Abstract:
The present invention refers to a new synergistic pharmaceutical combination of an antihyperalgesic, anti-inflammatory agent, wherein the antihyperalgesic, anti-inflammatory agent is pregabalin, and the anti-inflammatory agent is meloxicam. The present invention is also directed to pharmaceutical compositions comprising such combination, and the use of said combination and pharmaceutical compositions for prevention and/or treatment of pain caused by different neuropathic etiologies.
COMBINATION OF PREGABALIN AND MELOXICAM FOR THE TREATMENT OF NEUROPATHIC PAIN

FIELD OF THE INVENTION

The present invention refers to the pharmacological combination of an antihyperalgesic, antiallodynic, and anti-inflammatory agent, as well as pharmaceutical compositions comprising such a combination, as well as the use thereof for prevention and/or treatment of pain caused by different neuropathic etiologies.

More particularly, the present invention describes a combination of a γ-aminobutyric acid (GABA) analogue agent and non-steroidal anti-inflammatory agent (NSAID) revealing a synergistic effect, pharmaceutical compositions comprising it and the use of this combination and pharmaceutical compositions to treat and/or prevent neuropathic pain caused by diabetic neuropathy, neuropathy after appearance of herpes zoster, neuralgia of trigeminal nerve, HIV, pain of the phantom member after an amputation, neuropathic pain of lumbar and dorsal region.
BACKGROUND OF THE INVENTION

Pain involves an altered sensitivity which commonly is indescribable and of difficult assessment to experts in human health. All individuals under various circumstances have been exposed to painful conditions that trigger disruption and unbalance their well-being, which is manifested by multiple behavioral alterations including despair, discouragement, depression, irritability, fear, stress, loss of interest in activities that provide satisfaction, etc.

Pain has been classified in various ways since it may vary in its evolution (acute or chronic), meaning (adaptive or non-adaptive), intensity (mild, moderate or severe), quality (ardent, throbbing, stabbing, burning, electric shock-like), duration (transient, intermittent or persistent) or reference (superficial or deep, located or diffuse). However, according to its somatic origin and physiological mechanism pain is classified as nociceptive (transient pain in response to a noxious stimulus), inflammatory (spontaneous pain and hypersensitivity to pain in response to inflammation and tissue damage), neuropathic (spontaneous pain and pain hypersensitivity in association with nervous system damage or injury), psychogenic (the pain is only in patient’s mind, without any organic cause that justifies it) and functional
(no injury, pain hypersensitivity that results from an alteration of abnormal visceral processing or function).

Neuropathic pain is a chronic condition caused by nervous system injury. Unlike the protective acute pain, neuropathic pain persists and does not have a useful purpose severely affecting patient’s quality of life (Shah et al, 2003). Neuropathic pain is a consequence of various types of pathological processes affecting central or peripheral nervous system neurons (Zhuo, 2007). This type of pain is part of a wide range of conditions such as trauma, diabetes mellitus, herpes zoster, cancer, HIV, etc.

Neuropathic pain includes spontaneous stimulus-dependent and stimulus-independent pain characterized by hyperalgesia and allodynia (Zhuo, 2007). Many patients who experience nerve damage do not develop neuropathic pain. However, those who develop it suffer severe abnormal pain and long-lasting syndromes after central or peripheral neural damage.

For some years, the treatment of neuropathic pain has become the cornerstone and the primary objective of hospital units and/or pain clinical units. This happens not only because of its frequency, but essentially by its resistance to common analgesic treatments and to a broad lack of knowledge about the pathology administration that cause it,
inducing to resort periodically to pain treatment specialists.

Family physicians and many specialists are struggling to understand why some patients with intense and clearly organic pain, are reluctant to all used analgesic treatment, even to opioid drugs, demonstrating a huge difficulty to interpret symptoms and a so torpid disease evolution in this group of patients.

Treatments currently used in hospital units and/or pain clinical units for control of these patients are varied, using drugs that by their action mechanism are capable of decreasing nervous system excitability, severely damaged by the manifested disease process.

