphenous vein, or as a single dose via oral gavage. 2.0 mL of whole blood is collected from each dog prior to and at intervals of 0.083, 0.25, 0.5, 1, 2, 3, 4, 6, 9, 12, and 24 hours following the intravenous or oral administration of the optical isomers or racemic mixture of cisapride or of norcisapride. The dogs are placed in sling-restraint prior to administration of test substance and are transferred to metabolic cages following collection of the 0.083 hour blood sample. All blood samples are collected from an angiocatheter placed in a cephalic vein on the morning of the experiment.

The blood is drawn into a 3 cc syringe. The first 1.0-2.0 mL of blood is discarded. The next 2.0 mL of whole blood is quickly transferred to a heparinized tube. The heparinized tubes are kept on ice until the blood is added. After adding the blood to the tube, the contents of the tube are mixed and centrifuged to obtain plasma. The plasma is carefully decanted and transferred to a test tube labeled with: the animal number, the dose of test substance administered, the route of administration, the date of administration, and the time of blood collection. The tubes are stored at -20°C until analysis.

Analysis of the concentration of the optical isomers or racemates of norcisapride in each plasma sample is determined using high performance liquid chromatography. For each test substance the plasma concentration with respect to sample time is plotted for both routes of administration. The oral bioavailability of each test substance is determined by comparing the C_{max} and AUC for the oral route of administration versus those for the intravenous route. The $t_{½}$ for each test substance by both routes is calculated as an indicator of duration of action.

5.2 EXAMPLE 2: Receptor Activity

5-HT_{1A} Receptor Activity

Receptor selection and amplification technology (R-SAT) is used (Receptor Technologies Inc., Winooski, VT) to determine potential agonist and/or antagonist activity of racemic norcisapride, cisapride, and their enantiomers on cloned human serotonin 5-HT_{1A} receptor subtypes expressed in NIH 3T3 cells, such as in Burstein *et al.*, *J. Biol Chem.*, 270:3141-3146 (1995); and Messier *et al.*, *Pharmacol. Toxicol.*, 76(5):308-311 (1995).

The assay involves co-expression of a marker enzyme, β-galactosidase, with the serotonin receptor of interest. Ligands stimulate proliferation of cells that express the receptor and, therefore, the marker. Ligand-induced effects can be determined by assay of the marker.

NIH 3T3 cells are incubated, plated, and then transfected using human 5-HT_{1A} serotonin receptors, pSV-β-galactosidase, and salmon sperm DNA. The medium is changed one day later, and after 2 days, aliquots of the trypsinized cells are placed in wells of a 96 well plate. After five days in culture in the presence of the ligands, the levels of β-galactosidase are measured. The cells are then rinsed and incubated with the substrate, *o*-nitrophenyl β-D-galactopyranoside. After 16 hours, the plates are read at 405 nm on a plate-reader. Each compound is tested for activity in triplicate at seven different concentrations (10, 2.5, 0.625, 0.156, 0.039, 0.0098, and 0.0024 nM).

None of the compounds tested show agonist activity at human 5-HT_{1A} serotonin receptors. Data from antagonist inhibition of the compounds are fit to the equation:

$$\text{Response} = \text{Max Response} + \frac{\text{(Min Response)}}{1 + (\text{Ligand Conc}/EC_{50})}$$

IC_{50} values (concentration required to inhibit 50% of specific binding) are calculated for antagonist activity against a concentration of 2 μM 5-HT using the non-linear least squares analysis of KaleidaGraph, the results of which are set forth in Tables 1 and 2.

5-HT_2 Receptor Activity

Receptor selection and amplification technology (R-SAT) is used (Receptor Technologies Inc., Winooski, VT) to determine potential agonist and/or antagonist activity of racemic norcisapride, cisapride, and their enantiomers on cloned human serotonin 5-HT_2 receptor subtypes expressed in NIH 3T3 cells, such as in Burstein *et al.*, *J. Biol Chem.*, 270:3141-3146 (1995); and Messier *et al.*, *Pharmacol. Toxicol.*, 76(5):308-311 (1995).

The assay involves co-expression of a marker enzyme, β-galactosidase, with the serotonin receptor of interest. Ligands stimulate proliferation of cells that express the receptor and, therefore, the marker. Ligand-induced effects can be determined by assay of the marker.

NIH 3T3 cells are incubated, plated, and then transfected using human 5-HT_2 serotonin receptors, pSV-β-galactosidase, and salmon sperm DNA. The medium is changed one day later, and after 2 days, aliquots of the trypsinized cells are placed in wells of a 96 well plate. After five days in culture in the presence of the ligands, the levels of β-galactosidase are measured. The cells are then rinsed and incubated with the substrate, *o*-nitrophenyl β-D-galactopyranoside. After 16 hours, the plates are read at 405 nm on a plate-reader. Each compound is tested for activity in triplicate at seven different concentrations (10, 2.5, 0.625, 0.156, 0.039, 0.0098, and 0.0024 nM).

None of the compounds tested show agonist activity at human 5-HT_2 serotonin receptors. Data from antagonist inhibition of the compounds are fit to the equation:

$$\text{Response} = \text{Max Response} + \frac{\text{(Min Response)}}{1 + (\text{Ligand Conc}/EC_{50})}$$

IC_{50} values are calculated for antagonist activity against a concentration of 2 μM 5-HT using the non-linear least squares analysis of KaleidaGraph, the results of which are set forth in Tables 1 and 2.

TABLE 1

Calculated IC_{50} Values (μM) at 5-HT_{1A} and 5-HT_2 Receptors

Compound	5-HT_{1A}	5-HT_2
(±) Norcisapride	7.48	2.21
(+) Norcisapride	0.0054	0.38
(-) Norcisapride	1.30	----

TABLE 2

Calculated IC_{50} Values (μM) at 5-HT_{1A} and 5-HT_2 Receptors

Compound	5-HT_{1A}	5-HT_2
(±) Cisapride	----	0.26
(+) Cisapride	----	0.0050
(-) Cisapride	----	7.08

5.3 EXAMPLE 3: Receptor Binding

5-HT_3 Receptor

Racemic norcisapride, racemic cisapride and their (+)- and (-)- stereoisomers are tested (Cerep, Celle l'Evescault, France) for binding to 5-HT_3 receptor subtypes derived from N1E-115 cells.

Following incubation with the appropriate ligands, the preparations are rapidly filtered under vacuum through GF/B glass fiber filters and washed with ice-cold buffer using a Brandel or Packard cell harvester. Bound radioactivity is determined with a liquid scintillation counter (*LS 6000*, Beckman) using a liquid scintillation cocktail (Formula 989).

Specific radioligand binding to the receptor is defined as the difference between total binding and nonspecific binding determined in the presence of an excess of unlabeled ligand. Results are expressed as a percent inhibition of specific binding obtained in the presence of the compounds. IC_{50} are determined using concentrations ranging from 3×10^{-10} M to 10^{-5} M to obtain full competition curves and are calculated by non-linear regression analysis. The results are shown in Tables 3 and 4 below.

5-HT_4 Receptor

Racemic norcisapride, racemic cisapride and their (+)- and (-)- stereoisomers are tested (Cerep, Celle l'Evescault, France) for binding to 5-HT_4 receptor subtypes derived from guinea-pig striata.

Following incubation with the appropriate ligands, the preparations are rapidly filtered under vacuum through GF/B glass fiber filters and washed with ice-cold buffer using a Brandel or Packard cell harvester. Bound radioactivity is determined with a

liquid scintillation counter (LS 6000, Beckman) using a liquid scintillation cocktail (Formula 989).

Specific radioligand binding to the receptor is defined as the difference between total binding and nonspecific binding determined in the presence of an excess of unlabeled ligand. Results are expressed as a percent inhibition of specific binding obtained in the presence of the compounds. IC_{50} are determined using concentrations ranging from 3 x 10^{-10} M to 10^{-5} M to obtain full competition curves and are calculated by non-linear regression analysis. The results are shown in Tables 3 and 4 below.

TABLE 3

IC_{50} (nM) Values for Binding to 5-HT_3 and 5-HT_4 Sites

Compound	5-HT_3	5-HT_4	5-HT_3/5-HT_4 Ratio
(±) Norcisapride	8.2	686	0.012
(+) Norcisapride	4.5	331	0.014
(-) Norcisapride	30.4	1350	0.023

TABLE 4

IC_{50} (nM) Values for Binding to 5-HT_3 and 5-HT_4 Sites

Compound	5-HT_3	5-HT_4	5-HT_3/5-HT_4 Ratio
(±) Cisapride	365	169	2.2
(+) Cisapride	310	340	0.9
(-) Cisapride	2790	199	14.0

Agonist activity at 5-HT_4 receptor sites may also be assessed using an assay based on the ability of active compounds to increase cyclic AMP production in mouse embryo colloculi neurones grown in tissue culture, such as in Dumuis *et al.*, *N. S. Arch. Pharmacol.*, 340:403-410 (1989).

