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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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MILNACIPRAN PARA EL TRATAMIENTO A LARGO PLAZO DEL SINDROME
DE FIBROMIALGIA

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CYPRESS BIOSCIENCE, INC.

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SAN DIEGO, CA, ESTADOS UNIDOS DE AMÉRICA

74. APODERADO

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22. SANTAFE DE BOGOTA, D.C.

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1

SOLICITUD DE:



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II..

2

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10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$501.000
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☐ Poderes, si fuere el caso. **Fotocopia autenticada**
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
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- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
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- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: Tarjeta de Propietarios
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(54) Title: MILNACIPRAN FOR THE LONG-TERM TREATMENT OF FIBROMYALGIA SYNDROME

(57) Abstract: The present invention is directed to methods for providing long-term treatment of fibromyalgia syndrome (FMS) by administering a dual re-uptake inhibitor to a patient with FMS. More particularly, the present invention is directed to the long-term treatment of FMS by administering a norepinephrine-serotonin reuptake inhibitor (NSRI) to a patient with FMS.

MILNACIPRAN FOR THE LONG-TERM TREATMENT OF FIBROMYALGIA SYNDROME

FIELD OF THE INVENTION

The present invention relates to the long-term treatment of fibromyalgia and its symptoms by administering to a patient suffering from fibromyalgia a dual norepinephrine serotonin reuptake inhibitor. More particularly, the present invention relates to the long-term treatment of fibromyalgia and its symptoms by administering to a patient suffering from fibromyalgia a dual norepinephrine serotonin reuptake inhibitor that inhibits the reuptake of norepinephrine to an equal or greater extent than it inhibits the reuptake of serotonin.

BACKGROUND

Fibromyalgia, also known as the fibromyalgia syndrome (FMS) is a common systemic rheumatologic disorder estimated to affect 2% to 4% of the population, second in prevalence among rheumatologic conditions only to osteoarthritis. Wolfe et al., *Arthritis Rheum.* 1990;33(2):160-172; Wolfe et al., *Arthritis Rheum.* 1995;38(1):19-28. Fibromyalgia is associated with a reduced threshold for pain, generally identified by an increased sensitivity to pressure all over the body, and is often accompanied by fatigue, sleep disturbance, and morning stiffness. Other common symptoms include headache, migraine, variable bowel habits, diffuse abdominal pain, and urinary frequency. The diagnostic criteria for fibromyalgia require not only a history of widespread pain, but also the finding of tenderness on physical examination ("tender points"). In order to fulfill the criteria for fibromyalgia established in 1990 by the American College of Rheumatology (ACR), an individual must have *both* widespread pain involving all four quadrants of the body as well as the axial skeleton *and* the presence of 11 of 18 tender points on examination. Wolfe et al., *Arthritis Rheum.* 1990;33(2):160-172.

While there has been some suggestion that FMS may represent a form of somatization disorder, there is increasing evidence and acceptance that FMS is a medical problem, reflecting a generalized heightened perception of sensory stimuli. The abnormality is thought to occur within the central nervous system (CNS) rather than peripherally, and the proposed pathophysiological defect is termed "central sensitization." Clauw DJ and Chrousos GP, *Neuroimmunomodulation* 1997;4(3):134-153; Yunas MB, *J Rheumatol.* 1992;19(6):846-850; Bradley et al., *Curr Rheumatol Rep.* 2000;2(2):141-148; Simms RW, *Am J Med Sci.* 1998;315(6):346-350. FMS patients typically suffer from both allodynia (perceiving pain even from a non-painful stimulus such as light touch) and hyperalgesia (an augmentation of

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pain processing in which a painful stimulus is magnified and perceived with higher intensity than it would be by a normal volunteer). Mountz et al., *Arthritis & Rheumatism* 1995;38(7):926-938; Arroyo JF and Cohen ML, *J Rheumatol.* 1993; 20(11):1925-1931. In this regard, there are many parallels in its clinical presentation and proposed underlying mechanisms with neuropathic pain, such as diabetic neuropathy and trigeminal neuralgia. Sindrup SH and TS Jensen, *Pain* 1999;83(3):389-400; Woolf CJ, *Nature* 1983;306(5944):686-688; Woolf CJ and RJ Mannion, *Lancet* 1999;353(9168):1959-1964. As a result, FMS is treated today primarily within this medical model. It is most often diagnosed in the primary care setting, and almost half of the office visits are to internal medicine and family practice providers (1998 National Ambulatory Medical Care Survey). Visits to rheumatologists account for 16% of FMS patients' office visits. The remainder of visits are to a variety of tertiary care providers, including pain centers, physical medicine specialists, and psychiatrists.

Individuals with fibromyalgia suffer from a number of other symptoms, including a high incidence of recurrent non-cardiac chest pain, heartburn, palpitations, and irritable bowel syndrome. Wolfe, et al., *Arthritis Rheum.* 1990;33(2):160-172; Mukerji et al., *Angiology* 1995;46(5):425-430. Although the physiologic basis of these symptoms remains unclear, increasing evidence suggests that dysfunction of the autonomic nervous system is common in fibromyalgia and related illnesses. Clauw DJ and Chrousos GP, *Neuroimmunomodulation* 1997;4(3):134-153; Freeman R and Komaroff AL, *Am J Med.* 1997;102(4):357-364. Prospective studies of randomly selected individuals with fibromyalgia have detected objective evidence of dysfunction of several visceral organs, including a 75% incidence of echocardiographic evidence of mitral valve prolapse, a 40 - 70% incidence of esophageal dysmotility, and diminished static inspiratory and expiratory pressures on pulmonary function testing. Lurie et al., *Scand J Rehab Med.* 1990;22(3):151-155; Pellegrino et al., *Arch Phys Med Rehab.* 1989;70(7):541-543. Neurally-mediated hypotension and syncope also appear to occur more frequently in individuals with fibromyalgia. Rowe et al., *Lancet* 1995;345(8950):623-624. Fibromyalgia is also associated with high rates of disability, increased health care utilization, more frequent psychiatric consultations and a greater number of lifetime psychiatric diagnoses than controls.

Fibromyalgia research has recently emerged as a significant area of investigation separate from the study of other chronic pain conditions. A significant body of literature already supports the use of tricyclic antidepressants for FMS, and there are a few other controlled studies evaluating the efficacy of other therapeutic agents as well. However, the

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interpretation of trial data is complicated by factors such as the lack of an accepted binary definition of a "responder" versus a "non-responder," as is now commonly used for trials of other rheumatological conditions, such as Rheumatoid Arthritis. Felson et al., *Arthritis Rheum.* 1993;36(6):729-740; Felson DT, *J Rheumatol.* 1993;20(3):581-534. In addition, there is no consensus regarding many aspects of trial design, including the designation of appropriate end-points. Nonetheless, there is general agreement that the measurement and characterization of patients' pain is of paramount importance in the determination of an agent's effectiveness in FMS; assessments of fatigue, sleep, depression, physical functionality and overall well-being help to further illuminate an agent's overall effectiveness.

A broad array of medication has been used 'off-label' in patients with FMS with varying degrees of success. Buskila D, *Baillieres Best Pract Res Clin Rheumatol.* 1999;13(3):479-485; Leventhal LJ, *Ann Intern Med.* 1999;131(11):850-858; Lautenschlager J, *Scand J Rheumatol Suppl.* 2000;113:32-36. While antidepressants are the cornerstone of many treatment paradigms, other agents such as anti-convulsants, antispasticity agents, anxiolytics, sedatives, and opiates have been used. Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are also used by a large number of patients (Wolfe et al., *Arthritis Rheum.* 1997;40(9):1571-1579), even though peripheral inflammation has not been demonstrated (Clauw DJ and Chrousos GP, *Neuroimmunomodulation* 1997;4(3):134-153), and numerous studies have failed to confirm their effectiveness as analgesics in FMS. Goldenberg et al., *Arthritis Rheum.* 1986;29(11):1371-1377; Yunus et al., *J Rheumatol.* 1989;16(4):527-532; Wolfe et al., *Arthritis Rheum.* 2000;43(2):378-385; Russell et al., *Arthritis Rheum.* 1991;34(5):552-560; Quijada-Carrera et al., *Pain* 1996;65(2-3):221-225. These agents do, however, provide an element of protection against other peripheral pain generators, such as osteoarthritis.

Antidepressants of all varieties represent a common form of therapy for many chronic pain states, including FMS. Sindrup SH and Jensen TS, *Pain* 1999;83(3):389-400; Buskila D, *Baillieres Best Pract Res Clin Rheumatol.* 1999;13(3):479-485; Leventhal LJ, *Ann Intern Med.* 1999;131(11):850-858; Lautenschlager J, *Scand J Rheumatol Suppl.* 2000;113:32-36; Bennett RM, *J Functional Syndromes* 2001;1(1):79-92. The majority of available antidepressants directly and/or indirectly increase the levels of 5-HT and/or NE in the CNS. Monoaminergic levels are increased either by inhibiting re-uptake (by blocking transport proteins) or interfering with the breakdown of the monoamine (by inhibiting the monoamine oxidase enzymes) after its release into the synaptic cleft.

Tricyclic Antidepressants (TCAs)

The TCAs most commonly employed in the treatment of FMS include amitriptyline, doxepin, and cyclobenzaprine. Buskila D, *Baillieres Best Pract Res Clin Rheumatol*. 1999;13(3):479-485; Lautenschlager J, *Scand J Rheumatol Suppl*. 2000;113:32-36; Bennett RM, *J Functional Syndromes* 2001;1(1):79-92. While cyclobenzaprine is typically classified as a muscle relaxant, rather than an antidepressant, it shares structural and pharmacological similarities with the TCAs, although its sedating qualities often override its usefulness in other applications. Kobayashi et al., *Eur J Pharmacol*. 1996;311(1):29-35. TCAs block the re-uptake of both 5-HT and NE, but favor NE re-uptake blockade, and the efficacy of TCAs can be interpreted to support the primacy of NE agonism for analgesic activity. However, TCA's additional anti-cholinergic, antihistaminergic, and α -adrenergic receptor blockade activities impart a wide assortment of undesirable side effects, which often compromise their tolerability and clinical acceptance. Kent JM, *Lancet* 2000;355(9207):911-918.

TCAs have demonstrated moderate efficacy for the treatment of neuropathic pain conditions such as post-herpetic neuralgia and painful diabetic neuropathy. Max et al., *Neurology* 1988;38(9):1427-1432; Max et al., *N Eng J Med*. 1992;326(19):1250-1256; Watson et al., *Neurology* 1982;32(6):671-673; Watson et al., *Pain* 1992;48(1):29-36. Multiple studies of TCAs in the treatment of FMS support their use for this syndrome as well, and TCAs have frequently been used as the positive controls to which newer agents have been compared. Max et al., *N Eng J Med*. 1992;326(19):1250-1256; Watson et al., *Pain* 1992;48(1):29-36; Hammonen et al., *Br J Rheumatol*. 1998;37(12):1279-1286; Goldenberg et al., *Arthritis & Rheumatism* 1996;39(11):1852-1859.

Selective Serotonin Re-Uptake Inhibitors (SSRIs)

The SSRIs have revolutionized the treatment of depression with their improved side-effect profile secondary to more selective re-uptake inhibition. The SSRI agents fluoxetine, sertraline and citalopram have each been evaluated in randomized, placebo controlled trials in FMS. Goldenberg et al., *Arthritis & Rheumatism* 1996;39(11):1852-1859; Wolfe et al., *Scand J Rheum*. 1994;23(5):255-259; Anderberg et al., *Eur J Pain* 2000;4(1):27-35; Norregaard et al., *Pain* 1995;61(3):445-449. However, the results of these trials have been somewhat inconsistent, leaving much debate regarding the relative efficacy of the SSRIs, especially in comparison to TCAs.

Two placebo-controlled trials of citalopram, the most 5-HT-specific of the SSRIs, in FMS patients were both convincingly negative. Anderberg et al., *Eur J Pain*, 2000;4(1):27-35;

Norregaard et al., *Pain* 1995;61(3):445-449. This suggests that serotonergic enhancement alone is not sufficient to impart analgesia in the chronic pain setting. In fact, based on the evidence assembled to date, the SSRIs, as a class, are generally less efficacious than the TCAs in chronic pain states (Max et al., *N Engl J Med.* 1992;326(19):1250-1256; Ansari A, *Harv Rev Psych.* 2000;7(5):257-277; Atkinson et al., *Pain* 1999;83(2):137-145; Jung et al., *J Gen Intern Med.* 1997;12(6):384-389) although there are some exceptions (Saper et al., *Headache* 2001;41(5):465-474).

Dual Re-Uptake Inhibitors

Dual re-uptake inhibitors (DRI's) are pharmacologically similar to TCAs (such as amitriptyline and doxepin), exhibiting activity upon both 5-HT and NE re-uptake. Sanchez C and Hytell J, *Cell Mol Neurobiol.* 1999;19(4):467-489. Fortunately, these newer agents are generally devoid of significant activity at other receptor systems, resulting in diminished side effects and enhanced tolerability vs. TCA's. Therefore, this class of antidepressant may have significant potential for the treatment of FMS and/or other chronic pain conditions. DRIs that are commercially available in the U.S. include venlafaxine and duloxetine. A number of DRIs are in clinical development; these include milnacipran, bicifadine, viloxazine, LY-113821, SEP-227162, AD-337, and desvenlafaxine succinate (DVS-233).

An open-label trial of venlafaxine (EFFEXOR®) in 15 patients with FMS has been disclosed. Dwight et al., *Psychosomatics* 1998;39(1):14-17. Of the 11 patients that completed the study, 6 patients had a positive response to venlafaxine, which was defined as 50% or greater improvement in two different measurements of overall pain. Insomnia was the most common side effect reported, requiring adjunctive medical therapy in 3 of 11 completing patients.

U.S. Patent No. 6,602,911 describes the use of milnacipran for the treatment of FMS and its symptoms, the entire disclosure of which is incorporated herein by reference.

Opioids

Opiates exert their anti-nociceptive effects at various locations within both the ascending and descending pain pathways. Duale et al., *Neuroreport* 2001;12(10):2091-2096; Besse et al., *Brain Res.* 1990;521(1-2):15-22; Fields et al., *Nature* 1983;306(5944):684-686; Yaksh et al., *Proc Natl Acad Sci USA* 1999;96(14):7680-7686. Concerns regarding the use of opioids in chronic pain conditions are widely discussed and debated. Bennett RM, *J Functional Syndromes* 2001;1(1):79-92. However, opioids are used by some in the clinical management of FMS, especially when other analgesics have failed to provide sufficient relief. Bennett RM, *Mayo Clin Proc.* 1999;74(4):385-398.