These drugs are grouped under the name of neuromodulators and can act under two different capacities: a) decreasing pathological mechanisms that extend or trigger pain impulses, or b) enhancing the mechanisms that inhibit painful transmission or perception; in conclusion, negatively or positively modulating a neural activity.

Treatment of neuropathic pain in recent years has moved from being a simple control method of symptoms to an improved and comprehensive care of several different characteristics involved in a painful sensation, based on a better
understanding of those mechanisms which cause and maintain the pain.

A number of drugs belonging to the families of analgesics, non-steroidal anti-inflammatory, norepinephrine inhibitors, opioids and others have been used in neuropathic pain treatment basic care. Although these treatments are nowadays considered clinically significant in only fifty percent of the cases, the use of another type of antidepressant drugs and anticonvulsants, such as adjuvants for managing this type of pain, has been a choice, with relative success due to their high side effect incidence. One of the first choice treatments consists of administering the drug gabapentin, which demonstrates multiple side effects such as drowsiness, weakness or tiredness, dizziness, headache, uncontrollable tremor in any part of the body, double or blurred vision, instability, anxiety, nausea, vomiting, heartburn, diarrhea, dry mouth, constipation, increased appetite.

The problem in hospitals, particularly in specialized units in pain alleviation persists up to now by not having a completely satisfactory alternative for neuropathic pain treatment, due to a constant manifestation of severe side events caused by administering high doses of different analgesic agents for long periods of time, causing a high
percentage of patients to show treatment apathy or detachment, and even deciding to abandon it.

Human health experts explain that main objectives of an effective neuropathic pain therapeutic administration are the control or suppression of pain, the recovery of psychological well-being (quality of sleep, motivation, confidence, stability, etc.), recovery and proper maintenance of physiological, sensory, motor and reflex functions, and an overall improvement of the quality of life. The first difficulty in pharmacological treatment of painful diseases lies with the appreciation that conventional analgesics, opioids and NSAIDs, offer limited therapeutic effect. The second is that the response to the use of non-conventional antinociceptive treatments is not sufficiently effective.

The present invention provides new pharmacological proposals, such as pharmaceutical compositions comprising a synergistic combination of an antihyperalgesic, antiallodynic agent and an anti-inflammatory non-steroidal agent, manifesting minor side effects due to a decrease of administered daily doses of these agents with respect to those recommended when those are individually prescribed.

A preferred embodiment of antihyperalgesic, antiallodynic agent of the present invention is pregabalin, a gamma-aminobutyric acid (GABA) structural analogue, the main
neurotransmitter with central nervous system (CNS) inhibitory function. Structurally, it is a chemical modification of GABA, the (S)-3-isobutilgaba.

The mechanism of action whereby its pharmacological activity is developed is based on its ability to link to the alpha-2-delta subunit (α2δ), protein fraction associated to voltage-dependent calcium channels in the CNS. A reduction of calcium entry into the presynaptic nerve endings is produced by modulating these channels, with a decrease in releasing several excitatory neurotransmitters, including glutamate, noradrenaline, CGRP and substance P at the spinal cord level, this being the suggested mechanism to explain this drug analgesic, antiepileptic, and anxiolytic properties.

Its digestive absorption is fast, reaching maximum plasma concentrations in less than 1 hour. Its bioavailability is 90% reaching stable plasma levels 24-48 hours from starting its administration. Hepatic metabolism is not present and is not bound to plasma proteins, thus without significant drug interactions and crossing rapidly the blood brain barrier. Its absorption is unaffected by food intake and has a linear pharmacokinetics with low inter-individual variability. It is almost completely eliminated in urine without any change thus requiring dose adjustment in renal failure patients. Its elimination half-life is 6.3 h.
The possibility of administering 2-3 times a day and its linear pharmacokinetics over the recommended dose range, 150 - 600 mg/day, makes its use easier than Gabapentin. Another advantage over Gabapentin is that analgesic start effect of pregabalin is faster from 150 mg/day, noting a benefit after second day of treatment and a maximum effect observed at 2 weeks after reaching 300-600 mg daily doses.

Recent studies in Canada and Spain have shown that Pregabalin is more cost-effective than Gabapentin in treatment of patients with post-herpetic neuropathy and diabetic neuropathy. The improvement includes a reduction of pain measured by different scales, improvement of sleep disorder and improvement in some domains of quality of life scales, in the mood and perception of the patient about a successful evolution compared to pre-treatment status.