5.4 EXAMPLE 4: Oral Formulation

Tablets

Formula	Quantity per Tablet in mg.		
	A	B	C
Active Ingredient (-) Norcisapride	5.0	10.0	25.0
Lactose BP	62.0	57.0	42.0
Starch BP	20.0	20.0	20.0
Microcystalline Cellulose	10.0	10.0	10.0
Hydrogenated Vegetable Oil	1.5	1.5	1.5
Polyvinylpyrrolidinone	1.5	1.5	1.5
Compression Weight	100.0	100.0	100.0

The active ingredient, (-) norcisapride, is sieved through a suitable sieve and blended with the lactose until a uniform blend is formed. Suitable volumes of water are added and the powders are granulated. After drying, the granules are then screened and blended with the remaining excipients. The resulting granules are then compressed into tablets of desired shape. Tablets of other strengths may be prepared by altering the ratio of active ingredient to the excipient(s) or the compression weight.

5.5 EXAMPLE 5: Oral Formulation

Tablets

Formula	Quantity per Tablet in mg.		
	A	B	C
Active Ingredient (-) Norcisapride	5.0	10.0	25.0
Lactose BP	48.5	43.5	28.5
Starch BP	30.0	30.0	30.0
Pregelatinized Maize Starch BP	15.0	15.0	15.0
Magnesium Stearate BP	1.5	1.5	1.5
Compression Weight	100.0	100.0	100.0

The active ingredient, (-) norcisapride, is sieved through a suitable sieve and blended with lactose, starch, and pregelatinized maize starch until a uniform blend is formed. Suitable volumes of water are added and the powders are granulated. After drying, the granules are then screened and blended with the remaining excipients. The resulting granules are then compressed into tablets of desired shape. Tablets of other strengths may be prepared by altering the ratio of active ingredient to the excipient(s) or the compression weight.

5.6 EXAMPLE 6: Oral Formulation

Capsules

Formula	Quantity per Capsule in mg.		
	A	B	C
Active Ingredient (-) Norcisapride	5.0	10.0	25.0
Starch 1500	94.0	89.0	74.0
Magnesium Stearate BP	1.0	1.0	1.0
Total Weight	100.0	100.0	100.0

The active ingredient is sieved and blended with the excipients. The mix is filled into size No. 2 hard gelatin capsules using suitable machinery. Other doses may be prepared by altering the fill weight, and if necessary, changing the capsule size to suit.

5.7. EXAMPLE 7

INTRAVENOUS FORMULATION

Formula	
Active Ingredient (-) norcisapride	1000 µg/mL
Dilute Hydrochloric Acid BP	to pH 3.5
Sodium Chloride Injection BP	1 mL

The active ingredient is dissolved in dilute hydrochloric acid BP to form a solution having a concentration of 1000 μg/mL (-) norcisapride. The solution is then mixed with sodium chloride injection BP prior to use.

While the present invention has been described with respect to the particular embodiments, it will be apparent to those skilled in the art that various changes and modifications may be made without departing from the spirit and scope of the invention as defined in the claims. Such modifications are also intended to fall within the scope of the appended claims.

THE CLAIMS

What is claimed is:

1. A method of treating bulimia in a patient which comprises administering to said patient in need of such treatment a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

2. The method of claim 1, wherein the mammal is a human.

3. The method of claim 1, wherein (-) norcisapride is administered orally.

4. The method of claim 3, wherein (-) norcisapride is administered as a tablet or a capsule.

5. The method of claim 1, wherein the amount administered is from about 0.5 mg to about 500 mg.

6. The method of claim 5, wherein the amount administered is from about 1 mg to about 250 mg.

7. The method of claim 1, wherein (-) norcisapride is administered together with a pharmaceutically acceptable carrier.

8. The method of claim 3, wherein said (-) norcisapride is administered from one to four times per day.

9. The method of claim 1, wherein (-) norcisapride is administered parenterally, transdermally, rectally or sublingually.

10. A method of treating disorders mediated by vagal activity in a patient which comprises administering to said patient in need of such treatment a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

11. The method of claim 10, wherein the mammal is a human.

12. The method of claim 10, wherein (-) norcisapride is administered orally.

13. The method of claim 12, wherein (-) norcisapride is administered as a tablet or a capsule.

14. The method of claim 10, wherein the amount administered is from about 0.5 mg to about 500 mg.

15. The method of claim 14, wherein the amount administered is from about 1 mg to about 250 mg.

16. The method of claim 10, wherein (-) norcisapride is administered together with a pharmaceutically acceptable carrier.

17. The method of claim 12, wherein said (-) norcisapride is administered from one to four times per day.

18. The method of claim 10, wherein (-) norcisapride is administered parenterally, transdermally, rectally or sublingually.

19. A method of treating irritable bowel syndrome in a patient which comprises administering to said patient in need of such treatment a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

20. The method of claim 19, wherein the mammal is a human.

21. The method of claim 19, wherein (-) norcisapride is administered orally.

22. The method of claim 21, wherein (-) norcisapride is administered as a tablet or a capsule.

23. The method of claim 19, wherein the amount administered is from about 0.5 mg to about 500 mg.

24. The method of claim 23, wherein the amount administered is from about 1 mg to about 250 mg.

25. The method of claim 19, wherein (-) norcisapride is administered together with a pharmaceutically acceptable carrier.

26. The method of claim 21, wherein said (-) norcisapride is administered from one to four times per day.

27. The method of claim 19, wherein (-) norcisapride is administered parenterally, transdermally, rectally or sublingually.

28. A method of treating bradycardia or bradyarrhythmia in a patient which comprises administering to said patient in need of such treatment a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

29. The method of claim 28, wherein the patient is a human.

30. The method of claim 28, wherein (-) norcisapride is administered orally.

31. The method of claim 30, wherein (-) norcisapride is administered as a tablet or a capsule.

32. The method of claim 28, wherein the amount administered is from about 0.5 mg to about 500 mg.

33. The method of claim 32, wherein the amount administered is from about 1 mg to about 250 mg.

34. The method of claim 28, wherein (-) norcisapride is administered together with a pharmaceutically acceptable carrier.

35. The method of claim 30, wherein said (-) norcisapride is administered from one to four times per day.

36. The method of claim 28, wherein (-) norcisapride is administered parenterally, transdermally, rectally or sublingually.

37. A method of treating asthma in a patient which comprises administering to said patient in need of such treatment a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

38. The method of claim 37, wherein the patient is a human.

39. The method of claim 37, wherein (-) norcisapride is administered orally.

40. The method of claim 39, wherein (-) norcisapride is administered as a tablet or a capsule.

41. The method of claim 37, wherein the amount administered is from about 0.5 mg to about 500 mg.

42. The method of claim 41, wherein the amount administered is from about 1 mg to about 250 mg.

43. The method of claim 37, wherein (-) norcisapride is administered together with a pharmaceutically acceptable carrier.

44. The method of claim 39, wherein said (-) norcisapride is administered from one to four times per day.

45. The method of claim 37, wherein (-) norcisapride is administered parenterally, transdermally, rectally or sublingually.

46. A method of treating urinary incontinence in a patient which comprises administering to said patient in need of such treatment a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

47. The method of claim 46, wherein the patient is a mammal.

48. The method of claim 46, wherein (-) norcisapride is administered orally.

49. The method of claim 48, wherein (-) norcisapride is administered as a tablet or a capsule.

50. The method of claim 46, wherein the amount administered is from about 0.5 mg to about 500 mg.

51. The method of claim 50, wherein the amount administered is from about 1 mg to about 250 mg.

52. The method of claim 46, wherein (-) norcisapride is administered together with a pharmaceutically acceptable carrier.

53. The method of claim 48, wherein said (-) norcisapride is administered from one to four times per day.

54. The method of claim 46, wherein (-) norcisapride is administered parenterally, transdermally, rectally or sublingually.

55. A method of treating apnea or apnea disorders in a patient which comprises administering to said patient in need of such treatment a therapeutically effective amount of

(-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

56. The method of claim 55, wherein the apnea being treated comprises central apnea, deglutition apnea, obstructive apnea, sleep apnea, or sleep induced apnea.