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The majority of patients with fibromyalgia syndrome remain symptomatic for years. (Carette et al., Arthritis & Rheumatism 1994;37(1):32-40, 32-33, 39). Carette et al. reported the results of a clinical trial in which amitriptyline (a tricyclic antidepressant), cyclobenzaprine (a muscle relaxant structurally similar to tricyclic antidepressants) and placebo were administered to subjects suffering from fibromyalgia syndrome (Carette et al., Arthritis & Rheumatism 1994;37(1):32-40). After one month, 21% of the amitriptyline subjects, 12% of the cyclobenzaprine subjects, and 0% of the placebo subjects had significant clinical improvement. At three months, there was no difference between either treatment group and placebo. At six months, no long-term efficacy could be demonstrated because of a higher than expected placebo response, i.e., 19% improvement with placebo.

Thus, there remains a need for an effective, long-term treatment of fibromyalgia syndrome and its symptoms.

SUMMARY OF THE INVENTION

No compound, even if it has benefits for the short-term (acute) treatment of fibromyalgia and its symptoms, has been shown to provide a durable effect such that it provides effective, long-term treatment for fibromyalgia and its symptoms. Surprisingly, according to the methods of the present invention, the administration of a dual norepinephrine serotonin reuptake inhibitor (DRI) to a patient suffering from fibromyalgia syndrome provides effective, long-term treatment of fibromyalgia and its symptoms.

The double-blind, randomized, placebo-controlled clinical study, first reported here in Example 1 below, unexpectedly showed that a DRI may be used to provide effective long-term (e.g., at least three months) treatment for fibromyalgia and its symptoms in patients suffering from fibromyalgia. Further, the results of this clinical study surprisingly showed that a DRI may be used to provide effective, long-term treatment of FMS and its symptoms for at least 6 months.

Thus, the present invention provides methods of long-term treatment of fibromyalgia syndrome in a patient in need thereof comprising administering a DRI to the patient for at least three months. In some embodiments, the DRI is a compound that inhibits norepinephrine reuptake more than or equal to serotonin reuptake (NSRI). In exemplary embodiments, the NSRI is milnacipran.

For example, according to the methods of the present invention, long-term treatment of FMS and its symptoms may be provided to a patient suffering from FMS by administering 25 mg per day to 400 mg per day of milnacipran. In exemplary embodiments, milnacipran

may be administered in a dose of 100 mg per day for the long-term treatment of FMS and its symptoms in a patient suffering from FMS. In other exemplary embodiments, milnacipran may be administered in a dose of 200 mg per day for the long-term treatment of FMS and its symptoms in a patient suffering from FMS.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a timeline of the clinical study described in Example 1.

Figure 2 is a bar graph which illustrates the percentage of responders at 3 months and 6 months for the placebo, milnacipran 100 mg/day and milnacipran 200 mg/day groups described in Example 1.

DETAILED DESCRIPTION

As used herein, the term "subject" or "patient" includes human and non-human mammals.

As used herein, "treatment" or "effective treatment" means to relieve, alleviate, delay, reduce, reverse, improve or prevent at least one symptom of fibromyalgia.

The term "dual reuptake inhibitor" refers to a well-recognized class of antidepressant compounds that selectively inhibit reuptake of both norepinephrine and serotonin. "Norepinephrine-serotonin reuptake inhibitor" (NSRI) and "Serotonin-norepinephrine reuptake inhibitor" (SNRI) refer to subclasses of DRI's. DRI compounds that block the reuptake of norepinephrine preferentially are referred to as NSRI's, whereas those that preferentially block the reuptake of serotonin are referred to as SNRI's. Common DRI compounds include, but are not limited to, the SNRI's venlafaxine and duloxetine, and the NSRI's bicipradine and milnacipran.

NSRI compounds are described in detail in U.S. Patent No. 6,602,911, the contents of which are hereby incorporated by reference in their entirety.

According to some embodiments, the present invention provides methods of long-term treatment of fibromyalgia syndrome in a patient comprising administering a DRI to a patient in need thereof for at least three months. In exemplary embodiments, the DRI compounds are NSRI's.

In other exemplary embodiments, the NSRI is milnacipran. In some embodiments, milnacipran may be administered as a hydrochloride salt: Z-2-aminomethyl-1-phenyl-N, N-diethylcyclopropanecarboxamide hydrochloride (chemical formula $C_{15}H_{23}ClN_2O$). In other embodiments, milnacipran may be administered as a mixture of the dextro- and levrogyral enantiomers, e.g., as a mixture that includes more of one enantiomer or as a racemic

mixture. In some embodiments, milnacipran may be administered in an enantiomerically pure form (e.g., as the pure dextro- or pure levogyral enantiomer). Unless otherwise indicated, milnacipran can include all stereoisomeric forms, mixtures of stereoisomeric forms, diastereomeric forms, and pharmaceutically acceptable salts thereof, including both enantiomerically pure forms of milnacipran as well as mixtures of milnacipran enantiomers. Methods for separating and isolating the dextro- and levogyral enantiomers of milnacipran and other NE 5-HT SNRI compounds are well-known (see, e.g., Grard et al., 2000, Electrophoresis 2000 21:3028-3034).

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredient is contained in a therapeutically or prophylactically effective amount, i.e., in an amount effective to achieve therapeutic or prophylactic benefit for the long-term treatment of FMS and its symptoms. Determination of an effective amount is well within the capabilities of those skilled in the art, especially in light of the disclosure herein. Therapeutic amounts of DRI compounds typically range from about 1 μ g to 1 gm/day. The amount of the DRI compound administered to practice the methods of the invention will, of course, be dependent on the DRI, the subject being treated, the severity of the affliction, and the manner of administration. See, e.g., U.S. Application No. 10/678,767, the contents of which are hereby incorporated by reference in its entirety.

For example, therapeutically effective amounts can be determined from human data of DRI compounds used to treat depression. The therapeutically effective amount may be the same amount administered to treat depression or can be an amount higher or lower than the amount administered to treat depression. For example, the amount of milnacipran administered to treat depression may be in the range of about 50 mg to about 400 mg/day. Thus, about 50 mg to about 400 mg/day of milnacipran may be used for the long-term treatment of FMS and its symptoms. Dosages lower than about 50 mg/day of milnacipran may also be used for the long-term treatment of FMS and its symptoms. For example, for the treatment of FMS, CFS, or pain with milnacipran the dosage range is typically from 25 mg-400 mg/day, more typically from 100 mg-250 mg/day. The dosage may be administered once per day or several or multiple times per day.

Therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve circulating concentration that has been found to be effective in animals. Useful animal models of pain are well known in the art. For example, models of neuropathic pain are described in Zeltser et

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al., 2000, Pain 89:19-24; Bennett et al., 1988, Pain 33:87-107; Seltzer et al., 1990, Pain 43:205-218; Kim et al., 1992, Pain 50:355-363; and Decosterd et al., 2000, Pain 87:149-158. An animal model of inflammatory pain using complete Freund's adjuvant is described in Jasmin et al., 1998, Pain 75: 367-382. The stress-induced hyperalgesia model described in Quintero et al., 2000, Pharmacology, Biochemistry and Behavior 67:449-458 may be used as an animal model of FMS and CFS.

The route of administration of the pharmaceutical compositions of the present invention may be, for example, oral, enteral, intravenous, and transmucosal (e.g., rectal). A preferred route of administration is oral. Pharmaceutical compositions suitable for oral administration can be in the form of tablets, capsules, pills, lozenges, powders or granules, or solutions or dispersions in a liquid. Each form will comprise a predetermined amount of a compound of the invention as an active ingredient. The compositions may be prepared as a tablet employing any pharmaceutical excipient known in the art for that purpose, and conventionally used for the preparation of solid pharmaceutical compositions. The examples of such excipients include, but are not limited to, starch, lactose, microcrystalline cellulose, magnesium stearate. Binders, such as polyvinylpyrrolidone, may also be used in the compositions of the present invention. Furthermore, an active compound can be formulated as controlled-release preparation, such as tablets comprising a hydrophilic or hydrophobic matrix.

The pharmaceutical compositions of the present invention may be in the form of capsules formulated using conventional procedures, for example by incorporation of a mixture of an active compound and excipients into a hard gelatin capsule. Alternatively, a semi-solid matrix of an active compound and high molecular weight polyethylene glycol may be formed and filled into hard gelatin capsules, or soft gelatin capsules may be filled with a solution of an active compound in polyethylene glycol or dispersion thereof in edible oil. Powder forms for reconstitution before use (for example lyophilized powders) are also contemplated. Alternatively, oily vehicles that may be used as injectable formulations may be used as well.

Liquid forms for parenteral administration may also be formulated for administration by injection or continuous infusion. Accepted routes of administration by injection are intravenous, intraperitoneal, intramuscular and subcutaneous. A typical composition for intravenous injection comprises a sterile isotonic aqueous solution or dispersion, including, for example, an active compound and dextrose or sodium chloride. Other examples of suitable excipients are lactated Ringer solution for injections, lactated Ringer solution for

injections with dextrose, Normosol-M with dextrose, acylated Ringer solution for injections. The injection formulation can optionally include co-solvents (e.g., polyethylene glycol), chelating agents (e.g., ethylenediaminetetraacetic acid), stabilizing agents (e.g., cyclodextrin) and/or antioxidants (e.g., sodium pyrosulfate).

According to some embodiments, the DRI may be administered adjunctively with other active compounds for the long-term treatment of fibromyalgia syndrome. For example, active compounds that may be administered include antidepressants, analgesics, muscle relaxants, anorectics, stimulants, antiepileptic drugs, beta blockers, and sedative/hypnotics. Some examples of compounds that may be adjunctively administered with the DRI include, but are not limited to, modafinil, gabapentin, pregabalin, XP13512, pramipexole, 1-DOPA, amphetamine, tizanidine, clonidine, tramadol, morphine, tricyclic antidepressants, codeine, cambamazepine, sibutramine, valium, trazodone, caffeine, nicergoline, bifemelane, propranolol, atenolol, and combinations thereof. In an exemplary embodiment, the DRI may be milnacipran and may be adjunctively administered with an alpha-2-delta ligand such as, for example, pregabalin.

As used herein, adjunctive administration includes simultaneous administration of the compounds in the same dosage form, simultaneous administration in separate dosage forms, and separate administration of the compounds. For example, milnacipran may be simultaneously administered with valium, wherein both milnacipran and valium are formulated together in the same tablet. Alternatively, milnacipran may be simultaneously administered with valium, wherein both the milnacipran and valium are present in two separate tablets. In another alternative, milnacipran may be administered first followed by the administration of valium, or vice versa.

Milnacipran monotherapy for the treatment of fibromyalgia has been previously described in a Phase II trial of 125 fibromyalgia patients. See, e.g., U.S. Application No. 10/678,767, the contents of which are hereby incorporated by reference in its entirety. In this study, milnacipran was administered once or twice daily in a dosage escalation regimen to a maximum dose of 200 mg/day. The study showed that milnacipran provided effective acute (short-term) therapy for symptoms of FMS. In particular, twice-daily (BID) and once-daily (QD) dosing of milnacipran were approximately equally effective on fatigue, mood, global wellness, and function. Twice-daily dosing was better tolerated than QD dosing, and was more effective in treating pain than QD dosing. The patient global impression of change (PGIC) outcome measure showed that over 70% of completers in both milnacipran treatment groups reported an improvement in their overall status, while only 10% reported worsening.

In contrast, 40% of the placebo patients who completed the trial rated themselves as worse at endpoint. The differences between placebo and milnacipran on the PGIC were statistically significant, both in terms of a comparison of mean endpoint scores, as well as on a binary improved/ not-improved basis.

Milnacipran was well-tolerated in this Phase II study. There were no deaths or serious adverse events (AEs) associated with milnacipran treatment, and the majority of AEs reported were rated as mild or moderate in severity. The most frequently reported AE was nausea, reported (one or more times) by 33% of milnacipran-treated patients; all other AEs were reported in less than 9% of milnacipran-treated patients. The higher incidence of nausea, abdominal pain, headache and certain other AEs in the 200 mg QD treatment group suggests that larger doses taken once daily are not as well tolerated as smaller divided doses given twice a day. The reporting of dizziness, postural dizziness, hot flushes (and flushing), and palpitations was also greater in the QD treatment group, suggesting that peak drug level may be a significant factor in the generation of certain adverse effects.

Consistent with previous trial results, 7% of patients experienced mild increases in ALT and/or AST (≤ 2 times the upper limit of normal), without concomitant increases in bilirubin or alkaline phosphatase. Elevation in hepatic enzymes resulted in adverse events in only 2% of milnacipran-treated patients (i.e., 2 out of 7 patients with enzyme elevations reported the adverse event of "elevation in SGOT" or "elevation in SGPT").

A 4 to 8 beats-per-minute increase in mean heart rate was noted in milnacipran-treated patients, which was consistent with previous milnacipran trial results. Mean systolic and diastolic blood pressure among the milnacipran treatment groups showed only slight increases, ranging from 1.5 to 3.4 mmHg for supine systolic pressures (-1.1 to 2.7 mmHg in the placebo group), and 2.6 to 3.7 mmHg for supine diastolic pressures (-3.5 to 1.2 mmHg in the placebo group). Two (2%) milnacipran BID-treated patients reported an exacerbation of hypertension; both patients had pre-existing hypertension and were receiving antihypertensive drug therapy. One patient withdrew early from the trial due to an exacerbation of hypertension.

The potential for treatment-related orthostatic effects was also documented during previous trials, and 6 (6%) of milnacipran-treated patients during the FMS trial reported the adverse event of orthostatic/postural dizziness, with one patient discontinuing early due to moderate postural dizziness. Vital sign data revealed that 4% of placebo patients and 7% of milnacipran patients experienced one or more visits with a decrease of 20 mm Hg or more in systolic blood pressure after standing erect for one minute.

Thus, the Phase II trial showed that treatment with milnacipran was an effective acute (short-term) therapy for the symptom of pain in FMS, and milnacipran dosed either once or twice daily had measurable beneficial effects on a wide range of symptoms of FMS, including fatigue (measured on the FIQ), pain (multiple measures), quality of life (multiple measures), and, potentially, mood (Beck instrument).

It has not been previously shown that milnacipran, or any other active agent, is effective for the long-term (greater than three months) treatment of FMS and its symptoms. The clinical study described in Example 1 below provides the first, and surprising, report of effective long-term treatment of FMS using a NSRI.

The following examples are merely illustrative of the present invention and should not be construed as limiting the scope of the invention in any way as many variations and equivalents that are encompassed by the present invention will become apparent to those skilled in the art upon reading the present disclosure.

EXAMPLES

Example 1 A Multi-Center Double-Blind, Randomized, Placebo-Controlled Study of Milnacipran for the Treatment of Fibromyalgia

The primary objective of this study was to demonstrate safety and efficacy, both clinical and statistical, of milnacipran in the treatment of the fibromyalgia syndrome. The primary outcome was a composite responder analysis assessing response rate at weeks 14 and 15, and the secondary analysis assessed response rate at weeks 26 and 27.