Start treatment with 150 mg/day dose is recommended (said dose being the effective minimum) with weekly increases until reaching the maximum 600 mg/day dose. Daily doses of 300-600 mg are the most effective and with the most frequent side effects: drowsiness, dizziness, headaches, gait instability and lower limb edema. Severity of these symptoms is usually mild or moderate depending on administered dose.

Moreover, pregabalin improved pain, sleep, anxiety and quality of life scales in patients with central pain due to
spinal cord injury and patients with multiple cause central
pain: hemispheric, backbone, trunk, or ischemic injury.

Another preferred embodiment of present invention is
Meloxicam, as non-steroidal anti-inflammatory agent, which
inhibits prostaglandin biosynthesis more intensively on the
inflammation site in the gastric mucosa or in kidney, and it
has been postulated that such action may be related to the
selective inhibition of COX-2 over COX-1 a characteristic
absent in non-selective NSAIDs.

Meloxicam is an enolic acid derivative, having a good
gastrointestinal and renal tolerance profile. Compared to the
traditional non-steroidal anti-inflammatory drugs, Meloxicam
does not inhibit platelet aggregation induced by arachidonic
acid or collagen but significantly reduces thromboxane
platelet production.

Meloxicam is orally administered, but it may be also
intramuscularly or rectally administered. After oral
administration, its absorption is slow reaching higher plasma
concentrations at 4-5 hours. Absolute bioavailability is 90%.
The drug experiences gastrointestinal recirculation, since a
second maximum concentration peak is observed at 12-14 hours.
Drug absorption is not affected by the presence of food, but
increases 22% maximum plasma concentrations. The drug
extensively joins to plasma proteins (99%) particularly
albumin. Meloxicam is extensively metabolized by CYP2C9 (with a lower contribution from CYP3A4) enzyme system, producing 4 inactive metabolites. 43% of administered dose is urine excreted, primarily in the form of metabolites, while the rest is excreted in feces. Meloxicam exhibits a linear pharmacokinetic profile, with 15 to 20 hour elimination half-life. Equilibrium state is reached after five doses (one per day). Women show lower plasma concentrations of Meloxicam than men of the same age. In an equilibrium situation, elimination half-life is 17.9 hours for women and 21.4 hours for men. However, maximum concentrations are similar for both sexes.

Meloxicam is prescribed as an analgesic to relieve mild to moderate pain, as well as for treatment of osteoarthritis, acute and chronic rheumatoid arthritis, shoulder and hip periarthritis, muscle strain and gout attack signs and symptoms, and for treatment of ankylosing spondylitis symptoms. It is also useful for treatment of inflammation secondary to trauma, as well as soft tissue inflammatory processes (airways), gynecological diseases and primary dysmenorrhea.

Meloxicam has demonstrated safety and efficacy in pain and stiffness management in patients with osteoarthritis, with better gastrointestinal tolerability than other NSAIDs
such as diclofenac and Piroxicam, and same tolerability than placebo, favoring a better adherence to treatment. Incidence of digestive side reactions is lower with Meloxicam than that observed with other NSAIDs such as Piroxicam, diclofenac, or naproxen; however, the following side reactions have been described with its use: abdominal pain, diarrhea, dyspepsia, flatulence, nausea, vomiting, dizziness, flu-like symptoms, sore throat, upper respiratory tract infections, anemia, alopecia, rash, pruritus, photosensitizing agents, increased sweating and urticaria. Reported cases of serious bleeding and gastric perforations in some patients treated with this drug have been disclosed. It can also cause significant transaminase increase or hyperbilirubinemia, peripheral edema and fluid retention. Chronic administration of Meloxicam may eventually produce papillary necrosis and other renal injury.

For short-term treatment of mild to moderate intensity pain, an oral dose of 15 mg per day for 7 days is recommended in adults. Maximum recommended dose for adults is 15 mg per day.