57. The method of claim 55, wherein the patient is a human.

58. The method of claim 55, wherein (-) norcisapride is administered orally.

59. The method of claim 58, wherein (-) norcisapride is administered as a tablet or a capsule.

60. The method of claim 55, wherein the amount administered is from about 0.5 mg to about 500 mg.

61. The method of claim 60, wherein the amount administered is from about 1 mg to about 250 mg.

62. The method of claim 55, wherein (-) norcisapride is administered together with a pharmaceutically acceptable carrier.

63. The method of claim 58, wherein said (-) norcisapride is administered from one to four times per day.

64. The method of claim 55, wherein (-) norcisapride is administered parenterally, transdermally, rectally or sublingually.

65. A method of preventing or managing bulimia in a patient which comprises administering to said patient in need of such prevention or management a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

66. A method of preventing or managing disorders mediated by vagal activity in a patient which comprises administering to said patient in need of such prevention or management a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

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67. A method of preventing or managing irritable bowel syndrome in a patient which comprises administering to said patient in need of such prevention or management a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

10

68. A method of preventing or managing bradycardia or bradyarrhythmia in a patient which comprises administering to said patient in need of such prevention or management a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

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69. A method of preventing or managing asthma in a patient which comprises administering to said patient in need of such prevention or management a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

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70. A method of preventing or managing urinary incontinence in a patient which comprises administering to said patient in need of such prevention or management a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

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71. A method of preventing or managing apnea or apnea disorders in a patient which comprises administering to said patient in need of such prevention or management a therapeutically effective amount of (-) norcisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

30

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[57]摘要

使用基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐预防、治疗或控制呼吸暂停、呼吸暂停性疾病、贪食症、过敏性肠道综合征、尿失禁、心动过缓、过缓性心率失常、晕厥、其它疾病，或其症状的方法。

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权 利 要 求 书

1. 治疗患者贪食症的方法，其包括给予需要这种治疗的所述患者治疗有效量的基本不含(+)立体异构体的(-)降西沙必利(norcisapride)，或其药学上可接受的盐。

2. 权利要求 1 的方法，其中所述哺乳动物是人。

3. 权利要求 1 的方法，其中(-)降西沙必利经口服给药。

4. 权利要求 3 的方法，其中(-)降西沙必利以片剂或胶囊给药。

5. 权利要求 1 的方法，其中给药量是从约 0.5mg 至约 500mg。

6. 权利要求 5 的方法，其中给药量是从约 1mg 至约 250mg。

7. 权利要求 1 的方法，其中(-)降西沙必利与药学上可接受的载体一起给予。

8. 权利要求 3 的方法，其中所述(-)降西沙必利每天给药一至四次。

9. 权利要求 1 的方法，其中(-)降西沙必利经胃肠外、透皮、直肠或舌下给药。

10. 治疗患者中由迷走神经活性介导的疾病的方法，其包括以治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐给予需要这种治疗的所述患者。

11. 权利要求 10 的方法，其中所述哺乳动物是人。

12. 权利要求 10 的方法，其中(-)降西沙必利经口服给药。

13. 权利要求 12 的方法，其中(-)降西沙必利以片剂或胶囊给药。

14. 权利要求 10 的方法，其中给药量是从约 0.5mg 至约 500mg。

15. 权利要求 14 的方法，其中给药量是从约 1mg 至约 250mg。

16. 权利要求 10 的方法，其中(-)降西沙必利与药学上可接受的载体一起给予。

17. 权利要求 12 的方法，其中所述(-)降西沙必利每天给药一至

四次。

18. 权利要求 10 的方法，其中(-)降西沙必利经胃肠外、透皮、直肠或舌下给药。

19. 治疗过敏性肠道综合征患者的方法，其包括以治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐给予需要这种治疗的所述患者。

20. 权利要求 19 的方法，其中所述患者是人。

21. 权利要求 19 的方法，其中(-)降西沙必利经口服给药。

22. 权利要求 21 的方法，其中(-)降西沙必利以片剂或胶囊给药。

23. 权利要求 19 的方法，其中给药量是从约 0.5mg 至约 500mg。

24. 权利要求 23 的方法，其中给药量是从约 1mg 至约 250mg。

25. 权利要求 19 的方法，其中(-)降西沙必利与药学上可接受的载体一起给予。

26. 权利要求 21 的方法，其中所述(-)降西沙必利每天给药一至四次。

27. 权利要求 19 的方法，其中(-)降西沙必利经胃肠外、透皮、直肠或舌下给药。

28. 治疗心动过缓或过缓性心律失常患者的方法，其包括以治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐给予需要这种治疗的所述患者。

29. 权利要求 28 的方法，其中所述哺乳动物是人。

30. 权利要求 28 的方法，其中(-)降西沙必利经口服给药。

31. 权利要求 30 的方法，其中(-)降西沙必利以片剂或胶囊给药。

32. 权利要求 28 的方法，其中给药量是从约 0.5mg 至约 500mg。

33. 权利要求 32 的方法，其中给药量是从约 1mg 至约 250mg。

34. 权利要求 28 的方法，其中(-)降西沙必利与药学上可接受的

载体一起给予。

35. 权利要求 30 的方法，其中所述(-)降西沙必利每天给药一至四次。

36. 权利要求 28 的方法，其中(-)降西沙必利经胃肠外、透皮、直肠或舌下给药。

37. 治疗哮喘患者的方法，其包括以治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐给予需要这种治疗的所述患者。

38. 权利要求 37 的方法，其中所述患者是人。

39. 权利要求 37 的方法，其中(-)降西沙必利经口服给药。

40. 权利要求 39 的方法，其中(-)降西沙必利以片剂或胶囊给药。

41. 权利要求 37 的方法，其中给药量是从约 0.5mg 至约 500mg.

42. 权利要求 41 的方法，其中给药量是从约 1mg 至约 250mg.

43. 权利要求 37 的方法，其中(-)降西沙必利与药学上可接受的载体一起给予。

44. 权利要求 39 的方法，其中所述(-)降西沙必利每天给药一至四次。

45. 权利要求 37 的方法，其中(-)降西沙必利经胃肠外、透皮、直肠或舌下给药。

46. 治疗尿失禁患者的方法，其包括以治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐给予需要这种治疗的所述患者。

47. 权利要求 46 的方法，其中所述患者是人。

48. 权利要求 46 的方法，其中(-)降西沙必利经口服给药。

49. 权利要求 48 的方法，其中(-)降西沙必利以片剂或胶囊给药。

50. 权利要求 46 的方法，其中给药量是从约 0.5mg 至约 500mg.

51. 权利要求 50 的方法，其中给药量是从约 1mg 至约 250mg.

52. 权利要求 46 的方法，其中(-)降西沙必利与药学上可接受的载体一起给予.

53. 权利要求 48 的方法，其中所述(-)降西沙必利每天给药一至四次.

54. 权利要求 46 的方法，其中(-)降西沙必利经胃肠外、透皮、直肠内或舌下给药.

55. 治疗呼吸暂停或呼吸暂停性疾病患者的方法，其包括以治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐给予需要这种治疗的所述患者.

56. 权利要求 55 的方法，其中治疗的呼吸暂停包括中枢性呼吸暂停、吞咽性呼吸暂停、阻塞性呼吸暂停、睡眠性呼吸暂停、或睡眠诱发的呼吸暂停.

57. 权利要求 55 的方法，其中所述患者是人.

58. 权利要求 55 的方法，其中(-)降西沙必利经口服给药.

59. 权利要求 58 的方法，其中(-)降西沙必利以片剂或胶囊给药.

60. 权利要求 55 的方法，其中给药量是从约 0.5mg 至约 500mg.

61. 权利要求 60 的方法，其中给药量是从约 1mg 至约 250mg.

62. 权利要求 55 的方法，其中(-)降西沙必利与药学上可接受的载体一起给予.

63. 权利要求 58 的方法，其中所述(-)降西沙必利每天给药一至四次.

64. 权利要求 55 的方法，其中(-)降西沙必利经胃肠外、透皮、直肠或舌下给药.

65. 预防或控制患者贪食症的方法，其包括以治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐给予有这种预防或控制需要的所述患者.