Other objectives of this study were to:

1. compare statistical and clinical efficacy of 100 mg/day and 200 mg/day milnacipran in the treatment of the fibromyalgia syndrome based on each component of the composite responder analysis, as well as on a number of additional secondary endpoints including fatigue, sleep, mood and cognition; and
2. establish and compare the safety profiles of 100 and 200 mg milnacipran daily in patients with FMS.

Methodology

This was a multi-center, randomized, double-blinded, placebo-controlled three-arm study, which enrolled 888 patients who met the 1990 ACR criteria for fibromyalgia syndrome as well as the more detailed admission criteria outlined in the protocol.

Patients recorded baseline symptoms for the first two weeks after washing off anti-depressants, benzodiazepines, and certain other drugs that could potentially interfere with efficacy measurements.

Patients were randomized to receive placebo, 100 mg/day milnacipran, or 200 mg/day milnacipran in a ratio of a 1:1:2. All randomized medications (placebo and milnacipran) were administered in a split-dose (BID) fashion. The doses were administered in a dose escalation regimen as outlined below:

Step 1: 12.5 mg 1 day (12.5 mg pm)

Step 2: 25 mg 2 days (12.5 mg am, 12.5 mg pm)

Step 3: 50 mg 4 days (25 mg am, 25 mg pm)

Step 4: 100 mg 7 days (50 mg am, 50 mg pm)

Step 5: 200 mg 7 days (100 mg am, 100 mg pm).

All patients were scheduled to receive a total of 24 weeks of milnacipran or placebo after the 3 weeks of dose escalation steps, for a total of 27 weeks of milnacipran or placebo exposure.

Patients were required to complete electronic diary, as well as additional paper assessments as described in the schedule of study assessments.

Adverse event, physical examination, concomitant medication, vital sign and clinical laboratory data were collected as detailed in the schedule of study assessments.

Patients who successfully completed this double blind trial were eligible to participate in an open label trial for 15 to 28 additional weeks of therapy.

A timeline of the study is provided in Fig. 1.

Assessments

Safety:

Safety of milnacipran was assessed by analyzing the frequency and intensity of adverse events, changes in vital signs, as well as changes in physical examination and clinical laboratory data collected during the study period.

Efficacy:

In addition to the daily completion of a proprietary electronic patient diary, the following assessments were obtained:

- a. Primary Variables: patient global impression of change (PGIC) and the Fibromyalgia Impact Questionnaire (FIQ);
- b. Psychological Screening at baseline: M.I.N.I.;

c. Miscellaneous status assessments: periodically, as described in the schedule of evaluations: BDI, sleep quality scale, and the ASEX; and

d. FMS Status Assessments: Patient pain 24 hour and 7 day recall VAS, the SF-36, Multiple Ability Self-report Questionnaire (MASQ, cognitive function), the Multidimensional Health Assessment Questionnaire (MDHAQ) and the Multi-dimensional Fatigue Inventory (MFI). Diary assessments include current pain (morning, random daily, and evening reports); daily recall pain (morning report); medications taken (evening report); overall pain past week (weekly report), overall fatigue in the last week (weekly report), and the extent that pain kept the patient from caring for themselves (weekly report).

The primary endpoint of this study was a composite responder analysis implementing analysis of three domains of interest, evaluated at 24 weeks as the primary analysis, and 12 weeks as the secondary analysis. The domains measured were:

- 1) pain (measured by an electronic diary as a daily recall pain score, calculated to weekly average scores);
- 2) patient global (measured by the PGIC, 1-7 scale); and
- 3) physical function (measured by the FIQ-PF).

For the primary analysis, the pain domain score was determined by a calculation that compared the average of treatment weeks 14 and 15 to the two baseline weeks, and treatment weeks 26 and 27 vs. baseline for the secondary analysis. The last observation was carried forward if neither the week 14 nor week 15 (or week 26/27) patient self-reported pain score is available to compare to the baseline value.

The binary response rate for placebo (based on the composite endpoint) in this study was expected to be in the range of 10-13%, with a milnacipran response rate in the active arm(s) expected in the 27-29% range on an ITT/ LOCF basis. Based on these response rate assumptions, 125 patients randomized per arm (250 for high dose group) has been calculated to be the maximum sample size required (90% power). Secondary analyses included total area under the curve of pain intensity, and patient-reported weekly pain recall at the clinic visits as well as the FMS status assessments, and QOL measures.

Results:

A responder was defined as a subject who experienced a greater than 30% reduction in pain from baseline and improvement on the PGIC.

At three months, the percentage of responders was: 35.44% (56/158) in the placebo group; 53.33% (72/135) (p=0.001) in the milnacipran 100 mg/day group; and 55.00%

(143/260) ($p < 0.001$) in the milnacipran 200 mg/day group. At six months, the percentage of responders was: 32.86% (46/140) in the placebo group; 49.59% (60/121) ($p = 0.002$) in the milnacipran 100 mg/day group; and 51.74% (119/230) ($p < 0.001$) in the milnacipran 200 mg/day group. See Table 1 for a summary of the results in the Intent-to-Treat Population and Table 2 for a summary of the Last Observation Carried Forward (LOCF), Baseline Observation Carried Forward (BOCF) and study completer (OC) populations. LOCF is an analysis in which observations are carried forward to the last time point for patients who dropped out. The LOCF analysis treats the carried-forward data as observed data at the last time point. BOCF is an analysis that requires the patient remain active in the trial to be evaluated for response. If a patient withdraws from the trial for any reason they are classed as a non-responder irregardless of their pain and global scores at the time of withdrawal.

TABLE 1

Analysis of Responders for the Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 and 26-27 (Observed Cases) Intent-to-Treat Population

	Statistic	Placebo (N=223)	Milnacipran 100mg (N=224)	Milnacipran 200mg (N=441)
Baseline pain	n	223	224	441
	mean	68.37	68.32	69.41
	SD	11.98	11.54	11.85
	SEM	0.80	0.77	0.56
	median	66.5	67.9	69.1
	min, max	50, 100	41, 100	47, 99
Treatment weeks 14-15	n	158	135	260
	m (% = m/n)	56 (35.44)	72 (53.33)	143 (55.00)
	odds ratio		2.10	2.20
	95% CI		(1.31, 3.36)	(1.46, 3.31)
	p-value		0.002	<0.001
Treatment weeks 26-27	n	140	121	230
	m (% = m/n)	46 (32.86)	60 (49.59)	119 (51.74)
	odds ratio		1.96	2.20
	95% CI		(1.18, 3.26)	(1.42, 3.41)
	p-value		0.009	<0.001

TABLE 2

Summary of Composite Responder Rate -- FMS031						
	Pain Composite Resp					
	3 month			6 month		
	pbo N=223	100 mg N=224	200 mg N=441	pbo N=223	100 mg N=224	200 mg N=441
Primary Analysis (LOCF)	27.8%	33.5% p*=0.187	34.9% p*=0.058	25.1%	30.8% p*=0.197 ap*=0.393	32.2% p*=0.053 ap*=0.105
Sensitivity Analysis I (BOCF)	25.1%	32.1% p*=0.094	32.4% p*=0.048	20.6%	26.8% p*=0.167 ap*=0.334	27.0% p*=0.067 ap*=0.133
Sensitivity Analysis II	25.56%	32.% p*=0.113	32.7% p*=0.056	21.5%	27.2% p*=0.197 ap*=0.394	28.6% p*=0.048 ap*=0.095
Sensitivity Analysis III	25.1%	32.1% p*=0.094	32.4% p*=0.048	22.9%	29.5% p*=0.120 ap*=0.241	29.9% p*=0.051 ap*=0.102
OC Analysis	n*=158 35.4%	n=135 53.3% p*=0.002	n=260 55.0% p*<0.001	n=140 32.9%	n=121 49.6% p*=0.009	n=230 51.7% p*<0.001
Summary of Individual Component Responder Rate -- FMS031						
	Pain Composite Resp, 3 month			Pain Composite Resp, 6 month		
	pbo	100 mg	200 mg	pbo	100 mg	200 mg
Primary Analysis (LOCF)	27.8%	33.5% p*=0.187	34.9% p*=0.058	25.1%	30.8% p*=0.197 ap*=0.393	32.2% p*=0.053 ap*=0.105
Pain (LOCF)	31.4%	35.7% p=0.321	38.3% p=0.068	28.7%	35.7% p=0.110	35.4% p=0.072
PGIC (LOCF)	47.1%	54.0% p=0.143	50.6% p=0.397	46.2%	49.6% p=0.476	49.9% p=0.368
* p-value: nominal p-value. ap=adjusted p-value at Step 2 for Hochberg's procedure (only valid if p-value is ≤ 0.05 for 3-month pain for 200 mg compared to placebo at Step 1). n=number of patients having adequate data for OC analysis (completers of landmark endpoint with observed values for responder assessment).						

These results surprisingly establish that continued administration of milnacipran (e.g., daily administration for at least three months) to subjects suffering from fibromyalgia provides long-term (at least three months) relief from fibromyalgia and its symptoms. Further, these results surprisingly establish that continued administration of low dose milnacipran (e.g., 100 mg/day) is almost as effective as continued administration of high dose

milnacipran (e.g., 200 mg/day) for the long-term treatment of fibromyalgia and its symptoms.
Figure 2.

While the invention has been depicted and described by reference to exemplary embodiments of the invention, such a reference does not imply a limitation on the invention, and no such limitation is to be inferred. The invention is capable of considerable modification, alteration, and equivalents in form and function, as will occur to those ordinarily skilled in the pertinent arts having the benefit of this disclosure. The depicted and described embodiments of the invention are exemplary only, and are not exhaustive of the scope of the invention. Consequently, the invention is intended to be limited only by the spirit and scope of the appended claims, giving full cognizance to equivalence in all respects. All references cited herein are hereby incorporated by reference in their entirety.

Claims:

1. A method of providing long-term treatment of fibromyalgia syndrome in a patient in need thereof comprising administering a dual re-uptake inhibitor (DRI) to the patient for at least three months.
2. The method of claim 1, wherein the DRI is a norepinephrine-serotonin reuptake inhibitor (NSRI).
3. The method of claim 2, wherein the NSRI is milnacipran.
4. The method of claim 3, wherein the milnacipran is administered in a dose between about 25 mg per day and about 400 mg per day.
5. The method of claim 4, wherein the milnacipran is administered in a dose of about 200 mg per day.
6. The method of claim 4, wherein the milnacipran is administered in a dose of about 100 mg per day.
7. The method of claim 1, wherein the DRI is administered for at least 6 months.
8. A method of treating fibromyalgia and its symptoms in a patient suffering from fibromyalgia, which comprises:
 - (a) administering about 200 mg per day of milnacipran to the patient for the treatment of acute pain;
 - (b) decreasing the dose of milnacipran to about 100 mg per day when the acute pain has been treated; and
 - (c) administering about 100 mg per day of milnacipran to the patient for at least three months for the long-term treatment of fibromyalgia and its symptoms.
9. The method of any one of claims 1-8, comprising adjunctively administering a second active compound, wherein the second active compound is selected from the group consisting of an antidepressant, an analgesic, a muscle relaxant, an anorectic, a

stimulant, an antiepileptic drug, a beta blocker, a sedative, a hypnotic and combinations thereof.

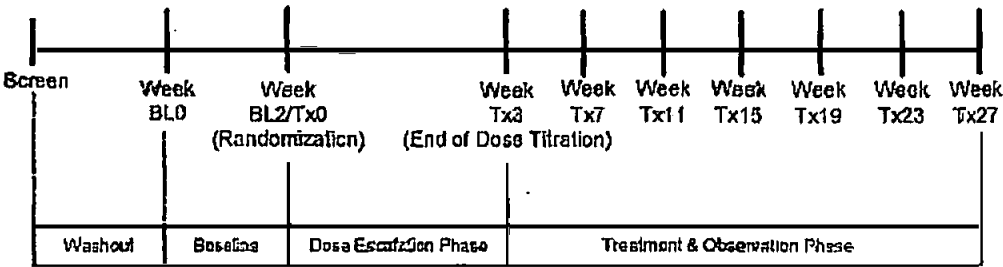
10. The method of claim 9, wherein the second active compound is selected from the group consisting of modafinil, XP13512, gabapentin, pregabalin, pramipexole, 1-DOPA, amphetamine, tizanidine, clonidine, tramadol, morphine, tricyclic antidepressants, codeine, cambamazepine, sibutramine, valium, trazodone, caffeine, nicergoline, bifemelanc, propranolol, atenolol and combinations thereof.
11. A method of providing long-term treatment of a pain symptom associated with fibromyalgia syndrome in a patient in need thereof comprising administering a dual re-uptake inhibitor (DRI) to the patient for at least three months.
12. The method of claim 1, wherein the DRI is a norepinephrine-serotonin re-uptake inhibitor (NSRI).
13. The method of claim 2, wherein the NSRI is milnacipran.
14. The method of claim 3, wherein the milnacipran is administered in a dose between about 25 mg per day and about 400 mg per day.
15. The method of claim 4, wherein the milnacipran is administered in a dose of about 200 mg per day.
16. The method of claim 4, wherein the milnacipran is administered in a dose of about 100 mg per day.
17. The method of claim 1, wherein the DRI is administered for at least 6 months.
18. A method of treating fibromyalgia and its symptoms in a patient suffering from fibromyalgia, which comprises:
 - a. administering about 200 mg per day of milnacipran to the patient for the treatment of acute pain;

- b. decreasing the dose of milnacipran to about 100 mg per day when the acute pain has been treated; and
 - c. administering about 100 mg per day of milnacipran to the patient for at least three months for the long-term treatment of fibromyalgia and its symptoms.
19. The method of any one of claims 11-18, comprising adjunctively administering a second active compound, wherein the second active compound is selected from the group consisting of an antidepressant, an analgesic, a muscle relaxant, an anorectic, a stimulant, an antiepileptic drug, a beta blocker, a sedative, a hypnotic and combinations thereof.
20. The method of claim 19, wherein the second active compound is selected from the group consisting of modafinil, XP13512, gabapentin, pregabalin, pramipexole, 1-DOPA, amphetamine, tizanidine, clonidine, tramadol, morphine, tricyclic antidepressants, codeine, cambamazepine, sibutramine, valium, trazodone, caffeine, nicergoline, bifemelane, propranolol, atenolol and combinations thereof.