Thus, the object of present invention is to provide a synergistic combination of pregabalin or pharmaceutically acceptable salts thereof and Meloxicam or pharmaceutically acceptable salts thereof, as well as pharmaceutical compositions comprising such combination in the same dosage
unit, which manifest minor side effects due to a decrease of administered daily doses of these drugs with respect to the recommended when they are prescribed separately, and the use of these for prevention and/or treatment of neuropathic pain caused by several etiologies, such as diabetic neuropathy, neuropathy after herpes zoster appearance, trigeminal nerve neuralgia, HIV, pain of the phantom member after an amputation, neuropathic pain of lumbar and dorsal region.

In this regard, there are not reported documents within the state of the art specifying a synergistic combination of pregabalin and Meloxicam, and pharmaceutical compositions comprising such combination in the same dosage unit, for use in treatment of pain caused by different neuropathic etiologies. Following are detailed some documents deemed relevant and their differences with regard to present invention.

MX 237693 B patent document refers to combinations of at least one antiepileptic compound and at least one selected compound of the group consisting of analgesics, NSAIDs and antagonists of NMDA receptor, for pain relief. Such patent specifically claims combinations of Gabapentin with naproxen and pregabalin with naproxen. This document neither describes nor suggests any antiallodynic, antihyperalgesic and anti-
inflammatory synergistic effect with a combination of pregabalin and Meloxicam.

MX 288732 B patent document claimed a pharmaceutical composition composed of active ingredients, Gabapentin and Meloxicam formulated in the same oral pharmaceutical forms.

Mexican patent MX 252662 B refers to a combination characterized by comprising a synergistic relationship of an alpha-2-delta ligand and a PDEV inhibitor, used for the preparation of a useful drug in curative, prophylactic or palliative treatment of pain, particularly neuropathic pain. Alpha-2-delta ligand is particularly selected from Gabapentin and pregabalin and PDEV inhibitor is particularly selected from sildenafil, Vardenafil, and tadalafil. The dose intervals of alpha-2-delta ligand and the PDEV inhibitor correspond to a range of synergistic doses in the order from 1:1 to 10:1 parts by weight, particularly in the range of 1 - 10 mg/kg and 0.1 - 1 mg/kg synergistic doses, respectively, in the rat model of static allodynia induced by CCI.

Mexican patent application PA/a/2006/003157 aims to the protection of a synergistic combination of an alpha-2-delta ligand and an AChE inhibitor and its use in the curative, prophylactic or palliative treatment of pain, particularly neuropathic pain. Particularly favorite alpha-2-delta ligands are Gabapentin and pregabalin, and particularly favorite AChE
inhibitors are Donepezil, Tacrine, rivastigmine, Physostigmine, Galantamine, Metrifonate, neostigmine and Icopezil. It also claims pharmaceutical compositions comprising a combination of these therapeutic agents.

US 7713957 B2 patent document refers to a pharmaceutical composition useful for the prevention and/or treatment of neuropathic pain, such as trigeminal neuralgia, post-herpetic neuralgia, or pain caused by infections with HIV, diabetic neuropathy, phantom limb pain, comprising a combination of a) Gabapentin or pregabalin, or pharmaceutically acceptable salts thereof, and b) N-type calcium channel antagonists, or pharmaceutically acceptable salts thereof.

WO 2009/046801 A1 patent document describes a pharmaceutical composition comprising Benfotiamine and one or more pharmaceutically active agents, selected from the group consisting of gabapentin, pregabalin, XP13512, carbamazepine, amitriptyline, ketorolac, diclofenac, ibuprofen, Flurpirtin, Paracetamol, and dexamethasone, process for its preparation and its use for the treatment and prevention of conditions and diseases selected from the group consisting of neuropathic pain conditions.

PA/a/2002/010764 A patent application aims the protection of an effective combination to relieve pain comprising an effective amount of Endothelin receptor
antagonist and 1 to 3 compounds selected from the group consisting of antiepileptic compounds that have properties to relieve pain such as pregabalin, and analgesics such as Meloxicam as an NSAID, and pharmaceutically acceptable salts thereof; and pharmaceutical compositions comprising them.