66. 预防或控制患者由迷走活性介导的疾病的方法，其包括以治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐给予有这种预防或控制需要的所述患者。

67. 预防或控制患者过敏性肠道综合征的方法，其包括以治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐给予有这种预防或控制需要的所述患者。

68. 预防或控制心动过缓或过缓性心律失常患者的方法，其包括以治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐给予需要这种治疗的所述患者。

69. 预防或控制患者哮喘的方法，其包括以治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐给予有这种预防或控制需要的所述患者。

70. 预防或控制患者尿失禁的方法，其包括以治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐给予有这种预防或控制需要的所述患者。

71. 预防或控制患者呼吸暂停或呼吸暂停性疾病的方法，其包括以治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐给予有这种预防或控制需要的所述患者。

01.02.12

说　明　书

光学纯度(-)-降西沙必利对治疗呼吸暂停、贪食症和其它疾病的用途

1. 本发明领域

本发明涉及预防、治疗或处理呼吸暂停、呼吸暂停性疾病、贪食症、其它疾病或其症状的方法。

2. 本发明背景

斯特曼医学词典(Stedman's Medical Dictionary), 第 26 版, Williams 和 Wilkins(1995), 将呼吸暂停定义为没有呼吸。与呼吸暂停相关的疾病有多种, 其特征是呼吸中断, 其中患者停止呼吸的时间长度足以使血液和脑部的氧含量减少而二氧化碳含量增加。典型的各种呼吸暂停涉及鼻腔或口腔的气流停止至少 10 秒钟。

存在多种呼吸暂停性疾病, 包括: 中枢性呼吸暂停, 其由延髓抑制以及抑制呼吸运动引起; 吞咽性呼吸暂停, 其为吞咽期间的呼吸抑制; 阻塞性或外周性呼吸暂停, 其或由呼吸道阻塞引起或由呼吸肌活动不足引起; 睡眠性呼吸暂停, 其为睡眠期间的中枢性和/或阻塞性呼吸暂停; 以及睡眠诱发的呼吸暂停, 其为睡眠期间呼吸中枢不能刺激足够的呼吸所致。

阻塞性呼吸暂停通常发生于过度肥胖男性, 而在妇女中不常见。肥胖, 可能与机体组织老化和其它因素结合, 导致上呼吸道狭窄。吸烟、过量饮酒和肺部疾病, 如肺气肿, 可增加阻塞性呼吸暂停加重的危险。

对于睡眠性呼吸暂停患者, 戒烟、避免过量饮酒和减轻体重通常是治疗疾病的第一个行为步骤。为抑制和避免呼吸暂停, 严重打鼾和睡眠中经常噎气的人不应使用安定药、睡眠辅助药或其它镇静剂。

睡眠性呼吸暂停是最常见的一种呼吸暂停形式。极少数严重睡眠性呼吸暂停患者需要进行气管造口术，一种穿过颈部通向气管的永久性开口的外科手术。有时进行其它外科手术以扩张上呼吸道和减轻病情。然而，这些极端的措施是很少需要并且决不是所希望的。

呼吸暂停还可通过给予患者治疗药物而以非损伤的方式治疗。美国专利 No. 5075290 公开了在睡眠期间给予核苷摄取阻断剂的药物双嘧达莫，治疗阻塞性睡眠呼吸暂停及相关症状，如打鼾的方法。美国专利 No. 5502067 和 5407953 公开了给予毛果芸香碱化合物治疗睡眠性呼吸暂停、精神迟钝和打鼾患者的方法。美国专利 No. 5422374 公开了以泛癸利酮给予患者而治疗睡眠性呼吸暂停的方法。美国专利 No. 5356934 公开了采用(R)-氟西汀治疗睡眠性呼吸暂停的方法。

神经性贪食症，即食欲过盛是美国精神病学会(American Psychiatric Association)1996 年(“DSM- IV”)在“精神疾病的诊断和统计指南(Diagnostic and Statistical Manual of Mental Disorders)”第 4 版中描述的一种疾病，其部分特征是反复狂食，在此期间患者失去控制导致过度进食和自发性的呕吐。该病主要危害中等或上等经济阶层的女性，尤其是大学年龄段的女性。

当前，有两种方法用于治疗贪食症：认知行为的和药理学的。传统药理学治疗涉及抗抑郁药。然而，对贪食症的基础病因的最新研究已经提出另外的药理学治疗。尤其是，一些研究人员提出驱动贪食症行为特征的病理生理学特征与迷走神经的基础活动增强有关，并且提出外消旋的昂丹司琼可能对治疗贪食症有益。Faris, P.L. 等, Biol. Psychiatry (生物神经病学), 32:462-466 (1992); Dumuis 等, N.S. Arch. Pharmacol. (药理学文献), 340:403-410 (1989).

西沙必利，化学名为顺-4-氨基-5-氯-N-[1-[3-(4-氟苯氧基)丙基]-3-甲氧基-4-哌啶基]-2-甲氧基苯甲酰胺，是苯甲酰胺的衍生物，其母体化合物是甲氧氯普胺。Schapira 等，Acta Gastroenterolog. Belg.(比利时胃肠道学报), LIII:446-457 (1990). 苯甲酰胺衍生物由于其作用于

由神经递质血清素调节的神经元系统而具有数种突出的药理学作用.

由于它们对胃肠道血清素神经元系统的调节，许多苯甲酰胺衍生物是有效的镇吐药并通常在癌症化疗和放疗期间用于控制呕吐。Costall 等, Neuropharmacology (神经药理学), 26:1321-1326 (1987). 这种作用几乎肯定是能够阻断特殊位点的血清素的结果，尤其是 3-型 5-羟色胺($5\text{-}HT_3$)受体. Clarke 等，Trends in Pharmacological Scienses(药理科学进展), 10:385-386(1989). 理论上，化疗和放疗能够通过损伤胃肠道的肠嗜铬细胞引起恶心和呕吐. 结果，神经递质血清素释放并且同时刺激迷走神经传入纤维(因此引发呕吐反射)和脑部最后区(postrema region)的化学感受器触发区(trigger zone)中的血清素受体. 苯甲酰胺衍生物这种作用的解剖学位置，以及这种作用是中枢性(CNS)的，还是外周性的，或者是两者的结合仍不清楚. Bames 等, J. Pharm. Pharmacol(药学药理学杂志), 40: 586-588 (1988).

外消旋的西沙必利主要用于治疗胃食管反流疾病(“GERD”)，其特征是胃内容物反流进入食管. 市售购得的西沙必利是名为 PROPULSID®(普瑞博思)的西沙必利的顺式非对映异构体的外消旋混合物.

外消旋的西沙必利与其它治疗药合用导致对肝脏西沙必利代谢的抑制问题. 例如，酮康唑由于其抑制西沙必利的代谢消除而对西沙必利的动力学具有显著的影响，并导致稳态血浆水平升高 8 倍. Physician's Desk Reference®, 第 52 版, Medical Economics Co., Inc., 1988. 外消旋西沙必利与其它治疗药物的相互作用还能够增强心血管副作用，如心脏毒性. 这种增强作用发生在患者系统中存在干扰西沙必利代谢的其它药物，因此使体内的外消旋西沙必利累积的时候.

这种相互作用显著限制了外消旋西沙必利的使用；尤其是，由于外消旋西沙必利通常先于、同时或紧接着其它治疗药物用药. 此外，已经发现患者服用西沙必利导致的不良副作用例如心律失常，

包括室性心动过速、心室纤维颤动、Q_T 时程延长、和尖端扭转性室性心动过速(torsades de pointes)，中枢神经系统(“CNS”)影响，增加收缩压，与其它药物相互作用，腹泻、腹部痉挛和心脏抑制。

外消旋西沙必利人体口服后几乎完全被吸收，但是西沙必利的生物利用度仅 40-50%因为在肝脏有迅速的首过代谢。Van Peer 等，见 Progress in the Treatment of Gastrointestinal Motility Disorders: The Role of Cisapride(胃肠道运动性疾病的治疗进展：西沙必利的作用)，1986 年 9 月德国法兰克福会议论文集，医学文摘(Excerpta Medica)，A.G. Johnson 和 G Lux 主编，阿姆斯特丹，23-29 页(1988)。人体内 90%以上的外消旋西沙必利代谢主要通过哌啶氮的氧化 N-脱烷基或发生在 4-氟苯氧基或苯甲酰胺环上的芳羟基化。Meuldermans 等，Drug Metab. Dispos.(药物降解代谢)，16(3):410-419(1988)；和 Meuldermans 等，Drug Metab. Dispos.(药物降解代谢)，16(3):403-409(1988)；降西沙必利(Norcisapride)，化学名 4-氨基-5-氯-N-(3-甲氧基-4-哌啶基)-2-甲氧基苯甲酰胺，是西沙必利的代谢产物。

最近，光学纯度(-)立体异构体的西沙必利代谢产物降西沙必利已被报道具有多种有用的特性，而没有外消旋西沙必利某些附带的副作用。美国专利 No. 5712293 公开了使用(-)降西沙必利治疗胃食管反流疾病和其它疾病，例如呕吐、消化不良、便秘、胃轻瘫、肠假梗阻和手术后梗阻的方法。

提供安全有效的预防、治疗和控制呼吸暂停、呼吸暂停性疾病、贪食症及相关疾病或其症状的方法，尤其是允许患者进行其它的相关治疗而没有药物-药物间相互作用的不良副作用的治疗方法是需要的。

3. 本发明概述

本发明包括基本不含(+)立体异构体的光学纯度的(-)降西沙必利，或其药学上可接受的盐在预防、治疗或控制呼吸暂停、呼吸暂停性

疾病、贪食症、过敏性肠道综合征、哮喘、尿失禁、晕厥、心动过缓、过缓性心律失常或其症状中的用途. 应当理解，本发明包括各种疾病或多种疾病的预防、治疗或控制的联合处理方法.