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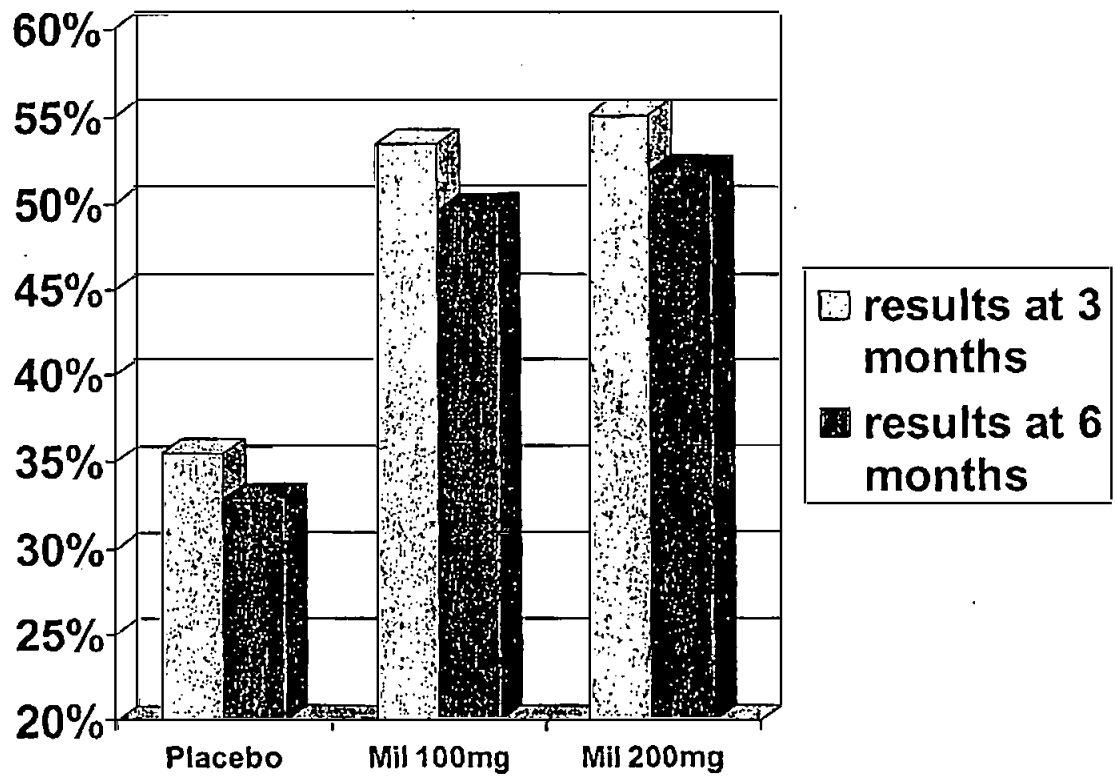
Figure 1

STUDY TIMELINE



2x

Figure 2



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(54) Título: MILNACIPRAN PARA EL TRATAMIENTO A LARGO PLAZO DEL SINDROME DE FIBROMIALGIA

[DIAGRAMA]

(57) Abstracto: Título: La presente invención es dirigida a los métodos para proveer el tratamiento a largo plazo del síndrome de fibromialgia (FMS) al administrar inhibidores de reabsorción dual a pacientes con FMS. Particularmente, la presente invención esta dirigida al tratamiento a largo plazo de FMS por medio de la administración de inhibidores de reabsorción de la serotina y norepinefrina (NSRI) a pacientes con FMS.

MILNACIPRAN PARA EL TRATAMIENTO A LARGO PLAZO DEL SINDROME DE FIBROMIALGIA

CAMPO DE LA INVENCION

La presente invención se relaciona al tratamiento a largo plazo de la fibromialgia y sus síntomas por medio de la administración al paciente que padece de fibromilagia un inhibidor dual de la serotina y norepinefrina. Particularmente, la presente invención esta dirigida al tratamiento a largo plazo de la fibromialgia y sus síntomas por medio de la administración de inhibidores de reabsorción dual de la serotina y norepinefrina que inhiben la reabsorción de la norepinefrina a un alcance igual o mayor que inhiba la reabsorción de la serotina.

ANTECEDENTES

Fibromialgia, conocida adicionalmente como síndrome de fibromialgia (FMS) es un desorden reumatológico sistemático común del cual se estima afecta del 2% al 4% de la población, segunda en prevalencia entre las condiciones reumatológicas después de la artrosis. Wolfe et. Al., Arthritis Rheum. 1990; 33(2):160-172; Wolfe et. Al., Arthritis Rheum. 1995; 38(1):19-28. La fibromialgia es asociada a una reducción del umbral del dolor, generalmente identificada por un incremento a la sensibilidad de presión en todo el cuerpo, y frecuentemente se acompaña con fatiga, desordenes para dormir y tensiones al despertar. Otros síntomas comunes incluyen dolor de cabeza, migrañas, hábitos variables de evacuaciones, dolor abdominal difuso y frecuencia urinaria. El criterio para el diagnostico de la fibromialgia no requiere únicamente el historial de dolor general, si no también el encontrar dolor al realizar exámenes físicos (puntos de dolor). Con el propósito de completar el criterio establecido para la fibromilagia establecido en 1990 por el American Collage of Rheumatology (ACR), un individuo debe de poseer tanto dolor general en los cuatro cuadrantes del cuerpo así como esqueleto axial y la presencia de 11 de los 18 puntos de dolor al realizarse el examen. Wolfe et. Al., Arthritis Rheum. 1990; 33 (2): 160-172.

Mientras existen ciertas sugerencias que el FMS puede representar una forma de desorden de somatización, existe evidencia en aumento y aceptación que el FMS es un problema medico, el cual refleja una percepción generalizada en aumento de sensori stimuli. La anormalidad se piensa es originada dentro del sistema nervios central (CNS) en lugar de áreas periféricas y el termino del defecto fisiopatologico es denominado "sensibilización central". Caluw DJ y Chrousos GP, Neuroimmunomodulation 1997; 4(3): 134-153, Yunas MB, J Rheumatol. 1992; 19 (6): 846-850; Bradley et al., Curr Rheumatol Rep. 2000; 2 (2): 141-148; Simas Rw, Am J Med Sci. 1998; 315 (6): 346-350. Pacientes con FMS típicamente sufren tanto de allodynia (dolor notable proveniente de un estimulo no doloroso tal como contacto leve) e hyperalgesia (aumento en el proceso del dolor en el cual un estimulo doloroso es magnificado y sentido con mayor intensidad en contraposicion a como lo hubiere sentido un voluntario

normal). Mountz et al., *Arthritis & Rheumatism* 1995; 38(7): 926-938; Arroyo JF y Cohen ML, *J Rheumatol.* 1993 20(11):1925-1931. En este aspecto existen varios paralelos en la presentación clínica y en los mecanismos fundamentales propuestos con el dolor neuropathic, tal como neuropatía diabética y neuralgia del trigémino. Sindrup SH y TS Jensen, *Pain* 1999; (3):389-400; Wolf CJ, *Nature* 1983;306 (5944):686-688; Wolf CJ y RJ Mannion, *Lancet* 1999; (9168): 1959-1964.

Como resultado, el FMS es tratado hoy en día, principalmente dentro de este modelo médico. Es frecuentemente diagnosticado en lugares de cuidado primarios y casi la mitad de las visitas a oficinas son llevadas a cabo por proveedores de medicina interna y de prácticas familiares (1998 Encuesta Nacional de Cuidado Médico Ambulatorio). Las visitas a los reumatólogos consisten en un 16% de visitas a despachos en relación a los pacientes con FMS. Las visitas restantes son llevadas a cabo a una variedad de proveedores de cuidado terciarios, incluyendo centros para el dolor, especialistas de medicina física y psiquiatras.

Los individuos con fibromialgia sufren de una variedad de síntomas, incluyendo una alta incidencia de dolores en el pecho no cardíacos, acidez, palpitaciones, síndrome de intestino irritable. Wolfe, et al., *Arthritis Rheum.* 1990;33 (2):160-172; Mukerji et al., *Angiology* 1995; 46(5):425-430. Aunque la base fisiológica de estos síntomas permanece incierta, la evidencia en aumento sugiere que la disfunción del sistema nervioso autónomo es común en la fibromialgia y con enfermedades relacionadas. Claiuw DJ y Chrousos GP, *Neuroimmunomodulation* 1997;4(3):134-153; Freeman R y Komaroff AL, *Am J Med.* 1997; 102(4):357-364.

Posibles estudios de individuos con fibromialgia seleccionados de manera aleatoria han detectado evidencia objetiva en relación a la disfunción de varios órganos viscerales, incluyendo la incidencia en un 75% de evidencia eco cardiografía de la válvula mitral, una incidencia del 40% al 70% de incidencia de esophageal dysmotility y disminución estática de la espiración de la presión de la función pulmonar Lurie et al., *Scand J Rehabil Med.* 1990, 22(3):151-155; Pellegrino et al., *Arch Phys Med Rehabil.* 1989, 70(7):541-543.

El estudio de la fibromialgia recientemente ha surgido como un área significativa de investigación diferente al estudio de otras condiciones de dolor crónicas. Un significativo cuerpo de literatura en este momento respalda el uso de antidepresivos tricíclicos para el FMS, y existen varios otros estudios controlados en los cuales se evalúa la eficacia de otros agentes terapéuticos. Sin embargo, la interpretación de la información de prueba se encuentra complicada por los factores, tales como la falta de una definición binaria aceptada de "receptor" versus "no-receptor", de conformidad a como se encuentra actualmente utilizada en pruebas de otras condiciones reumatológicas, tales como artritis reumatoide. Nelson et al., *Arthritis Rheum.* 1993; 36 (6): 729-740; Nelson DT, *J Rheumatol.* 1993; 20(3):581-534. Adicionalmente, no existe consenso en relación a varios aspectos del diseño de la prueba, incluyendo la designación de puntos apropiados. Sin embargo, existe un acuerdo generalizado el cual expresa que la medición y la caracterización del dolor del paciente son de suma importancia para la determinación de la efectividad del agente en el FMS; evaluación de fatiga, sueño, depresión, función habilidad física y bienestar general ayudan a iluminar adicionalmente la efectividad general del agente.

Una amplia gama de medicamentos han sido utilizados fuera de su indicación terapéutica en pacientes con FMS con niveles de éxito variables. Buskila D. Baillieres Best Pract Res Clin Rheumatol. 1999; 13 (3):479-485; Leventhal LJ, Ann Intern Med. 1999; 131 (11): 850-858; Lautenschlager J, Scand J Rheumatol Suppl. 2000;113:32-36. Mientras que los antidepresivos son la base de varios tratamientos, otros agentes tales como anticonvulsivos, agentes antispasticidad, ansiolíticos, sedantes y agentes opiáceos han sido utilizados. Adicionalmente, drogas anti inflamatorias sin esteroides y acetaminophen son utilizadas por un gran número de pacientes (Wolfe et al., Arthritis Rheum. 1997; 40(9): 1571-1579), independientemente aunque inflamación periférica no ha sido demostrada (Clauw DJ y Chrousos GP, Neuroimmunomodulation 1997; 4(3): 134-153), y varios estudios han fracasado en confirmar la efectividad de analgésicos en FMS.

Goldberg et al., Arthritis Rheum. 1986;29 (11): 1371-1377; Yunus et al., J Rheumatol. 1989; 16 (4): 527-532; Wolfe et al., Arthritis Rheum. 2000; 43 (2): 378-385; Russell et al., Arthritis Rheum. 1991; 34 (5): 552-560; Quijada-Carrera et al., Pain 1996; 65 (2-3):221-225. Estos agentes, sin embargo proveen un elemento de protección en contra de otros generadores de dolor periférico, tales como artrosis.

Antidepresivos de todas las variedades representan una forma común de terapia para muchos estados de dolor crónico, incluyendo FMS. Sindrup SH y Jensen TS, Pain 1999; 83 (3): 389-400; Buskila D, Baillieres Best Pract Res Clin Rheumatol. 1999; (3): 479-485; Leventhal LJ, Ann Intern Med. 1999; 131 (11): 850-858; Lautenschlager J, Scand J Rheumatol Suppl. 2000; 113:32-36; Bennett RM, J Functional Syndroms 2001; 1 (1): 79-92. La mayoría de los antidepresivos que se encuentran en el mercado directa o indirectamente incrementan los niveles de 5-HT y/o NE en el CNS.

Los niveles monoamines se incrementan ya sea por medio de la inhibición de la absorción (bloqueando proteínas de transporte) o interfiriendo con la descomposición de la monoamines (inhibiendo las enzimas de monoamines de oxidasa) cuando se libera en la hendidura sináptica.

Antidepresivos triciclicos (TCAs)

Los TCAs mayormente empleados para el tratamiento de FMS incluyen amitriptilina, doxepina y ciclobenzaprina. Buskila D, Baillieres Best Pract Res Clin Rheumatol. 1999; 13 (3): 479-485; Lautenschlager J, Scand J Rheumatol Suppl. 2000; 113:32-36; Bennett RM, J Functional Syndromes 2001; 1 (1):79-92. Mientras que la ciclobenzaprina es típicamente catalogada como un relajante muscular, en lugar de un antidepresivo, la misma comparte similitudes estructurales y farmacológicas con los TCAs. Aunque sus cualidades de sedante frecuentemente puede anular su utilidad en otras aplicaciones. Kobayashi et al., Eur J Pharmacol. 1996; 311(1): 29-35. Los TCAs bloquean la absorción tanto de 5-HT y NE, pero favorecen el bloqueo de la absorción del NE, la eficacia del TCAs puede ser interpretada en fundamentar la primacía de NE como agonista para la actividad analgésica. Sin embargo, las actividades adicionales de anticolinérgico, antihistamínico y α -adrenérgico de bloqueo imparten una amplia variedad de efectos secundarios indeseables, los cuales frecuentemente comprometen su tolerancia y aceptación clínica. Kent JM, Lancet 2000; 355 (9297): 911-918.

Los TCAs han demostrado una eficacia moderada para el tratamiento de condiciones del dolor proveniente de la neuropatía, tales como neuralgia y neuropatía diabética dolorosa. Max et al., *Neurology* 1988; 38 (9): 1427-1432; Max et al., *N Eng J Med.* 1992; 326 (19):1250-1256; Watson et al., *Neurology* 1982; 32 (86): 671-673; Watson et al., *Pain* 1992; 48 (1) 29-36.

Múltiples estudios de los TCAs relacionado al tratamiento de FMS respaldan el uso para el síndrome, siendo los TCAs utilizados frecuentemente como control positivo en contra de los cuales se compra a los agentes nuevos. Max et al., *N Eng J Med.* 1992; 326 (19): 1250-1256; Watson et al., *Pain* 1992; 48 (1): 29-36; Hannonen et al., *Br J Rheumatol.* 1998; 37 (12):1279-1286; Goldenberg et al., *Arthritis & Rheumatism* 1996; 39 (11): 1852-1859.