MX/a/2010/005680 A patent application provides a pharmaceutical composition for treating pain and conditions related to pain, using the administration of a therapeutically effective amount of slow-release Tapentadol hydrochloride and a therapeutically effective amount of a second analgesic to a patient in need thereof,, where the second analgesic is Tramadol, a gamma-aminobutyric acid (GABA) analogue further comprising a NSAID such as Meloxicam.

Present MX/a/2007/014422 patent application refers to synergistic combinations of non-steroidal anti-inflammatory drugs, particularly Carprofen, with alpha-2-delta ligands, such as Gabapentin or pregabalin, for veterinary treatment of pain or inflammation, especially in dogs, cats and horses.

MX 2011014042 patent document describes pharmaceutical combinations of two antiepileptic drugs, such as Oxcarbazepine, pregabalin and combinations of an antiepileptic, pregabalin or Oxcarbazepine with B-complex vitamins, as well as pharmaceutical compositions comprising
such combinations, and their use for treatment of neuropathic pain.

Scientific paper entitled "Pharmacokinetics of oral Gabapentin alone or co-administered with Meloxicam in ruminant beef calves". Johann F. Coetzee, Ruby A. Mosher, Laura E. Kohake, Charley A. Cull, Lindsey L. Kelly, Stacy L. Mueting, Butch Kukanich. The Veterinary Journal 190 (2011) 98-102, concludes that the administration of 10 mg/kg gabapentin capsules to ruminating calves or Gabapentin powder at 15 mg/kg in combination with 0.5 mg/kg of Meloxicam resulted in plasma concentrations above the minimum therapeutic concentration which was previously reported in other species. This dose and route of administration of gabapentin can be used in clinical trials that could lead to development of effective drug regimens for mitigating syndromes of chronic pain in cattle.

Scientific paper entitled "Gabapentin and Pregabalin can interact synergistically with Naproxen to produce antihyperalgesia". Robert W. Hurley, MD., PhD., Debika Chatterjea, B.S., Meihua Rose Feng, Ph.d., Charles P. Taylor, Ph.d., Donna L. Hammond, Ph.d. Anesthesiology 2002; 97: 1263-73, refers in its results that gabapentin, pregabalin and naproxen only reverse thermal hyperalgesia with values ED$_{50}$ of 19.2, 6.0 and 0.5 mg/kg, respectively. Mixtures of gabapentin
+ naproxen in fixed dose ratios of 50:1, 10:1 or 1:1 interacted synergistically to reverse thermal hyperalgesia induced by carrageenan. However, Gabapentin + naproxen 1:50 produced only additive effects. Any combination of gabapentin + naproxen did not decrease leg edema in a way greater than additive. Plasma concentrations of gabapentin and naproxen were not modified by addition of other drugs. Pregabalin + naproxen 10:1 mix interacted synergistically to reverse thermal hyperalgesia in swollen rear leg, while 1:1 or 1:10 mixtures produced additive effects.

Scientific paper entitled "Celecoxib, Pregabalin, and their combination for treatment of chronic low-back pain". J Carlo Luca Romano, Delia Romano, Cristina Bonora, Giuseppe Mineo. J Orthopaed Traumatol (2009) 10: 185-191, set in its results that Celecoxib and pregabalin were effective in reducing back pain. The association of Celecoxib and pregabalin was more effective than monotherapy in a mixed population of patients with chronic low back pain, the data were grouped according to LANSS score. Side effects of drug association and monotherapies were similar, with a reduction of drug the consumption in combination therapy.

Another scientific paper entitled "Premedication with Pregabalin 75 or 150 mg with Ibuprofen to control pain after day-case gynaecological laparoscopic surgery". R. Jokela, J.
Ahonen, M. Tallgren, M. Haanpää and K. Korttila. British Journal of Anaesthesia 100 (6): 834-40 (2008), concludes that analgesia was higher after premedication with pregabalin 150 mg than after Diazepam 5 mg both with ibuprofen 800 mg, during the early recovery after laparoscopic gynecological outpatient surgery. Pregabalin 150 mg does not reduce the amount of needed postoperative analgesics.

Unlike above referred documents, the present invention comprises the synergistic combination of pregabalin and Meloxicam, using lower doses of these active principles than those commonly prescribed when they are administered separately.