本发明还涉及适用于预防、治疗或控制迷走神经介导的疾病或其症状患者的药用组合物，其包括治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐.

本发明还涉及适用于预防、治疗或控制呼吸暂停、呼吸暂停性疾病或其症状患者的药用组合物，其包括治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐.

本发明进一步涉及适用于预防、治疗或控制哺乳动物贪食症、过敏性肠道综合征、哮喘、尿失禁、心动过缓、过缓性心律失常、晕厥、相关疾病、或其症状的药用组合物，其包括治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐，所述量应当足以减轻所述疾病的症状同时减少或避免与服用外消旋西沙必利相关的不良副作用.

本发明还包括单个单位剂型的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐，其包括每粒压片中含约 0.5mg 至约 500mg 的活性成分. 此剂型特别适合于预防、治疗或控制呼吸暂停、呼吸暂停性疾病、贪食症、过敏性肠道综合征、哮喘、尿失禁、心动过缓、过缓性心律失常、晕厥、相关疾病或其症状.

4. 本发明详述

本发明包括基本不含(+)立体异构体的光学纯度(-)降西沙必利，或其药学上可接受的盐在预防、治疗或控制疾病中的用途，包括，但不限于，呼吸暂停、呼吸暂停性疾病、贪食症、过敏性肠道综合征、哮喘、尿失禁、心动过缓、过缓性心律失常、晕厥及相关疾病，或其症状. 呼吸暂停，或呼吸暂停性疾病包括，但不限于，中枢性呼吸暂停，吞咽性呼吸暂停，阻塞性或外周性呼吸暂停，睡眠性呼

吸暂停，和睡眠诱发的呼吸暂停或其复合形式。

本发明还涉及基本不含(+)立体异构体的光学纯度的(-)降西沙必利，或其药学上可接受的盐在预防、治疗或控制呼吸暂停、呼吸暂停性疾病、贪食症、过敏性肠道综合征、哮喘、尿失禁、心动过缓、过缓性心律失常、晕厥及相关疾病，或其症状中的用途，优选同时减少或避免与服用外消旋西沙必利相关的不良副作用。

在一种实施方案中，本发明涉及预防、治疗或控制贪食症的方法，包括给予患者治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐。

在另一种实施方案中，本发明涉及预防、治疗或控制呼吸暂停或呼吸暂停性疾病的方法，包括给予患者治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐。

在另一种实施方案中，本发明涉及预防、治疗或控制患者迷走活性介导的症状的方法，包括给予患者治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐。

本发明还包括预防、治疗或控制过敏性肠道综合征的方法，包括给予患者治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐。

在另一种实施方案中，本发明涉及预防、治疗或控制晕厥，尤其是血管迷走神经性晕厥和心脏或颈动脉窦性晕厥的方法，其包括给予患者治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐。

本发明进一步包括预防、治疗或控制心动过缓或心动过缓性心律失常的方法，其包括给予患者治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐。

在另一种实施方案中，本发明涉及预防、治疗或控制哮喘或哮喘综合征的方法，其包括给予患者治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐。

本发明还包括预防、治疗或控制尿失禁的方法，其包括以治疗有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐给予患者.

在另一种实施方案中，本发明包括单次单位剂型的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐，其包括每粒压片中含约 0.5mg 至约 500mg 的活性成分. 此剂型特别适合于预防、治疗或控制呼吸暂停、呼吸暂停性疾病、贪食症、过敏性肠道综合征、哮喘、尿失禁、心动过缓、过缓性心律失常、晕厥及相关疾病或其症状.

迷走神经是最大的颅神经. 迷走神经有两条主要的分支，其中每一条均提供运动和感觉功能. 迷走神经含有传出纤维，其将大脑固有的延髓神经起源的冲动传送到组织或内脏器官，以及传入纤维，其将冲动从组织送回大脑. 这存在于躯体的大部分，从脑干延伸至颈、胸、和腹部器官. 迷走刺激发生在许多器官，包括心脏、肺、支气管、气管、食管、胃、胰腺、小肠、大肠、结肠、肝、胆囊和泌尿道.

不限于理论，一般认为贪食症、过敏性肠道综合征、尿失禁、心动过缓、过缓性心律失常、哮喘和晕厥，尤其是血管迷走神经性晕厥和心脏或主动脉窦性晕厥的症状受迷走神经的基础活动影响.

不限于理论，一般还认为(-)降西沙必利通过阻断 5-HT 导致的迷走神经去极化而减轻或抑制这些疾病的症状. 因此，在一种实施方案中，本发明涉及基本不含(+)立体异构体的光学纯度的(-)降西沙必利，或其药学上可接受的盐在预防、治疗或控制贪食症、过敏性肠道综合征、哮喘、尿失禁、心动过缓、过缓性心律失常、晕厥以及相关疾病，或其症状中的用途

此外，本发明包括基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐，在与其它治疗药物联用中的用途. 其它治疗药的实例包括，但不限于，氟西汀或其 R 或 S 型立体异构体；

decarboethoxyloratidine; 昂丹司琼或其 R 或 S 型立体异构体(优选 R-昂丹司琼)、泛癸利酮、双嘧达莫、毛果芸香碱或其立体异构体、扑米酮或其 R 或 S 型立体异构体、枸橼酸奥芬那君等，及其任何活性代谢产物．在与其它这些治疗药的联合用药以预防、治疗或控制呼吸暂停、呼吸暂停性疾病、贪食症、过敏性肠道综合征、尿失禁、心动过缓、过缓性心律失常、哮喘、晕厥、或其症状的本发明方法中，基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐，可以同时也可以顺次给药，即，(-)降西沙必利与至少一种其它药物合并给药、同时但分开给药、或顺次给药．在这些方法中各种组合物可以同时、顺次、或任何联用形式的同时或顺次给药．

本发明的这些方法和组合物还包括有利于减轻或避免与外消旋西沙必利给药相关的不良副作用．本发明还允许同时或顺次使用抗抑郁药，如三环类抗抑郁药，氟西汀或其 R 或 S 型立体异构体，舍曲林(Zoloft®)，和同类药，以及其它药物，如抗焦虑药．

本说明书所用术语“患者”指哺乳动物，尤其是人类．

本发明中预防、治疗或控制贪食症的方法特别适用于青少年或青年成人．在优选实施方案中，预防、治疗或控制贪食症的方法适用于 13-25 岁的女性．应当认识到本发明的方法可用于预防、治疗或控制男性和女性，包括儿童和成人的贪食症，尽管优选上面提及的那些．

本发明中预防、治疗或控制呼吸暂停或呼吸暂停性疾病的方法特别适用于过度肥胖的男性．在优选实施方案中，该方法适用于预防、治疗或控制过度肥胖的男性的阻塞性呼吸暂停．应当认识到本发明的方法可用于预防、治疗或控制男性和女性，包括儿童和成人的呼吸暂停或呼吸暂停性疾病，尽管优选上面提及的那些．

本说明书所用术语“不良作用”或“不良副作用”包括，但不限于，心脏心律失常、心脏传导阻滞、刺激食欲、体重增加、镇静、胃肠道疾病、头痛、口干、便秘、腹泻和药物-药物相互作用．例见，

Physician's Desk Reference®(内科医生手册)，第 52 版，Medical Economics Co., Inc., 1308-1309 页，1988. 术语“心脏心律失常”包括，但不限于，室性心动过速、尖端扭转性室性心动过速、Q_T 时程延长和室性纤维性颤动.

本说明书所用术语“外消旋”意思是化合物的(-)和(+)对映体混合物其中(-)和(+)对映异构体的存在比例约为 1:1.

本文使用的术语“基本光学纯度”、“光学纯度”、和“光学纯度对映异构体”，意思是以降西沙必利总重量计，组合物中含有重量比大于约 90%的(-)降西沙必利立体异构体，优选重量比大于约 95%的需要的对映异构体，并且更优选重量比大于约 99%的需要的对映异构体. 换而言之，术语“基本不含”意思是根据本发明存在相应的(+)降西沙必利重量百分比小于 10%，优选重量百分比小于 5%，而且更优选的重量百分比小于 1%.