Inhibidores selectivos de reabsorción de la Serotina (SSRIs)

Los SSRIs han revolucionado el tratamiento de la depresión debido a sus mejoras en su perfil efectos secundarios, el cual es secundario a muchos inhibidores de reabsorción selectiva. Los agentes de la SSRIs tales como fluoxetina, sertralina y citalopram han sido evaluados de manera aleatoria, pruebas controladas de placebo en FMS. Goldenberg et al., *Arthritis & Rheumatism* 1996; 39 (11): 1852-1859; Wolfe et al., *Scand J Rheum.* 1994; 23 (5): 255-259; Anderberg et al., *Eur J Pain* 2000; 4 (1): 27-35; Norregaard et al., *Pain* 1995; 61 (3): 445-449. Sin embargo, los resultados de estas pruebas han sido un poco inconsistentes, dejando un gran debate en relación a la relativa eficacia de los SSRIs, especialmente en comparación con los TCAs.

Dos pruebas controladas de placebo de citalopram, las más específicas de 5-HT de los SSRIs, en pacientes con FMS fueron ambas convincentemente negativas. Anderberg et al., *Eur J Pain*, 2000; 4 (1): 27-35; Norregaard et al., *Pain* 1995; 61 (3): 445-449. Esto sugiere que el valor mayor de la serotina en si sola no es suficiente para impartir analgesia en un cuadro de dolor crónico. De hecho, basados en la evidencia recogida recopilada hasta la fecha, el SSRIs, como clase, son generalmente menos efectivo que los TCAs in estados de dolor cronico (Max et al., *N Engl J Med.* 1992; 326 (19):1250-1256; Ansari A, *Harv Rev Psych.* 2000; 7 (5): 257-277; Atkinson et al., *Pain* 1999; 83 (2): 137-145; Jung et al., *J Gen Intern Med.* 1997; 12 (6): 384-389), aunque existan ciertas excepciones (Saper et al., *Headache* 2001; 41 (5): 465-474).

Inhibidores de reabsorción dual

Los inhibidores de reabsorción dual (DRIs) son farmacologicamente similar a los TCAs (tales como amitriptilina y doxepina), demostrando actividad en ambos 5-HT y reabsorción NE. Sanchez C and Hytell J, *Cel Mol Neurobiol.* 1999; 19 (4): 467-489. Afortunadamente, estos agentes nuevos generalmente no poseen actividad significativa en otros sistemas receptores, resultando en efectos secundarios reducidos y tolerancia aumentada vs. TCAs. Por lo cual, esta categoría de antidepresivos pueden tener potencial significativo para el tratamiento de FMS y/o otras condiciones de dolor crónico. Los DRIs que se encuentra comercialmente disponibles en los Estados Unidos incluyen venlafaxine y duloxetine. Un numeroo de DRIs se encuentran en desarrollo clinico; estos incluyen milnacipran, bicipadine, viloxazine, LY- 113821, sep-227162, ad-337, y desvenlafaxine succinate (DVS-233).

Un estudio de etiqueta abierta de venlafaxine (EFEXOR®) en 15 pacientes con FMS ha sido revelado. Dwight et al., Psychosomatics 1998; 39(1): 14-17. De los 11 pacientes que completaron el estudio, 6 pacientes obtuvieron una respuesta positiva a la venlafaxine, la cual se definió como un 50% o más en la mejoría en dos diferentes medidas de dolor general. El insomnio fue el efecto secundario mayormente reportado, requiriendo terapia médica adyacente en 3 de los 11 pacientes que completaron.

La Patente de los Estados Unidos No. 6, 602, 911 describe los usos de la milnaciprina para el tratamiento del FMS y sus síntomas, la totalidad de la revelación se incorpora a la presente como referencia.

Opioides

Los opioides ejercen su efectos anti-nocioreceptivos en varias localidades dentro de los canales ascendientes y descendientes del dolor. Duale et al., Neuroreport 2001; 12 (10): 2091-2096; Besse et al., Brain Res. 1990; 521 (1-2): 15-22; Fields et al., Nature 1983; 306 (5944): 684-686; Yaksh et al., Proc Natl Acad Sci USA 1999; 96 (14): 7680-7686. Inquietudes relacionadas con el uso de opioides para el uso en condiciones de dolor crónico han sido ampliamente discutidas y debatidas. Bennett RM, J Functional Síndromes. 2001; 1 (1): 79-92. Sin embargo, opioides son utilizados por varias en el manejo clínico de FMS, especialmente cuando otros analgésicos han fracasado en proveer suficiente mejoría. Bennett RM, Mayo Clin Proc. 1999; 74 (4): 385-398.

La mayoría de los pacientes afectados por el síndrome de fibromialgia padecen de los síntomas por años. (Carette et al., Arthritis & Rheumatism 1994; 37 (1): 32-40, 32-33, 39). Carette et al., reportaron los resultados del estudio clínico en el cual amitriptilina (antidepresivo tricíclico), cyclobenzaprina (un relajante muscular estructuralmente similar al antidepresivo tricíclico) y placebo fueron administrados a sujetos que sufrían del síndrome de fibromialgia (Carette et al., Arthritis & Rheumatism 1994; 37 (1): 32-40. Después de un mes, 21% de los sujetos de amitriptilina, 12 % de los sujetos de la cyclobenzaprina, y un 0% de los sujetos del placebo obtuvieron mejoría clínica significativa. A los tres meses, no existía diferencia entre cualquiera de los grupos de tratamiento o placebo. A los seis meses, ningún efecto a largo plazo pudo ser demostrado debido a una respuesta de placebo más alta de lo esperada, 19% de mejoría con placebos.

Por consiguiente, la necesidad para un efectivo, tratamiento a largo plazo para el síndrome de la fibromialgia y sus síntomas.

RESUMEN DE LA INVENCION

Ningún componente, aunque tenga beneficios para el tratamiento a corto plazo de la fibromialgia y sus síntomas, ha proporcionado ningún efecto duradero que proporcione efectivamente un tratamiento a largo plazo para la fibromialgia y sus síntomas. Sorpresivamente de conformidad a los métodos de la presente invención, la administración de un inhibidor de absorción dual de serotina y norepinefrina proporciona a un paciente que sufre del síndrome de fibromialgia un tratamiento efectivo y a largo plazo de la fibromialgia y sus síntomas.

El método a doble ciego, al azar y estudio clínico del placebo controlado, primeramente reportado en el ejemplo 1 abajo descrito, inesperadamente demostró que DRI puede ser utilizado efectivamente a largo plazo (por lo menos tres meses) para el tratamiento de la fibromialgia y sus síntomas en el caso de pacientes que sufren de fibromialgia. Adicionalmente los resultados de este estudio clínico sorpresivamente demuestran que el DRI puede proveer efectivamente un tratamiento a largo plazo del FMS y sus síntomas por lo menos para seis meses.

Por lo tanto, la presente invención proporciona métodos para el tratamiento a largo plazo del síndrome de la fibromialgia en pacientes que lo requieren, administrando DRI por lo menos por tres meses. En algunas aplicaciones, el DRI es un componente que inhibe la reabsorción de la norepinefrina en mayor cantidad o equitativamente a la reabsorción de serotina (NSRI). En aplicaciones de ejemplo el NSRI es milnaciprina.

Por ejemplo, de conformidad a los métodos de la presente invención el tratamiento a largo plazo de FMS y sus síntomas puede ser proporcionado a un paciente que sufre de FMS por medio de la administración de 25 mg por día a 400 mg por día. En aplicaciones de ejemplo la milnaciprina puede ser administrada en dosis de 100 mg por día para el tratamiento a largo plazo de FMS y sus síntomas en pacientes sufriendo de FMS. En aplicaciones de ejemplo la milnaciprina puede ser administrada en dosis de 200 mg por día para el tratamiento a largo plazo de FMS y sus síntomas en pacientes sufriendo de FMS.

BREVE DESCRIPCION DE LAS FIGURAS

La figura una es un cronograma del estudio clínico descrito en el ejemplo 1. La figura 2 es una grafica de barras que ilustra el porcentaje de receptores a tres meses y seis meses para el placebo, milnaciprina 100 mg/día y milnaciprina 200 mg/día para los grupos descritos en el ejemplo 1.

DESCRIPCION DETALLADA

De conformidad a lo descrito en el presente, el termino (sujeto) o (paciente) incluye a humanos y mamíferos no humanos.

De conformidad a lo descrito en el presente (tratamiento) o (tratamiento efectivo) significa aliviar, retrasar, reducir, revertir, mejorar o prevenir al menos un síntoma de la fibromialgia. El término "inhibidores de reabsorción dual" se refiere una tipo bien reconocido de componentes antidepresivos que selectivamente inhiben la reabsorción de ambos norepinefrinas y serotina.

"Norepinefrina inhibidores de reabsorción norepinefrina-serotina" (NSRI) e inhibidores de reabsorción serotina-norepinefrina (SNRI) se refieren a subclases de DRI. Componentes de DRI que bloquean la reabsorción preferiblemente de la norepinefrina son referidos como NSRI. Mientras que los que bloquean preferiblemente la reabsorción de norepinefrina son referidos como SNRI. Compuestos comunes de DRI incluyen pero no están limitados a SNRIs belafaxine y duloxetine y los NSRIs bicifadine y milnacipran.

Los componentes de SNRI se encuentran detallados en la patente de Estados Unidos No. 6,602,911, el contenido de la cual se encuentran incorporados a la presente por referencia en su totalidad.

De acuerdo a algunas aplicaciones, la presente invención provee métodos de tratamiento a largo plazo del síndrome de fibromialgia en un paciente a quien se le administra DRI por lo menos por tres meses. Como aplicación de ejemplo, los componentes de DRI son NSRI.

Como ejemplo, el SNRI es milnaciprina. En algunas aplicaciones, la milnaciprina puede ser administrada como sal clorhídrica: Z-2-aminomethyl-1-phenyl-1-N, N-DIETHYLCYCLOPROPANECARBOXAMIDE CLORHIDRICO (formula quimica C15 H23 Cl N2 O). En otras aplicaciones la milnaciprina puede ser administrada como mezcla de dextro - y levrogyral enantiomeros, ejemplo como mezcla que incluye más de un enantiomero o mezcla racemica.

Composiciones farmacéuticos apropiados para su uso en la presente invención incluyen composiciones en el cual el ingrediente activo esta contenido en una cantidad terapéutica o profiláctica efectiva, en un monto efectivo para alcanzar beneficios terapéuticos y profilácticos para el tratamiento a largo plazo de FMS y sus síntomas. El determinar la cantidad efectiva se encuentra dentro de las capacidades de esos habilitados en el arte, específicamente a luz de lo revelado en el presente.

Cantidades terapéuticas de los componentes de DRI típicamente oscilan dentro del rango 1 µg a 1 gm/al día. La cantidad del componente de DRI administrado para practicar los métodos de la invención serán, dependientes del DRI, el sujeto a tratarse, la severidad de la afectación y la manera de administración. Ver Aplicación de los Estados Unidos No. 10/678,767, el contenido de la cual se incorporan por referencia en su totalidad.

Por ejemplo, cantidades terapéuticamente efectivas pueden ser determinadas de la información humana de los componentes de la DRI utilizados para tratar la depresión. La cantidad terapéuticamente efectiva puede ser la misma cantidad administrada para tratar la depresión o puede ser una cantidad mayor o menor de la cantidad administrada para tratar la depresión. Por ejemplo, la cantidad de milnaciprina administrada para tratar la depresión puede estar en el rango de aproximadamente 50 mg a aproximadamente 400mg al día.

Cerca de aproximadamente 50 mg al día a 400 mg al día de milnaciprina puede ser empleada para el tratamiento a largo plazo de FMS y sus síntomas. Por ejemplo, para el tratamiento de FMS, CFS, o dolor con milnaciprina el rango de dosificación es típicamente de 25 mg a 400 mg al día, típicamente mas de 100mg a 250 mg al día. La dosis puede ser administrada una vez al día o varias o multiples veces al día.

Cantidades terapéuticamente efectivas para el uso en humano puede ser determinada de modelos de animales. Por ejemplo, la dosificación para humanos puede ser formulada para alcanzar concentración circulatoria la cual se ha encontrado ser efectiva en los animales.

Modelos Útiles

Para el dolor de animales, son bien conocidos en el campo. Por ejemplo, modelos de dolor neuropático están descritos en ZELTSER et al., 2000, pain89:19-24; Bennett et al., 1988, pain33:87-107; ZELTSER et al., 1990, pain43:205-208; kim et. Al., 1992, pain50:355-363; y decoster et al., 2000, pain87:149-158.

Un modelo de animal para el dolor inflamatorio utilizando el modelo completo de Freund está descrito en Jasmin et al., 1998, pain75:367-382. El modelo inducido de estrés descrito en quintero et al., 2000, Pharmacology, biochemistry and behaviour 67:449-458 puede ser utilizado como un modelo de animal DFMSICFS.

La ruta de administración de la composición farmacéutica de la presente invención, puede ser por ejemplo oral, enteral, intravenosa y transmucosal (ejemplo rectal). La ruta preferida de la administración es oral. Las composiciones farmacéuticas apropiadas para la administración oral pueden presentarse en forma de tabletas, capsulas, píldoras, polvos y gránulos o soluciones o dispersiones en líquido. En cada fórmula se contendrá una cantidad predeterminada del compuesto de la invención como ingrediente activo. La composición puede ser preparada como tableta utilizando cualquier excipiente farmacéutico conocido en el campo para dicho propósito, y convencionalmente utilizado para la preparación de composiciones farmacéuticas sólidas. Los ejemplos de dichos excipientes incluyen, pero no están limitados, a almidón, lactosa, celulosa microcristalina, y estercato de magnesio. Componente tal como polyvinylpyrrolidone puede ser adicionalmente utilizado en la composición de la presente invención. Adicionalmente, un compuesto activo puede ser formulado como una preparación controlada, tales como tabletas compuestas de hidrofílico o hidrofóbico.

La composición farmacéutica de la presente invención pueden estar en la forma de capsulas formuladas utilizando procedimientos convencionales, por ejemplo incorporando una mezcla de compuestos activos y excipientes en una capsula de gelatina dura. Alternativamente una matriz semisólida de un compuesto activo y un glycol de alto peso molecular puede ser formado y rellenado en capsulas de gelatinas duras o las capsulas de gelatinas blandas pueden ser rellenas con una solución de compuesto activo de glycol polyethylen o una dispersión de aceites comestibles. Formas en polvos pueden ser adicionalmente contemplado. Alternativamente transportadores de aceite pueden ser utilizados como formulaciones inyectables.