**SUMMARY OF THE INVENTION**

The persistence of the problem raised above to achieve adequate control and treatment of neuropathic pain faces pharmaceutical industry to propose new pharmacological alternatives with the aim to ensure pain abolition, restoration of psychological well-being (quality of sleep, security, tranquility, motivation, confidence, etc.), recovery, and proper maintenance of physiological, sensory, motor and reflex functions in general, a better quality of life to individuals suffering from painful diseases.
Therefore, it is important to focus efforts towards development of a novel proposal as first choice therapy for prevention and/or treatment of neuropathic pain caused by multiple causes.

In this regard, the present invention discloses a novel combination of pregabalin, an $\gamma$-aminobutyric acid (GABA) analogue agent and Meloxicam, a non-steroidal anti-inflammatory agent (NSAID), which exhibits a surprising synergistic effect, useful for the prevention and/or treatment of pain caused by different neuropathic etiologies.

The present invention is also aimed at pharmaceutical compositions comprising such synergistic combination, as well as pharmaceutically acceptable excipients or vehicles, formulated to be administered in a single dosage unit, and their use to treat and/or prevent neuropathic pain caused by diabetic neuropathy, neuropathy after herpes zoster appearance, trigeminal nerve neuralgia, HIV, pain of the phantom member after an amputation, neuropathic pain of lumbar and dorsal region.

Also, the combination and pharmaceutical compositions subject of present invention provide the following not obvious or apparent significant benefits: a) synergic effective interaction between pregabalin and Meloxicam for the prevention and/or treatment of neuropathic pain caused by
several etiologies, b) decrease of administered doses of these drugs, particularly those corresponding to the antihyperalgesic, antiallodynic agent compared to the recommended doses of each drug separately, c) administration of a single daily dose, d) better efficacy of the therapeutic synergistic effect which remains throughout the day, e) improved safety profile that allows its administration for prolonged periods, f) minor side effects with respect to those induced with single drug administration.

**BRIEF DESCRIPTION OF THE FIGURES**

Figure 1. Time courses of Von Frey test controls. Nociceptive response in percentage (%) generated in rats with chronic constriction of sciatic nerve ("CCI by its acronym in Spanish") (●) and administered with vehicle ("CMC" carboxymethylcellulose in saline) upon stimulation with a 15 g filament, for a 180 minute period. Also showed the CT of rat control group Sham (●), receiving surgery, but not chronic constriction of sciatic nerve. This group shows that even giving a 15 g filament stimulation a response of hyperalgesia is not evidenced. Data represent the mean ± SD, n = 6.

Figure 2. Time courses of pregabalin (Pgb) antihyperalgesic effect with Von Frey test in rats with
chronic constriction injury (CCI). Oral administration in increasing logarithmically doses (0.5 units of logarithm) from 0.1 to 10 mg/kg. 15 g of Von Frey filament was employed to demonstrate hyperalgesia. Data represent the mean ± SD, n = 6.

Figure 3. Global antihyperalgesic (AUC) effect bars of pregabalin (Pgb) in rats with chronic constriction injury (CCI) in the Von Frey test. Each bar represents the area under the curve of pregabalin antihyperalgesic effect in doses of 0.1 to 10 mg/kg orally. The bars represent mean ± E.E., n = 6.

Figure 4. Dose-response curve of pregabalin antihyperalgesic effect in rats with chronic constriction injury (CCI) in the Von Frey test. DRC of pregabalin antihyperalgesic effect in doses of 0.1 to 10 mg/kg orally. Dispersion lines represent mean ± SD, n = 6.

Figure 5. Time course of control animal group in allodynia test using acetone. Nociceptive response in cummulated seconds from limb removal in rats with CCI (♦), after administration of acetone, and administered with vehicle (CMC in saline) in 180 minutes. Data represent the mean ± SD, n = 6.

Figure 6. Time courses of pregabalin antiallodynic effect (Pgb) in acetone test (cold allodynia). Oral
administration of pregabalin dose with logarithmic increments (0.5 units of logarithm) from 0.1 to 10 mg/kg orally in rats with chronic constriction injury (CCI). Data represent mean ± SD, n = 6.