本文使用的术语“5-羟色胺受体拮抗剂”、“血清素受体拮抗剂”、和“5-HT_3 受体拮抗剂”，意思是能够可逆性地结合 5-羟色胺受体的化合物，无论是位于哺乳动物的迷走神经还是其它位置.

本说明书使用的词汇“贪食症”和“神经性贪食症”与 DSM-IV 的定义一致.

本文使用的术语“呼吸暂停”和“呼吸暂停性疾病”包括，但不限于，以呼吸中断为特征的疾病，其中患者停止呼吸的时间长度足以使血液和脑部的氧含量减少而二氧化碳含量增加.

本文使用的术语“哮喘”被定义为以气管和支气管对多种刺激的反应性增强为特征的疾病，其所致的症状包括，但不限于，喘鸣、咳嗽、呼吸急促、呼吸困难等. 哮喘包括，例如，过敏性哮喘.

本文使用的术语“晕厥”的定义是以大脑血流减少导致失去知觉和体位张力为特征的疾病. 晕厥包括，例如，亚-斯(Adams-Stokes)二氏晕厥、心原性晕厥、颈动脉窦性晕厥、癔病性晕厥、喉性晕厥、局部呼吸暂停、排尿晕厥、立位性晕厥、体位性晕厥、吞咽晕厥、

癫痫发作引起的晕厥、肺栓塞引起的晕厥、逐步发作的晕厥、剧咳后晕厥、血管减压神经性晕厥、或血管迷走神经性晕厥。

本文使用的术语“治疗有效量的(-)降西沙必利”，意思指单独使用或与其它药物联用的基本光学纯度的(-)降西沙必利，或其药学上可接受的盐的量，在预防、治疗或控制呼吸暂停、呼吸暂停性疾病、贪食症、过敏性肠道综合征、尿失禁、心动过缓、过缓性心律失常、哮喘、晕厥、或其一种或数种症状中能够发挥治疗作用。适用于各种疾病的治疗有效量可能不同，此易为本领域内一般技术人员所了解。

基本纯净的(-)降西沙必利可以由西沙必利的外消旋混合物获得，其化学合成按照 1983 年 4 月 13 日发布的欧洲专利申请 No. 0076530 A2 和美国专利 No. 4962115、5057525、5137896 描述的方法进行，其公开内容通过引用结合到本文中。还见于 Van Aaele 等，Drug Development Res.(药物发展研究), 8:225-232(1986)。西沙必利代谢为降西沙必利的描述见 Meuldermans, W.等, Drug Metab. Dispos. (药物代谢降解), 16(3):410-419(1988)和 Meuldermans, W.等, Drug Metab. Dispos.(药物代谢降解), 16(3):403-409(1988)。外消旋降西沙必利的制备也为本领域内一般技术人员所知，特别见于 Van Daele 的欧洲专利 0076530 A2 和美国专利 No. 5137896，其公开内容通过引用结合到本文中。

光学纯度的(-)降西沙必利也可以通过 HPLC 分离或采用常规方法，例如，通过旋光活性的溶剂酸拆分对映异构体而得自外消旋的降西沙必利。拆分外消旋的降西沙必利也为本领域内一般技术人员所知，特别是来自 Jacques, J.等, Enantiomers, Rasemates and Resolutions [对映异构体、外消旋体及其拆分] (Wiley-Intersciencs, 纽约, 1981); Wilen, S. H. 等, Tetrahedron (四面体), 33 : 2725 (1977); Eliel, E. L. Stereochemistry of Carbon Compounds (含碳化合物的立体化学) (McGraw-Hill, 纽约, 1962); Milen, S. H. Tables of Resolving Agents and

Optical Resolution (拆分试剂和光学拆分一览表), 268 页(E. L. Eliel 主编, Univ. of Notre Dame Press, Notre Dame, IN, 1972).

除分离技术外，如上文所述的那些，还可以采用本领域内一般技术人员所知的方法，通过立体特异性合成方法合成(-)降西沙必利。手性合成可以得到高纯度的对映异构体产品。然而，在某些情况下，对映异构体的产物纯度不够高。熟练的技术员应当懂得上述可以用于进一步提高手性合成所得的(-)降西沙必利对映异构体纯度的分离方法。

光学纯度的(-)降西沙必利也可以通过酶的生物催化拆分而由外消旋混合物制备。例见，美国专利 No. 5057427 和 5077217, 其公开内容通过引用结合到本文中。

基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐，在紧急或长期控制上述疾病或不适中的预防或治疗剂量的大小根据预防、治疗或控制的病情严重程度和给药途径而变化。例如，可采用口服、粘膜(包括直肠)、胃肠外(包括皮下、肌内、大剂量注射和静脉内)、舌下、透皮、鼻内、颊内及类似途径。剂型包括片剂、锭剂、糖锭、分散液、悬浮液、栓剂、溶液、胶囊、软明胶胶囊、贴剂等。剂量，或许是剂量次数，将根据个体患者的年龄、体重及反应而变化。本领域内技术人员可根据这些因素的考虑，容易地选择合适的剂量方案。一般来说，对于本文所述疾病，总的日剂量范围是从约 0.5mg 至约 500mg 基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐。优选的日剂量范围是从约 1mg 至约 250mg，更优选的日剂量范围是从约 1mg 至约 100mg。活性成分优选以每日一至四次以单一剂量或分剂量口服，或以缓慢的静脉注射给药。本发明最优选的给药途径是口服。口服剂型通常可以单位剂型存在并以药学领域熟知的任何方法制备。

在处理患者时，其治疗可以从较低剂量，例如，从约 0.5mg 至约 10mg 开始，并根据患者整体反应增加至推荐剂量或更高。进一步

推荐的是儿童、65 岁以上的患者、以及有肾或肝功能损伤的患者，开始时接受低剂量，并在个体反应及血液水平的基础上进行滴定。在某些情况下可能需要采用这些范围之外的剂量，这对于本领域普通技术人员来说是显而易见的。此外，需要注意的是，临床医师和内科大夫应当知道，结合患者的个体反应，怎样及何时中断、调整、或结束治疗。

可以采用任何合适的给药途径给予患者有效量的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐。在任何给定情况下，最适途径将取决于预防、治疗或控制的疾病的性质和严重程度。

用于本发明的药用组合物包括作为活性成分的基本不含(+)立体异构体的光学纯度的(-)降西沙必利，或其药学上可接受的盐，并且可以含有药学上可接受的载体，并任选含有其它治疗成分。本文所用术语“药学上可接受的盐”指由药学上可接受的无毒酸包括无机酸、有机酸制备的盐、溶剂化物、水合物或其包合物。这些无机酸的实例有盐酸、氢溴酸、氢碘酸、硝酸、硫酸和磷酸。合适的有机酸可选自，例如，脂肪酸、芳香酸、羧酸和磺酸类有机酸，其实例有甲酸、乙酸、丙酸、琥珀酸、樟脑磺酸、柠檬酸、富马酸、葡萄糖酸、羟乙磺酸、乳酸、苹果酸、粘酸、酒石酸、对甲苯磺酸、羟基乙酸、葡萄糖醛酸、马来酸、糠酸、谷氨酸、苯甲酸、邻氨基苯甲酸、水杨酸、苯基乙酸、扁桃酸、扑酸、甲磺酸、乙磺酸、泛酸、苯磺酸(besylate)、硬脂酸、对氨基苯磺酸、海藻酸、半乳糖醛酸等。特别优选的酸是氢溴酸、盐酸、磷酸和硫酸。在优选的实施方案中，以(-)降西沙必利的游离碱或水合物给药。

在实际应用中，可根据常规药物配方技术将基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐，作为活性成分与药用载体充分混合。载体可以采用多种形式并且可以根据所需给药的制剂形式含有多种成分。本发明的组合物包括，但不限于，悬浮液、

溶液和酏剂，气雾剂，或载体，包括(但不限于)淀粉、糖、微晶纤维素、稀释剂、颗粒剂、润滑剂、粘合剂、崩解剂等。由于其给药方便，优选片剂和胶囊并代表了最有利的口服单位剂型，在此情况下采用固体药用载体。如果需要，片剂可以采用标准含水或无水技术包衣。