Formas líquidas para la administración parenteral adicionalmente pueden ser formuladas para la administración por inyección o infusión continua. Las rutas aceptadas para la administración por inyección son intravenosa, intraperitoneal, intramuscular y subcutáneas. A una composición típica para inyecciones intravenosas comprende una solución acuosa estéril isotónica o dispersión, incluyendo, por ejemplo, un compuesto activo y dextrosa o cloruro de sodio. Otros ejemplos de excipientes aceptables son soluciones Ringer para inyecciones, las soluciones Ringer para inyecciones con dextrosa, Normosol-M con dextrosa, solución Ringer acylated para inyecciones. La formulación de inyecciones puede opcionalmente incluir co-solventes (ejemplo glycol polietileno y otros agentes (ácido ethylenediaminetetraacetic, agentes estabilizadores (ejemplo cyclodextrine) y/o antioxidantes (ejemplo piro-sulfato de sodio).

De acuerdo a ciertas aplicaciones, el DRI puede ser administrado en conjunto con otros compuestos activos para el tratamiento a largo plazo del síndrome de fibromialgia. Por ejemplo, compuestos activos que pueden ser administrados incluyen antidepresivos, analgésicos, relajantes musculares, anorecticos, estimulantes, drogas antiepilépticas, bloqueadores beta y sedantes/hipnóticos. Ciertos ejemplos de compuestos que pueden ser administrados en conjunto con el DRI incluyen, pero no están limitados, a modafinil, gabapentin, pregabalin, XPI3512, pramipexola, L-DOPA, anfetamina, tizanidine, clonidine, tramadol, morfina, antidepresivos tricíclicos, codeína, cambamazepine, sibutramine, valium, trazodone, cafeína, nicergoline, bifemelane, propranolol, atenolol, y combinaciones de estas. En ciertos ejemplos el DRI puede ser milnaciprina y puede ser conjuntamente administrado con una liga α -2-delta tal como, por ejemplo, pregabalin.

De conformidad a lo utilizado en el presente, a la administración conjunta incluye la administración simultánea de los compuestos en la misma forma de dosificación, simultánea administración en forma de dosificación separadas y administración separadas de componentes. Por ejemplo, la milnaciprina puede ser simultáneamente administrada con valium, en donde ambas, milnaciprina y valium se encuentran combinadas en la misma tableta. Alternativamente, milnaciprina puede simultáneamente ser administrada con valium, en donde ambas milnaciprina y valium se encuentran presentes en dos tabletas separadas. Y otra alternativa en la cual milnaciprina puede ser administrada primeramente, seguida por la administración de la valium, o viceversa.

La monoterapia de milnaciprina para el tratamiento de fibromialgia ha sido previamente descrita en una prueba de Fase II de 125 pacientes de fibromialgia. Ver, ejemplo Aplicación de Estados Unidos No. 10/678,767, cuyo contenido se encuentra incorporado como referencia en este documento en su totalidad. En este estudio la milnaciprina fue administrada una o dos veces al día en un régimen de dosificación escalonado, a un máximo de dosificación de 200 mg/día. El estudio demostró que la milnaciprina proveía terapia efectiva y aguda (a corto plazo) para los síntomas de FMS. En particular, 2 veces al día (BID) y 1 vez al día (QD) dosificaciones de milnaciprina fueron aproximadamente efectivas para fatigas, ánimos, bienestar general y función. La dosificación de 2 veces al día fue mejor tolerada que la dosificación QD y fue más efectiva en el tratamiento del dolor que la dosificación QD. El resultado del cambio global del paciente (PGIC) demostró que más del 70% de quienes completaron ambos tratamientos de milnaciprina reportaron una mejoría de su estatus general, mientras que solo un 10% reportaron que empeoraron.

En contraste, el 40% de los pacientes de placebos que completaron la prueba se catalogaron como que empeoraron al final. La diferencia entre placebo y milnaciprina en la PGIC fueron estadísticamente significantes tanto en términos de comparación de los valores en el final, así como en la base binaria mejoría/no mejoría.

La milnaciprina fue bien tolerada en la Fase II del estudio, no se presentaron muertes o serios eventos adversos (AEs) asociados con el tratamiento de la milnaciprina y la mayoría de los AEs reportados fueron catalogados de severidad media o moderada. El AE frecuentemente reportado fue náusea, reportado (1 o más veces) por el 33% de los pacientes tratados con milnaciprina; los restantes AEs fueron reportados en menos del 9% de los pacientes tratados con milnaciprina. La incidencia más alta de náusea, dolor abdominal, dolor de cabeza y ciertos otros AEs, en el grupo de tratamiento de 200 MG

QD sugieren que las dosificaciones altas tomadas una vez al día no fueron bien toleradas en comparación a dosificaciones pequeñas tomadas dos veces al día.

El reporte de mareos de postura, calores corporales, y palpitaciones fueron adicionalmente mayores en los grupos de tratamientos QD, sugiriendo que niveles de droga picos pueden ser un factor determinante en la generación de diversos factores adversos.

Consistentemente con los resultados de las pruebas anteriores, 7% de los pacientes experimentaron incrementos medios en ALT y/o AST (≤ 2 al límite más alto de lo normal), sin incrementos concomitantes en bilirrubina o fosfatasa alcalina. La elevación de enzimas epáticas resultaron como evento adverso en solamente 2% de los pacientes tratados con milnaciprina (ejemplo 2 de siete pacientes con elevaciones de enzima reportaron el evento adverso de "elevación en SGOT" o "elevación en SGPT").

El incremento de 4 a 8 latidos por minutos de latidos del corazón fue notado en pacientes tratados con milnaciprina, los cuales son consistentes con los resultados de prueba de milnaciprina previamente realizados. La media de la presión sanguínea sistólica y diastólica en los grupos tratados con milnaciprina demostraron unicamente un incremento leve entre 1.5 a 3.4 mmHg para presiones sistólica supine (-1.1 a 2.7 mmHg en el grupo de placebos), y 2.6 a 3.7 mmHg para presiones diastólica supine (-3.5 a 1.2 mmHg en grupo de placebos. 2% de pacientes tratados con milnaciprina BID experimentaron una exacerbación de hipertensión; ambos pacientes tenían preexistencia de hipertensión y estaban recibiendo tratamiento médico para la hipertensión. Un paciente se retiró temprano de la prueba debido a una exacerbación de la hipertensión.

El potencial para el tratamiento de efectos relacionados a la ortostática fue adicionalmente documentado durante las pruebas anteriores, y 6 (6%) de los pacientes tratados con milnaciprina durante las pruebas de FMS reportaron eventos adversos de ortostática/mareo de postura, con una paciente descontinuada temprano debido a mareo postural moderado. La información de signos vitales revelaron que 4% de los pacientes de placebo y el 7% de los pacientes de milnaciprina experimentaron una o dos visitas con reducción de 20 mmHg o más en presión sanguínea sistólica después de encontrarse de pie un minuto.

Por lo tanto, las pruebas de la Fase II demostraron que el tratamiento con milnaciprina fue una terapia agudamente efectiva (corto plazo) para el síntoma del dolor en FMS y la milnaciprina ya sea dosificada una o dos veces al día tenía efectos beneficios verificables en una variedad amplia de síntomas de FMS, incluyendo fatiga (medido en FIQ, dolor (medidas múltiples), calidad de vida (medidas múltiples), y potencialmente ánimo (instrumentos Beck).

Se ha demostrado previamente que la milnaciprina o cualquier otro agente activo es efectivo a largo plazo (mayor a 3 meses) para el tratamiento de FMS y sus síntomas. El estudio clínico descrito en el ejemplo 1 a continuación proporciona el primero y sorpresivo reporte del tratamiento efectivo a largo plazo del FMS utilizando el NSRI.

Los siguientes ejemplos son meramente ilustrativos de la presente invención y no deben ser considerados como limitantes al ámbito de la invención de ninguna manera ya que varias variaciones y equivalentes que se encuentran comprendidos en la presente

invención resultaran aparentes a aquellas personas calificadas en este campo a leer la presente revelación.

EJEMPLOS

Ejemplo 1 Método en multi centros y al doble ciego, de estudio controlado de placebos de milnacipran para el tratamiento de la fibromialgia.

El principal objetivo de este estudio era demostrar seguridad y eficacia clínica y estadística de la milnaciprina en el tratamiento del síndrome de fibromialgia. El resultado principal fue un conjunto de análisis de evaluaciones en las semanas 14 y 15, y un análisis secundario en las semanas 26 y 27.

Otros objetivos de este estudio eran:

1. comparar la eficacia clínica y estadística de 100 mg/día y 200 mg/día de milnaciprina en el tratamiento del síndrome de fibromialgia, basado en cada componente del conjunto de análisis de evaluaciones, así mismo en un número adicional de puntos secundarios incluyendo fatiga, sueño, ánimo y percepción.
2. establecer y comparar los perfiles de seguridad de 100 y 200 mg. de milnaciprina administrados diariamente en pacientes con SMF.

Metodología

Este fue un método en multi centros y al doble ciego, de estudio controlado de placebos de milnacipran para el tratamiento de la fibromialgia, que enlistó a 888 pacientes que cumplieran con el criterio 1990 ACR para el síndrome de fibromialgia, así como un criterio de admisión mayormente detallado en el protocolo.

Los pacientes registraban síntomas base en las primeras dos semanas después de eliminar antidepresivos, benzodiazepina y ciertas otras drogas que potencialmente podrían interferir con la medida de eficacia.

Los pacientes fueron seleccionados aleatoriamente para recibir placebo, 100 mg./día de milnaciprina o 200 mg./día de milnaciprina en una ración de 1:1:2. Los medicamentos administrados aleatoriamente (placebo y milnaciprina) fueron administrados en dosis divididas (BID). Las dosis fueron administradas en un régimen de dosis escaladas detallado a continuación.

- | | |
|---------|---|
| Paso 1: | 12.5 mg 1 día (12.5 mg p.m.) |
| Paso 2: | 25 mg 2 días (12.5 mg a.m., 12.5 mg p.m.) |
| Paso 3: | 50 mg 4 días (25 mg a.m., 25 mg p.m.) |
| Paso 4: | 100 mg 7 días (50 mg a.m., 50 mg p.m.) |
| Paso 5: | 200 mg 7 días (100 mg a.m., 100 mg p.m.) |

Todos los pacientes fueron programados a recibir un total de 24 semanas de milnaciprina o placebos después de 3 semanas de pasos de dosificación escalonados, para un total de 27 semanas de exposición a milnaciprina o placebos.

Los pacientes fueron requeridos a completar un diario electrónico así como adicionalmente evaluaciones en papel de conformidad a lo descrito en el programa de evaluaciones de estudio.

Eventos Adversos, exámenes físicos, medicamentos concomitantes, signos vitales e información clínica de laboratorios fueron recolectadas a lo detallado en el programa de evaluaciones de estudio.

Pacientes que satisfactoriamente concluyeron el método de doble ciego fueron elegibles a participar en una prueba abierta para 15 a 28 semanas adicionales de terapia.

Un cronograma del estudio se prevé en la **figura No. 1.**

Evaluaciones

Seguridad:

La seguridad de la milnaciprina fue evaluada por medio del análisis a la frecuencia e intensidad de los eventos adversos, cambio en los signos vitales así como cambios en la examinación física e información clínica de laboratorio recolectada durante el periodo de estudio.

Eficacia:

Adicionalmente al requisito de cumplir el diario electrónico del paciente propietario las siguientes evaluaciones fueron obtenidas:

- a. Variables primarias: Impresión global de cambio del paciente (PGIC) y el cuestionario de impacto de fibromialgia (FIQ);
- b. Rastreo psicológico de base: M.I.N.I
- c. Estatus de evaluaciones misceláneas: periódicamente, de conformidad a lo descrito, en el programa de evaluaciones: BDI escala de calidad de sueño y ASEX; y
- d. Evaluaciones de estatus FMS: dolor en pacientes en 24 horas y 7 días, VAS, y el cuestionario SF-36, y el cuestionario de habilidades múltiples para el reporte propio (MASQ), el cuestionario multidimensional para la evaluación de la salud (MDHAQ) y el inventario multidimensional de fatiga (FMI). Evaluaciones diarias incluyen dolor (en la mañana, aleatoriamente diarias y reportes en la tarde); dolor diario (reporte de la mañana), medicamentos tomados (reporte en la tarde), dolor general de la semana anterior (reporte semanal), fatiga general de la semana anterior (reporte semanal), incluyendo el dolor que mantuvo al paciente de cuidarse por si mismo (reporte semanal).

El punto primario de este estudio fue un conjunto de análisis de las evaluaciones que implementa el análisis de 3 dominios de interés, evaluados a 24 semanas

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como análisis primarios y 12 semanas como análisis secundarios. Los dominios medidos eran:

1. dolor medido por un diario electrónico por medio un parámetro de dolor calculado a un puntaje promedio de dolor;
2. global de pacientes medido por (PGIC, escala 1-7); y
3. funciones físicas, medido por (FIQ-PF).

Para el análisis primario el rango de dominio de dolor fue determinado por un cálculo que comparó el promedio de tratamiento de las semanas 14 y 15 contrapuestas a las dos semanas tomadas de base y de las semanas de tratamiento 26 y 27 contrapuesto a la base del análisis secundario. La última observación fue llevada en adelante en caso de que ni la semana 14 ni semana 15 (o semanas 26/27) del parámetro de dolor de los reportes de pacientes estuviese disponible para comparar los valores base.

El rango de respuesta binaria para el placebo, en el presente estudio se espera estar en el rango del 10-13%, con un rango de respuesta de milnacipran en los rangos esperados de 27-29% en los rangos ITT/LOCF. Basados en estos rangos de respuestas asumidos, 125 pacientes aleatoriamente (250 para grupos de dosificación alta), fue calculado en ser el máximo tamaño de pruebas requeridas (90% de fuerza). Los análisis secundarios incluyen el área total bajo la curva de la intensidad de dolor, y de los reportes semanales de pacientes en la clínica así como las evaluaciones de los status de FMS y las mediciones QOL.

Resultados:

Un sujeto fue definido como el que experimenta una reducción mayor al 30% de dolor, partiendo de la base y mejoras del PGIC.

A los tres meses, el porcentaje de sujetos era: 35.44% (56/158) en el grupo de placebo; 53.33 % (72/135) ($p=0.001$) en el grupo de milnacipran 100 mg/ al día, y 55.00% (143/260) ($p<0.001$) en el grupo de milnacipran 200 mg/ al día. A los seis meses el porcentaje de sujetos era: 32.86 % (46/140) en el grupo de placebo; 49.59 % (60/121) ($p=0.002$) en el grupo de milnacipran 100 mg/ al día, y 51.74% (119/230) ($p<0.001$) en el grupo de milnacipran 200 mg/ al día. Ver tabla No. 1 para el sumario de los resultados en el intento de curar a la población y la tabla No. 2 para el sumario de la última observación realizada (LOCF), observación base realizada (BOCF) y culminación de estudios (OC). El LOCF es un análisis en el cual se realizan observaciones en el último punto para pacientes que se retiraron. Los análisis LOCF maneja la información realizada como información observado al último punto. BOCF es un análisis que requiere que el paciente se mantenga activo. Si el paciente se retira de la prueba por cualquier razón, los mismos son catalogados como no sujeto. Independientemente los resultados globales y de dolor al momento de retirarse.