适合口服的本发明药用组合物可以分散的药用单位剂型存在，例如胶囊、扁囊剂、软塑明胶胶囊、片剂或气雾剂，每种剂型含预定量的为粉末或颗粒形式的活性成分，或为在含水液体、不含水液体、水包油乳液或油包水乳液中的溶液或悬液。这些组合物可以通过任何药学方法制备，但所有方法均包括将活性成分与一种或一种以上必需成分组成的药学上可接受的载体混合的步骤。一般地，组合物的制备是将活性成分与液体载体或精细粉碎的固体载体或两者均匀且精细混合，然后(如果需要)使产品形成所需的外型。口服固体制剂优于口服液体制剂。一种优选的口服固体制剂是胶囊，但最优选的口服固体制剂是片剂。

例如，可以任选与一种或一种以上的辅助成分经压片或铸模来制备片剂。压制片剂的制备可以将自由流动形式的活性成分，如粉末或颗粒，任选与粘合剂、润滑剂、惰性稀释剂、成粒剂、表面活性剂、分散剂等混合，再在合适的机器中压制成片。模压片可通过将湿润的活性化合物粉末与惰性液体稀释剂的混合物在合适的机器中铸模来制备。每粒片剂优选含有约 0.5mg 至约 500mg，更优选约 1mg 至约 250mg 的活性成分。每粒扁囊剂或胶囊优选含有约 0.5mg 至约 500mg，更优选约 1mg 至约 250mg 的活性成分。然而，组合物中的活性成分的含量可以根据欲给予患者的活性成分的量而改变。

基本不含(+)立体异构体的光学纯度的(-)降西沙必利，或其药学上可接受的盐，可以采用本领域中熟知的常规方法，例如在 Ebert, Pharm. Tech(制药技术), 1(15):44-50 (1977)中的方法，配制为软塑明胶胶囊单位剂型的药用组合物。软塑明胶胶囊具有比硬明胶胶囊外壳

厚一些的柔软、球形的明胶外壳，其中明胶通过加入增塑剂，例如，甘油、山梨醇或类似的多元醇塑造。胶囊壳硬度可以通过改变采用的明胶类型和增塑剂及水的用量而改变。软明胶壳可以含有防腐剂，例如甲基-或丙基对羟基苯甲酸酯和山梨酸，以防止真菌生长。活性成分可以溶解或悬浮于液体溶媒或载体中，如植物或矿物油、乙二醇类如聚乙二醇和丙二醇、甘油三酯、表面活性剂如聚山梨醇酯、或它们的混合物。

除上文指出的常见剂型外，本发明化合物还可以通过控释方式、传递装置、或两者结合而给药，此为本领域普通技术人员所熟知，例如描述于美国专利 No. 3845770; 3916899; 3536809; 3598123; 4008719; 5674533; 5059595; 5591767; 5120548; 5073543; 5639476; 5354556;和 5733566 中的那些技术，这些专利的公开内容通过引用结合到本文中。这些药用组合物可以用于提供本文所用活性成分的缓慢或控制释放，例如，提供所需的释放模式的不同比例的氢化丙基甲基纤维素、其它聚合物基质、凝胶、渗透膜、渗透系统、多层包衣、微粒、脂质体、微球等或它们的组合。本领域普通技术人员所知的合适的控释制剂，包括在此所述的那些，可以容易地选用于含有本发明(-)降西沙必利的组合物。因此，本发明包括适用于控制释放的适合口服给药的单一单位剂型，如片剂、胶囊、微胶囊(gelcaps)、caple 等。

所有控释药用产品与其非控释的对应产品相比都具有提高药物疗效的共同目标。理想条件下，在药物治疗中采用最佳设计的控释制剂的特点是，在最短的时间内使用最少量的药物治愈或控制疾病。控释制剂的优点可包括：1) 延长药物的活性期；2)减少给药次数；及 3) 增强患者的适应性。

大多数控释制剂被设计成在开始时释放一定量的药物以迅速产生所需的疗效，并逐渐和持续释放其它量的药物，以便在延长的时间段内维持这种水平的疗效。为维持体内这种稳定的药物水平，必

须使药物以一定的速率从剂型中释放，这种释放速率应能替代体内已代谢的和从体内排出的药物的量.

活性成分的控释可能受到多种诱导因素的刺激，例如，pH、温度、酶、水、或其它生理条件或化合物。本发明说明书中的术语“控释组分”在此定义为有利于药用组合物中的活性成分(例如，(-)降西沙必利)的控释的一种化合物或多种化合物，包括聚合物、聚合物基质、凝胶、渗透膜、脂质体、微球等，或它们的组合。

基本不含(+)立体异构体的光学纯度的(-)降西沙必利，或其药学上可接受的盐，也可以配制为用于胃肠外注射(皮下、大剂量注射、肌内、或静脉内)给药的制剂，并且可以配制成单位剂型，例如多剂量的容器或安瓿。用于胃肠外给药的基本不含(+)立体异构体的(-)降西沙必利，或其药学上可接受的盐的组合物可以是在水性或油性溶媒中的悬液、溶液、乳液等，并且除活性成分外还可以含有一种或一种以上的处方试剂，如扩散剂、悬浮剂、稳定剂、防腐剂等。

当使用静脉注射或输注组合物时，合适的日剂量范围是，例如，从约 0.5mg 至约 500mg 的每日总剂量，优选约 1mg 至约 250mg，更优选约 1mg 至约 100mg。

另一种优选的给药途径是透皮给药，例如，通过腹部皮肤贴剂给药.

本发明通过参考下列实施例进一步定义，这些实施例详细叙述本发明化合物及其组合物的制备，以及它们的用途。在不脱离本发明的目的和精神下的许多修改，无论针对材料还是针对方法，都是可行的，这对于本领域内的技术人员是显而易见的.

5 实施例

5.1 实施例 1: 生物利用度

采用 23 号蝶式针头一分钟内大剂量静脉注射进入隐静脉，或经口管饲单一剂量，给予雄性毕格(beagle)狗单一剂量的实验药物或溶

媒．每条狗在静脉注射或口服西沙必利或降西沙必利的旋光异构体或外消旋混合物之前或之后的 0.083、0.25、0.5、1、2、3、4、6、9、12 和 24 小时采集 2.0ml 全血．这些狗在给予实验药物之前以绷带固定并在采集 0.083 小时的血液样品后转移到代谢笼中．实验中所有血样均在早晨从插入头静脉的血管导管中采集。

将这些血液抽入 3cc 注射器中．弃去开始时的 1.0-2.0mL 的血液．将其后的 2.0mL 全血快速转移到肝素化试管中．此肝素化试管保存在冰上直到加入血液．血液加入到试管后，混合试管的内容物并离心获得血浆．小心倒出该血浆并转移至有下列标签的试管中：动物编号、实验药物的给药剂量、给药途径、给药日期和采集血液的时间．这些试管在分析前一直保存于-20°C 下．

每个血浆样品中的降西沙必利旋光异构体或外消旋体的浓度分析采用高效液相色谱法测定．两种给药途径下的各实验药物的血浆浓度对采样时间作图．通过比较口服给药途径和静脉途径的 C_{max} 和 AUC 确定各实验药物的口服生物利用度．计算经两种途径下各实验药物的 $t_{1/2}$ 作为药物作用时间的指标。

5.2 实施例 2：受体活性

5-HT_{1A} 受体活性

采用受体选择性和扩增技术(R-SAT)(Receptor Technologies Inc., Winooski, VT)测定外消旋降西沙必利、西沙必利、以及它们的对映体对表达在 NIH 3T3 细胞上的克隆人血清素 5-HT_{1A} 受体亚型的潜在激动和/或拮抗活性，例如，见 Burstein 等, J. Biol. Chem.(生物化学杂志), 270:3141-3146(1995); 和 Messier 等, Pharmacol. Toxicol.(药理学和毒理学), 76(5):308-311(1995)。

检测涉及标记酶，β-半乳糖苷酶与有关的血清素受体的共表达．配体刺激表达受体以及标记物的细胞增殖．配体诱导的效应可以由标记物分析测定。

孵育 NIH 3T3 细胞，接种、然后采用人 5-HT_{1A} 血清素受体、pSV-β-半乳糖苷酶、和鲑鱼精子 DNA 转染。一天后更换培养基，并于 2 天后，将胰蛋白酶消化的细胞等份接种到 96 孔培养板的孔中。在配体的存在下培养 5 天后，测定β-半乳糖苷酶水平。然后漂洗细胞并与底物、对硝基苯基-β-D-吡喃半乳糖苷一起孵育。16 小时后，在平板读出仪上于 405nm 处读出该板。以七种不同浓度(10, 2.5, 0.625, 0.156, 0.039, 0.0098 和 0.0024nM)检测每个化合物(一式三份)的活性。

没有一个实验化合物显示出对人 5-HT_2 血清素受体的激动活性。将这些化合物的拮抗抑制数据代入等式:

$$\text{反应}=\text{最大反应}+\frac{(\text{最小反应})}{1+(\text{配体浓度}/EC_{50})}$$

采用 KaleidaGraph 非线性最小方差分析法计算拮抗浓度 2μM 的 5-HT 活性的 IC_{50} 值(抑制 50%特异性结合所需的浓度)，其结果列于表 1 和 2.

5-HT_2 受体活性

采用受体选择性和扩增技术(R-SAT)(Receptor Technologies Inc., Winooski, VT)测定外消旋降西沙必利、西沙必利、以及它们的对映异构体对表达在 NIH 3T3 细胞上的克隆人血清素 5-HT_2 受体亚型的潜在激动和/或拮抗活性，例如，见 Burstein 等, J. Biol. Chem.(生物化学杂志), 270:3141-3146(1995); 和 Messier 等, Pharmacol. Toxicol.(药理学和毒理学), 76(5):308-311(1995).

检测涉及标记酶，β-半乳糖苷酶与有关的血清素受体的共表达。配体刺激表达受体以及标记物的细胞增殖。配体诱导的效应可以由标记物分析测定。

孵育 NIH 3T3 细胞，接种、然后采用人 5-HT_2 血清素受体、pSV-β-半乳糖苷酶和鲑鱼精子 DNA 转染。一天后更换培养基，并于 2 天后，将胰蛋白酶消化的细胞等份接种到 96 孔培养板的孔中。在配体的存

在下培养 5 天后，测定β-半乳糖苷酶水平．然后漂洗细胞并与底物、对硝基苯基β-D-吡喃半乳糖苷一起孵育．16 小时后，在平板读出仪上于 405nm 处读出该板．以七种不同浓度(10, 2.5, 0.625, 0.156, 0.039, 0.0098, 和 0.0024nM)检测每个化合物(一式三份)的活性。

没有一个实验化合物显示出对人 5-HT_2 血清素受体的激动活性．将这些化合物的拮抗抑制数据代入等式:

$$\text{反应}=\text{最大反映}+\frac{(\text{最小反应})}{1+(\text{配体浓度}/EC_{50})}$$

采用 KaleidaGraph 非线性最小方差分析法计算拮抗浓度 2μM 5-HT 活性的 IC_{50} 值，其结果列于表 1 和 2.

表 1

5-HT_{1A} 和 5-HT_2 受体的 IC_{50} 计算值(μM)

化合物	5-HT_{1A}	5-HT_2
(±)降西沙必利	7.48	2.21
(+)降西沙必利	0.0054	0.38
(-)降西沙必利	1.30	--

表 2

5-HT_{1A} 和 5-HT_2 受体的 IC_{50} 计算值(μM)

化合物	5-HT_{1A}	5-HT_2
(±)西沙必利	--	0.26
(+)西沙必利	--	0.0050
(-)西沙必利	--	7.08

5.3 实施例 3: 受体结合

5-HT_3 受体

检测(Cerep, Celle I'Evescault, France)外消旋降西沙必利、外消旋西沙必利以及它们的(+)-和(-)-立体异构体对衍生自 N1E-115 细胞的5-HT_3 受体亚型的结合。

与适当的配体孵育后，采用 Brandel 或 Packard 细胞收获器通过 GF/B 玻璃纤维滤纸真空下迅速过滤制品并用冰冷缓冲液洗涤。采用液闪混合液(Formula 989)以液体闪烁计数器(LS6000, Beckman)测定结合放射活性。

结合受体的特异性放射配体由结合总量与过量未标记配体存在下测定的非特异性结合的差值决定。结果以在化合物存在下测得的特异性结合抑制百分率表示。采用 3×10^{-10}M 至 10^{-5}M 浓度范围内获得的完全竞争曲线并以非线性回归分析法计算确定 IC_{50}。其结果见下列表 3 和 4。

5-HT_4 受体

检测(Cerep, Celle I'Evescault, France)外消旋降西沙必利、外消旋西沙必利以及它们的(+)-和(-)-立体异构体对来自豚鼠 striata 的 5-HT_3 受体亚型的结合。

与适当的配体孵育后，采用 Brandel 或 Packard 细胞收集器通过 GF/B 玻璃纤维滤纸真空下迅速过滤样品并以冰冷缓冲液洗涤。采用液闪混合液(Formula 989)以液体闪烁计数器(LS6000, Beckman)测定结合的放射活性。

结合受体的特异性放射配体由结合总量与过量未标记配体存在下测定的非特异性结合的差值决定。结果以在化合物存在下测得的特异性结合抑制百分率表示。采用 3×10^{-10}M 至 10^{-5}M 浓度范围内获得的完全竞争曲线并以非线性回归分析法计算确定 IC_{50}。其结果见下列表 3 和 4。

表 3

结合 5-HT_3 和 5-HT_4 位点的 IC_{50}(nM)值

化合物	5-HT_3	5-HT_4	5-HT_3/5-HT_4 比值
(±)降西沙必利	8.2	686	0.012
(+)降西沙必利	4.5	331	0.014
(-)降西沙必利	30.4	1350	0.023

表 4

结合 5-HT_3 和 5-HT_4 位点的 IC_{50}(nM)值

化合物	5-HT_3	5-HT_4	5-HT_3/5-HT_4 比值
(±)西沙必利	365	169	2.2
(+)西沙必利	310	340	0.9
(-)西沙必利	2790	199	14.0

采用基于活性化合物提高组织培养基中生长的小鼠胚胎胶质(colloculi)神经元中环 AMP 生成量的能力分析法也可以用于评价对 5-HT_4 受体位点的激动活性，例如，见 Dumuis 等，N. S. Arch. Pharmacol.(药理学文献), 340:403-410 (1989).

5.4 实施例 4: 口服制剂

片剂

配方	每片的含量(mg)		
	A	B	C
活性成分	5.0	10.0	25.0
(-)降西沙必利			
乳糖 英国药典	62.0	57.0	42.0
淀粉 英国药典	20.0	20.0	20.0
微晶纤维素	10.0	10.0	10.0
氢化植物油	1.5	1.5	1.5

聚乙烯吡咯烷酮	1.5	1.5	1.5
压片重量	100.0	100.0	100.0

通过用合适的药筛过筛活性成分(-)降西沙必利，并与乳糖混合直至形成均一的混合物。加入适当体积的水并将粉末制粒。干燥后，将此颗粒过筛并与其余的赋形剂混合。然后将所得颗粒压制成所需形状的片剂。其它含量的片剂可以通过改变活性化合物对赋形剂的比例或压片重量而制备。

5.5 实施例 5: 口服制剂

片剂

配方	每片的含量(mg)		
	A	B	C
活性成分 (-)降西沙必利	5.0	10.0	25.0
乳糖 英国药典	48.5	43.5	28.5
淀粉 英国药典	30.0	30.0	30.0
预凝胶玉米淀粉 英国药典	15.0	15.0	15.0
硬脂酸镁 英国药典	1.5	1.5	1.5
压片重量	100.0	100.0	100.0

通过用合适的药筛过筛活性成分(-)降西沙必利，并与乳糖、淀粉、以及预凝胶玉米淀粉混合直至形成均一的混合物。加入适量的水并将粉末制粒。干燥后，将此颗粒过筛并与其余的赋形剂混合。然后将所得颗粒压制成所需形状的片剂。其它含量的片剂可以通过改变活性化合物对赋形剂的比例或压片重量而制备。

5.6 实施例 6: 口服制剂

胶囊

配方	每粒胶囊的含量(mg)		
	A	B	C
活性成分	5.0	10.0	25.0
(-)降西沙必利			
淀粉 1500	94.0	89.0	74.0
硬脂酸镁 英国药典	1.0	1.0	1.0
总重量	100.0	100.0	100.0

将活性成分过筛并与赋形剂混合。采用合适的机器将此混合物填充到 2 号大小的硬明胶胶囊中。可以通过改变填充重量，并且如果需要，改变合适的胶囊大小以制备其它剂量的胶囊。

5.7 实施例 7

静脉制剂

配方	
活性成分	1000 μg/mg
(-)降西沙必利	
稀盐酸 英国药典	至 pH 3.5
氯化钠注射液 英国药典	1 mL

将活性成分溶解于稀盐酸(英国药典)中形成(-)降西沙必利浓度为 1000 μg/mL 的溶液。然后，在临用前将该溶液与氯化钠注射液(英国药典)混合。

尽管已借助具体实施方案对本发明进行了描述，但在不背离权利要求定义的本发明的精神和范围下显然可以进行各种改变和修饰，这对本领域内技术人员是显而易见的。这些修饰也打算列入所附权利要求的范围内。