TABLA 1

Análisis de sujetos para el tratamiento de dolor de la fibromialgia durante el
tratamiento
Semanas 14-15 y 26-27 (observar clases) Intención de tratar a la población

	Estadística	Placebo (N=223)	Milnacipran 100 mg(N=224)	Milnacipran 200 mg(N=441)
Dolor base	n	223	224	441
	promedio	68.37	68.32	69.41
	DS	11.98	11.54	11.85
	SEM	0.80	0.77	0.56
	media	66.5	67.9	69.1
	min., máx.	50, 100	41, 100	47, 99
Tratamiento Semanas 14-15	n	158	135	260
	m (%=m/n)	56 (35.44)	72 (53.33)	143 (55.00)
	razón de probabilidades		2.10	2.20
	95% CI		(1.31, 3.36)	(1.46, 3.31)
	valor-p		0.002	<0.001
Tratamiento Semanas 26-27	n	140	121	230
	m (%=m/n)	46 (32.86)	60 (49.59)	119 (51.74)
	razón de probabilidades		1.96	2.20
	95% CI		(1.18, 3.26)	(1.42, 3.41)
	valor-p		0.009	<0.001

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TABLA 2

Sumario de Rango						
	Valor					
	3 meses			6 meses		
	pbo N=223	100 mg N=224	200 mg N=441	pbo N=223	100 mg N=224	200 mg N=441
Análisis Primario (LOCF)	27.8%	33.5%	34.9%	25.1%	30.8%	32.2%
		p*=0.187	p*=0.058		p*=0.197 ap*=0.393	p*=0.053 ap*=0.105
Análisis de Sensibilidad (BOCF)	25.1%	32.1%	32.4%	20.6%	26.8%	27.0%
		p*=0.094	p*=0.048		p*=0.167 ap*=0.334	p*=0.067 ap*=0.133
Análisis de Sensibilidad II	25.56%	32.0%	32.7%	21.5%	27.2%	28.6%
		p*=0.113	p*=0.056		p*=0.197 ap*=0.394	p*=0.048 ap*=0.095
Análisis de Sensibilidad III	25.1%	32.1%	32.4%	22.9%	29.5%	29.9%
		p*=0.094	p*=0.048		p*=0.120 ap*=0.241	p*=0.051 ap*=0.102
Análisis OC	n*=158	n=135	n=260	n=140	n=121	n=230
	35.4%	53.3%	55.0%	32.9%	49.6%	51.7%
		p*=0.002	p*<0.001		p*=0.009	p*<0.001
Sumario Individual						
	Dolor 3 meses			Dolor 6 meses		
	pbo	100 mg	200 mg	pbo	100 mg	200 mg
Análisis Primario (LOCF)	27.8%	33.5%	34.9%	25.1%	30.8%	32.2%
		p*=0.187	p*=0.058		p*=0.197 ap*=0.393	p*=0.053 ap*=0.105
Dolor (LOCF)	31.4%	35.7%	38.3%	28.7%	35.7%	35.4%
		p=0.321	p=0.068		p=0.110	p=0.072
PGIC (LOCF)	47.1%	54.0%	50.6%	46.2%	49.6%	49.9%
		p=0.143	p=0.397		p=0.476	p=0.368

Estos resultados sorpresivamente establecen que la administración continua de milnaciprina (administración diaria por lo menos en 3 meses), a sujetos sufriendo de fibromialgia provee a largo plazo (por lo menos 3 meses) de alivio de la fibromialgia y sus síntomas. Adicionalmente estos resultados sorpresivamente establecen que la administración continua de dosificaciones bajas de milnaciprinas (ejemplo 100 mg/día) es casi efectiva como a la administración continua de dosificaciones altas de milnaciprinas (200 mg/día).

Para el tratamiento a largo plazo de la fibromialgia y sus síntomas

Figura 2.

Mientras que la invención ha sido detallada y descrita por referencia en aplicaciones de ejemplo de la invención, dicha referencia no implica o limita a la invención, y dicha limitación no debe ser inferida. La invención tiene capacidad de modificaciones considerables, alteraciones y equivalentes en forma y función, a los que se les ocurrirá a los conocedores de la materia los cuales tendrán el beneficio de esta revelación. Las aplicaciones descritas y detalladas son como ejemplos únicamente, y nos son exhaustivas del ámbito de la invención. Consecuentemente, se pretende que la invención sea limitada solo por el espíritu y ámbito de las reivindicaciones suplementarias, otorgando amplia reconocimiento a su equivalente en todos los aspectos. Todas las referencias citadas por la presente por medio de la presente se incorporan por referencia en su totalidad.

Reivindicaciones:

1. Un método para prever el tratamiento a largo plazo del síndrome de fibromialgia en un paciente que lo requiere por medio de la administración de un inhibidor de absorción dual (DRI) al paciente por lo menos por tres meses.
2. El método de la reivindicación 1 en el cual el DRI es un inhibidor de reabsorción de norepinefrina-serotina (NSRI).
3. El método de la reivindicación 2 en el cual el NSRI es milnaciprina.
4. El método de la reivindicación 3 en el cual la milnaciprina es administrada en una dosis comprendida dentro un aproximado de 25 mg/día y de 400 mg/día.
5. El método de la reivindicación 4 en el cual la milnaciprina es administrada en una dosis aproximada de 200 mg/día.
6. El método de la reivindicación 4 en el cual la milnaciprina es administrada en una dosis aproximada de 100 mg/día.
7. El método de la reivindicación 1 en el cual el DRI es administrado por lo menos por seis meses.
8. El método de tratamiento de la fibromialgia y sus síntomas en pacientes sufriendo de fibromialgia, el cual comprende: a. administrando aproximadamente 200 mg/día de milnaciprina al paciente para el tratamiento de dolor agudo; b. disminuyendo la dosificación de milnaciprina aproximadamente a 100 mg/día cuando el dolor agudo ha sido tratado; y c. administrando aproximadamente 100 mg/día al paciente por lo menos por tres meses para el tratamiento a largo plazo de la fibromialgia y sus síntomas.
9. El método de cualesquiera de las reivindicaciones 1-8 comprendiendo en adición la administración de un segundo componente activo en el cual el segundo componente activo es seleccionado del grupo que consiste de antidepresivos, analgésicos, relajantes musculares, anorectica, estimulantes, droga antiepilépticas, un bloqueador beta, sedantes, hipnóticos y combinación de los mismos.
10. El método de la reivindicación 9 en el cual el segundo componente activo es seleccionado del grupo consistiendo de modafinil, XP13512, gabapentin, pregabalin, pramipexole, 1- DOPA, anfetamina, tizanidine, clonidine, tramadol, morfina, antidepresivos tricíclicos, codeína, cambamazepina, sibutramina, valium, trazodone, cafeína, nicergolina, bifemelane, propranolol, atenolol y combinaciones de las mismas.

11. El método de proporcionar el tratamiento a largo plazo de los síntomas de dolor asociados con el síndrome de fibromialgia en el paciente que lo requiera por medio de la administración de un inhibidor de recaptación dual (DRI) a un paciente por lo menos por tres meses.
12. El método de la reivindicación 1 en el cual el DRI es un inhibidor de recaptación dual de norepinefrina-serotonina (NSRI).
13. El método de la reivindicación 2 en el cual el NSRI es milnaciprina.
14. El método de la reivindicación 3 en el cual la milnaciprina es administrada en una dosis que comprende aproximadamente entre 25 mg/día y aproximadamente 400 mg/día.
15. El método de la reivindicación 4 en el cual la milnaciprina es administrada en una dosis aproximada de 200 mg/día.
16. El método de la reivindicación 4 en el cual la milnaciprina es administrada en una dosis aproximada de 100 mg/día.
17. El método de la reivindicación 1 en el cual el DRI es administrado por lo menos seis meses.
18. Un método de tratamiento de fibromialgia y sus síntomas en un paciente sufriendo de fibromialgia, que incluye:
 - a. 200 mg/día de milnaciprina a un paciente para el tratamiento de dolor agudo;
 - b. Disminución de la dosis de milnaciprina a aproximadamente 100 mg/día cuando el dolor agudo ha sido tratado
 - c. Administración aproximadamente de 100 mg/día de milnaciprina al paciente por lo menos por 3 meses para el tratamiento a largo plazo de la fibromialgia y sus síntomas
19. El método de cualesquiera de las reivindicaciones 11-18 comprendiendo en adición la administración de un segundo componente activo en el cual el segundo componente activo es seleccionado del grupo que consiste de antidepresivos, analgésicos, relajantes musculares, anorecticos, estimulantes, drogas antiepilépticas, un bloqueador beta, sedantes, hipnóticos y combinación de los mismos.
20. El método de reivindicación 19 en el cual el segundo componente activo es seleccionado de un grupo que consiste del grupo consistiendo de modafinil, XP13512, gabapentin, pregabalin, pramipexole, 1- DOPA, amfetamina, tizanidine, clonidine, tramadol, morfina, antidepresivos tricíclicos, codeína, cambamazepina, sibutramina, valium, trazodone, cafeína, nicergolina, bifenelane, propranolol, atenolol y combinaciones de las mismas.

Figura 1

CRONOGRAMA DEL ESTUDIO

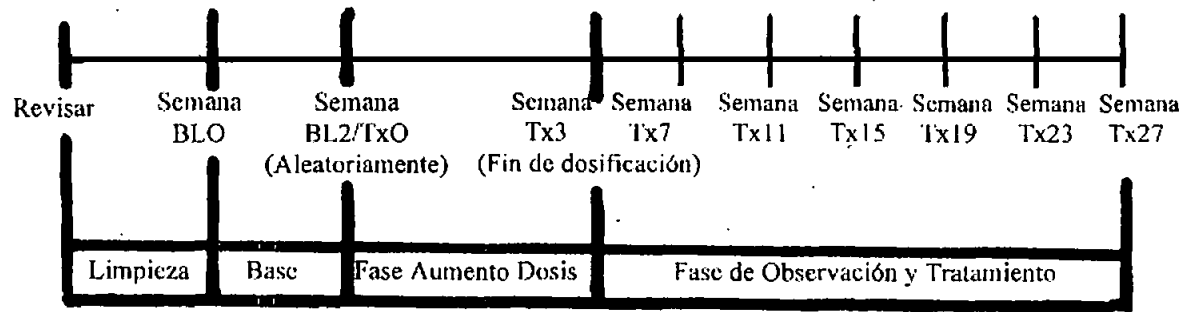
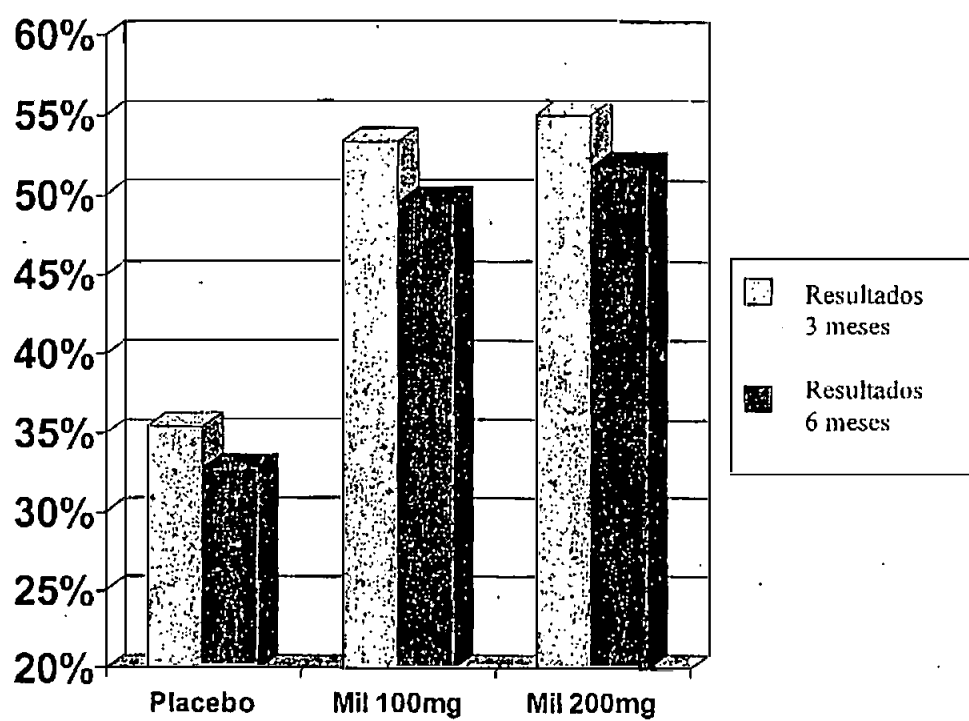


Figura 2.



PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To: S. Peter Ludwig
Darby & Darby PC
P.O. Box 5257
New York, New York 10150-5257

Date of mailing
(day/month/year) **23 AUG 2007**

Applicant's or agent's file reference
2203444-WOO

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US06/37714

International filing date
(day/month/year) **27 September 2006 (27.09.2006)**

Applicant **Cypress Bioscience, Inc.**

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: +41 22 740 14 35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 2203444-W00	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US06/37714	International filing date (day/month/year) 27 September 2006 (27.09.2006)	(Earliest) Priority Date (day/month/year) 28 September 2005 (28.09.2005)
Applicant Cypress Bioscience, Inc.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (see Box No. II)

3. ☐ Unity of invention is lacking (see Box No. III)

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
- b. ☒ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US06/37714

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8): A61K 31/165 (2007.01)

USPC: 514/619

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

USPC: 514/619

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST(USPT,PGPB,EPAB,JPAB); PubMed; Google Scholar

Search Terms Used: fibromyalgia, syndrome, milnacipran, treat

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/0228830 A1 (Hirsh et al.) 18 November 2004 (18.11.2004); entire document, especially para [0004], [0007], [0008], [0010], [0017], [0086], [0087]	1-20

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

29 April 2007 (29.04.2007)

Date of mailing of the international search report

23 AUG 2007

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: S. Peter Ludwig
Darby & Darby PC
P.O. Box 5257
New York, New York 10150-5257

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

23 AUG 2007

Applicant's or agent's file reference
2203444-WOO

FOR FURTHER ACTION

See paragraph 2 below

International application No.
PCT/US06/37714

International filing date (day/month/year)
27 September 2006 (27.09.2006)

Priority date (day/month/year)
28 September 2005 (28.09.2005)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K31/165 (2007.01)
USPC - 514/619

Applicant Cypress Bioscience, Inc.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1460, Alexandria, Virginia 22313-1460
Facsimile No. 571-273-3201

Date of completion of this opinion
29 April 2007 (29.04.2007)

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US06/37714

Box No. 1 Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:



the international application in the language in which it was filed



a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material



a sequence listing



table(s) related to the sequence listing

b. format of material



on paper



in electronic form

c. time of filing/furnishing



contained in the international application as filed



filed together with the international application in electronic form



furnished subsequently to this Authority for the purposes of search

3. ☐

In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US08/37714

Box No. V Reasoned statement under Rule 43b/s.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-20	YES
	Claims	none	NO
Inventive step (IS)	Claims	none	YES
	Claims	1-20	NO
Industrial applicability (IA)	Claims	1-20	YES
	Claims	none	NO

2. Citations and explanations:

Claims 1-20 lack an inventive step under PCT Article 33(3) as being obvious over US 2004/0228630 A1 to Hirsh et al. (hereinafter 'Hirsh').

As per claim 1, 2, and 3, directed to a method of providing long-term treatment of fibromyalgia syndrome, Hirsh discloses that milnacipran which is a norepinephrine (NE) and serotonin (5-HT) reuptake inhibitor (NSRI) (para [0004]) could produce a therapeutic effect over fibromyalgia syndrome patients (para [0017]) and that Patients received either milnacipran 75-100 mg/day twice daily for 8 weeks (para [0007]). It would have been obvious for a person having ordinary skills in the art to administer milnacipran, an NSRI and a dual re-uptake inhibitor (DRI), to provide a long-term treatment for fibromyalgia.

As per claim 4, directed to the method of claims 3, respectively, It is obvious for reasons set forth for claim 3, and further because Hirsh discloses that patients received either milnacipran 75-100 mg/day twice daily (para [0007]). It would have been obvious for a person having ordinary skills in the art to further specify that the milnacipran is administered in a dose between about 25 mg per day and about 400 mg per day.

As per claims 5, 6, directed to the method of claim 4, respectively, they are obvious for reasons set forth for claim 4, and further because Hirsh discloses that in a double-blind, randomized, multicenter clinical study, patients received 100 mg/day milnacipran or 200 mg/day (para [0007]). It would have been obvious for a person having ordinary skills in the art to further specify that the milnacipran is administered in a dose of about 100 mg per day or 200 mg per day.

As per claim 7, directed to the method of claim 1, it is obvious for reasons set forth for claim 1, and further because It would have required only ordinary knowledge in the art to administer DRI for at least 6 months to provide a longer-term treatment and durable effect for fibromyalgia.

As per claims 8 and 18, they are obvious for reasons set forth for claim 1, and further because Hirsh discloses that milnacipran could provide relief from pain (para [0017]) and that in one of the early clinical trials, milnacipran dosage of 200 mg/day was superior to the lower doses (para [0010]) and that the incidence of certain adverse events increases with dosage, including nausea, vomiting, sweating, hot flashes, palpitations, tremor, anxiety, dysuria, and insomnia (para [0008]). It would have been obvious for a person having ordinary skills in the art to administer about 200 mg per day of milnacipran for the treatment of acute pain so as to get better therapeutic effect and then decrease the dose of milnacipran to about 100 mg per day when the acute pain has been treated to decrease the incidence of certain adverse events and administer about 100 mg per day of milnacipran to the patient for at least three months for the long-term treatment of fibromyalgia and its symptoms.

As per claim 9, directed to the method of claim 1, it is obvious for reasons set forth for claim 1, and further because Hirsh discloses that milnacipran can be administered adjunctively with other active compounds such as analgesics, antidepressants, antiepileptics, antihistamines, antimigraine drugs, antimuscarinics, sedatives, hypnotics, antipsychotics, bronchodilators, anti asthma drugs, cardiovascular drugs, corticosteroids, dopaminergics, electrolytes, gastro-intestinal drugs, muscle relaxants, nutritional agents, vitamins, parasympathomimetics, stimulants, anorectics and anti-narcoleptics (para [0088]).

As per claim 10, directed to the method of claim 9, it is obvious for reasons set forth for claim 9, and further because Hirsh discloses that "[s]pecific examples of compounds that can be adjunctively administered with milnacipran include, but are not limited to, amphetamine, caffeine, clonidine, codeine, modafinil, morphine, gabapentin, propranolol, pregabalin, pramipexole, sibutramine, tizanidine, tramadol, and isomers, salts, and combinations thereof." (para [0087])

As per claim 11, it is obvious for reasons set forth for claims 1 and 8, and further because It would have been obvious for a person having ordinary skills in the art to administer a dual re-uptake inhibitor (DRI) to the patient for at least three months to provide long-term treatment of a pain symptom associated with fibromyalgia syndrome in a patient.

As per claims 12, 13, 14, 15, 16, 17, they are obvious for reasons set forth for claim 11, and, individually for claims 2, 3, 4, 5, 6, 7, respectively.

--Please See Continuation Sheet--

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US08/37714

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
Claims 12-18 are objected to because they are identical to claims 2-8, respectively.

Claim 12 was searched as being dependent on claim 11 instead of claim 1;
Claim 13 was searched as being dependent on claim 12 instead of claim 2;
Claim 14 was searched as being dependent on claim 13 instead of claim 3;
Claims 15 and 16 were searched as being dependent on claim 14 instead of claim 4;
Claim 17 was searched as being dependent on claim 11 instead of claim 1.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US06/37714

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

As per claim 19, directed to the method of claim 11, comprising adjunctively administering a second active compound, wherein the second active compound is selected from the group consisting of an antidepressant, an analgesic, a muscle relaxant, an anorectic, a stimulant, an antiepileptic drug, a beta blocker, a sedative, a hypnotic and combinations thereof, Hirsh discloses that "milnacipran can be administered adjunctively with other active compounds such as analgesics, antidepressants, antiepileptics, antihistamines, antimigraine drugs, antimuscarinics, sedatives, hypnotics, antipsychotics, bronchodilators, anti asthma drugs, cardiovascular drugs, corticosteroids, dopaminergics, electrolytes, gastro-intestinal drugs, muscle relaxants, nutritional agents, vitamins, parasympathomimetics, stimulants, anorectics and anti-narcoleptics." (para [0086])

As per claim 20, directed to the method of claim 19, wherein the second active compound is selected from the group consisting of modafinil, XP13512, gabapentin, pregabalin, pramipexole, L-DOPA, amphetamine, tizanidine, clonidine, tramadol, morphine, tricyclic antidepressants, codeine, clobazepam, sibutramine, valium, trazodone, caffeine, nicergoline, bifenmelane, propranolol, atenolol and combinations thereof, Hirsh discloses that "[s]pecific examples of compounds that can be adjunctively administered with milnacipran include, but are not limited to, amphetamine, caffeine, clonidine, codeine, modafinil, morphine, gabapentin, propranolol, pregabalin, pramipexole, sibutramine, tizanidine, tramadol, and isomers, salts, and combinations thereof." (para [0087])

Claims 1-20 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

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NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1bis(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43bis.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

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From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

LUDWIG, S., Peter
DARBY & DARBY P.C.
P.O. Box 5257
New York, NY 10150-5257
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 07 February 2007 (07.02.2007)	
Applicant's or agent's file reference 2203444-WOO	IMPORTANT NOTIFICATION
International application No. PCT/US2006/037714	International filing date (day/month/year) 27 September 2006 (27.09.2006)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 28 September 2005 (28.09.2005)
Applicant CYPRESS BIOSCIENCE, INC. et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
3. (If applicable) An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
28 September 2005 (28.09.2005)	60/721,722	US	30 October 2006 (30.10.2006)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Athina Nickitas-Etienne

Facsimile No. +41 22 338 82 70

Facsimile No. +41 22 338 90 84

Telephone No. +41 22 338 94 43

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 2203444-WOO

Box No. I TITLE OF INVENTION

MILNACIPRAN FOR THE LONG-TERM TREATMENT OF FIBROMYALGIA SYNDROME

Box No. II APPLICANT

☐ This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

CYPRESS BIOSCIENCE, INC.
4350 Executive Drive, Suite 325
San Diego, California 92121
United States of America

Telephone No.

Facsimile No.

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality:
USState (that is, country) of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

RAO, Srinivas G.
1477 Paseo de las Flores
Encinitas, California 92024
United States of America

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:
USState (that is, country) of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

LUDWIG, S. Peter
Darby & Darby P.C.
P.O. Box 5257
New York, New York 10150-5257
United States of America

Telephone No.

(212) 527-7770

Facsimile No.

(212) 527-7701

Teleprinter No.

Agent's registration No. with the Office
25,351

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
<i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) GENDREAU, Michael 12730 Shadowline Street Poway, California 92064 United States of America	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: US	State (that is, country) of residence: US
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) KRANZLER, Jay D. 7935 Via Capri La Jolla, California 92037 United States of America.	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: US	State (that is, country) of residence: US
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

Supplemental Box. *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, except Boxes Nos. VIII(f) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

Continuation of Box No. IV:

BARRISON, Flynn (53,970); COLLAZO, Maxie (44,085); and ZAGAR, Paul M. (52,392)

- (i) If more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
- (ii) If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
- (iii) If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor-applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
- (iv) If, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box IV;
- (v) If, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.
2. If the applicant intends to make an indication of the wish that the international application be treated, in certain designated States, as an application for a patent of addition, certificate of addition, inventor's certificate of addition or utility certificate of addition: in such a case, write the name or two-letter code of each designated State concerned and the indication "patent of addition," "certificate of addition," "inventor's certificate of addition" or "utility certificate of addition," the number of the parent application or parent patent or other parent grant and the date of grant of the parent patent or other patent grant or the date of filing of the parent application (Rules 4.11(a)(iii) and 49bis.1(a) or (b)).
3. If the applicant intends to make an indication of the wish that the international application be treated, in the United States of America, as a continuation or continuation-in-part of an earlier application: in such a case, write "United States of America" or "US" and the indication "continuation" or "continuation-in-part" and the number and the filing date of the parent application (Rules 4.11(a)(iv) and 49bis.1(d)).

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Box No. V DESIGNATIONS

The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

- ☐ DE Germany is not designated for any kind of national protection.
- ☐ JP Japan is not designated for any kind of national protection.
- ☐ KR Republic of Korea is not designated for any kind of national protection.
- ☐ RU Russian Federation is not designated for any kind of national protection.

(The check-boxes above may be used to exclude (irrevocably) the designations concerned if, at the time of filing, the international application contains in Box No. VI a priority claim to an earlier national application filed in the particular State concerned, in order to avoid the ceasing of the effect, under the national law, of this earlier national application. See the Notes to Box No. V as to the consequences of such national law provisions in these and certain other States.)

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

	Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
			national application: country or Member of WTO	regional application: * regional Office	international application receiving Office
item (1)	28 September 2005 (28.09.2005)	60/721,722	US		
item (2)					
item (3)					

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☒ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)).

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA /US

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)	Number	Country (or regional Office)
26 September 2006 (26.09.2006)	1.1/535,237	US

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

Number of
declarations

- ☐ Box No. VIII (i) Declaration as to the identity of the inventor :
- ☐ Box No. VIII (ii) Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent :
- ☐ Box No. VIII (iii) Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application :
- ☐ Box No. VIII (iv) Declaration of inventorship (only for the purposes of the designation of the United States of America) :
- ☐ Box No. VIII (v) Declaration as to non-prejudicial disclosures or exceptions to lack of novelty :

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:	This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):	Number of items
(a) on paper, the following number of sheets:	1. ☒ fee calculation sheet	1
request (including declaration sheets) : 6	2. ☐ original separate power of attorney	:
description (excluding sequence listings and/or tables related thereto) : 17	3. ☐ original general power of attorney	:
claims : 3	4. ☐ copy of general power of attorney; reference number, if any:	:
abstract : 1	5. ☐ statement explaining lack of signature	:
drawings : 2	6. ☐ priority document(s) identified in Box No. VI as item(s):	:
Sub-total number of sheets : 29	7. ☐ translation of international application into (language):	:
sequence listings :	8. ☐ separate indications concerning deposited microorganisms or other biological material	:
tables related thereto :	9. ☐ sequence listing in electronic form (indicate type and number of carriers)	:
(for both, actual number of sheets if filed on paper, whether or not also filed in electronic form; see (c) below)	(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)	:
Total number of sheets : 29	(ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter	:
(b) ☐ only in electronic form (Section 801(a)(i))	(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column	:
(i) ☐ sequence listings	10. ☐ tables in electronic form related to sequence listing (indicate type and number of carriers)	:
(ii) ☐ tables related thereto	(i) ☐ copy submitted for the purposes of international search under Section 802 (b-quarter) only (and not as part of the international application)	:
(c) ☐ also in electronic form (Section 801(a)(ii))	(ii) ☐ (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802 (b-quarter)	:
(i) ☐ sequence listings	(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column	:
(ii) ☐ tables related thereto	11. ☒ other (specify): check no. _____	1
Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the		
☐ sequence listing:		
☐ tables related thereto:		
(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)		
Figure of the drawings which should accompany the abstract:	Language of filing of the international application: English	

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

CYPRESS BIOSCIENCE, INC.

Name:

Title:

Additional signatures on following sheet

For receiving Office use only	
1. Date of actual receipt of the purported international application:	2. Drawings:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	☐ received:
4. Date of timely receipt of the required corrections under PCT Article 11(2):	☐ not received:
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid.
For International Bureau use only	
Date of receipt of the record copy by the International Bureau:	

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Box No. X (supplemental) SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE
_____ Srinivas G. Rao, Inventor of Record
_____ Michael Gendreau, Inventor of Record
_____ Jay D. Kranzler, Inventor of Record

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-039648- -00000-0000

Fecha: 2008-04-18 16:29:37 Dep. 2020 NUECREACION
Tra. 11 PATENTE IYM Eje: 378 FASE NACIONAL
Act. 411 PRESENTACION Folios: 65

SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION



MODELO DE UTILIDAD []

- ◆ Indicación de que se solicita la concesión de una patente []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Descripción de la invención []
- ◆ Dibujos de ser estos pertinentes []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

DISEÑO INDUSTRIAL []

- ◆ Indicación de que se solicita el registro de Diseño Industrial []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

ESQUEMA DE TRAZADO []

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica del esquema trazado []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

Fdo B

Firma Responsable

Fecha 17-10-8

Carrera 13, No. 27-00 Piso 5, 7 y 10
Teléfono: 3 82 09 40
Fax: 350 52-20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CADENA SARMIENTO JUAN PABLO

REFERENCIA	Radicación No.	8 39648
	Solicitud internacional	PCT/US2006/037714
	Fecha inicio fase nacional	28/04/2008
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	- 8109

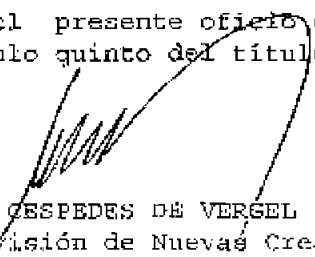
Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

2. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No.10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 20 JUN 2008
adpail