Figure 7. Bar graph of global antiallodynic effect for 180 min of pregabalin in rats with chronic constriction injury (CCI) in acetone test (cold allodynia). We calculated the area under the curve of the global antiallodynic effect shown in the time courses of pregabalin in doses of 0.1 to 10 mg/kg orally. The bars represent mean ± E.E., n = 6.

Figure 8. Dose-response curve of pregabalin antiallodynic effect in rats with chronic constriction injury (CCI) in acetone test (cold allodynia). DRC in area under the curve of the pregabalin antiallodynic effect in doses of 0.1 to 10 mg/kg orally. The bars represent mean ± E.E., n = 6.

Figure 9. Time courses of Meloxicam anti-hyperalgesic effect (Melox) with Von Frey test in rats with chronic constriction injury (CCI). Oral administration in increasing log doses (0.5 units of logarithm) from 1.0 to 31.6 mg/kg (given that Meloxicam doses from 0.1 and 0.3 mg/kg showed no effects these are not presented, to avoid saturation of the graph). 15 g of Von Frey filament was used to demonstrate hyperalgesia. Data represent mean ± SD, n = 6.
Figure 10. Bar graph of the global antihyperalgesic effect of Meloxicam (Melox) in rats with chronic constriction injury (CCI) in the Von Frey test. The bars represent the area under the curve of Meloxicam antihyperalgesic effect in doses of 1.0 to 31.6 mg/kg orally. The bars represent mean ± E.E., n = 6.

Figure 11. Dose-response curve of Meloxicam antihyperalgesic effect in rats with chronic constriction injury (CCI) in the Von Frey test. DRC in area under the curve of Meloxicam antihyperalgesic effect in doses of 1.0 to 31.6 mg/kg orally. The bars represent mean ± SD, n = 6.

Figure 12. Time courses of Meloxicam antiallodynic effect (Melox) in acetone test (cold allodynia). Oral administration of Meloxicam in doses with logarithmic increments (0.5 units of logarithm) from 1.0 to 31.6 mg/kg in rats with chronic constriction injury (CCI). Data represent mean ± SD, n = 6.

Figure 13. Antiallodynic effect bars of Meloxicam in rats with chronic constriction injury (CCI) in acetone test (cold allodynia). Bar obtained from the area under the curve of Meloxicam antiallodynic effect in doses of 1.0 to 31.6 mg/kg orally. The bars represent mean ± E.E., n = 6.

Figure 14. Dose-response curve of Meloxicam antiallodynic effect in rats with chronic constriction injury
(CCI) in acetone test (cold allodynia). DRC in area under the curve of Meloxicam antiallodynic effect in doses of 1.0 to 31.6 mg/kg orally. The bars represent mean ± SD, n = 6.

Figure 15. Dose-response curve of pregabalin and Meloxicam antihyperalgesic effect in rats with chronic constriction injury (CCI) in oral Von Frey (15 g filament) test. The bars represent mean ± SD, n = 6.

Figure 16. Dose-response curve of pregabalin and Meloxicam antiallodynic effect in rats with chronic constriction injury (CCI) in oral acetone test (cold allodynia). The bars represent mean ± SD, n = 6.

Figure 17. Time courses of the antihyperalgesic effect of a combination of Meloxicam + pregabalin in acute treatment, with Von Frey test in rats with chronic constriction injury (CCI). The combination Mel 0.1 mg/kg + Pgb 0.3 mg/kg produced slightly better antihyperalgesic effects than those generated by Pgb 0.3 mg/kg alone.

Figure 18. Bars representing hyperalgesia degree after each treatment (AUC of corresponding CT) that generated the drugs alone and combined at the ratio used in acute treatment in rats with neuropathic pain.

Figure 19. Time courses of antihyperalgesic effect of a combination of Meloxicam 0.3 + 0.3 pregabalin in acute treatment, with Von Frey test in rats with chronic
constriction injury (CCI). The combination Mel 0.3 mg/kg + Pgb 0.3 mg/kg generated best antihyperalgesic effects than those generated by Meloxicam or Pgb alone.

Figure 20. Bars representing the degree of hyperalgesia which remains after treatment (AUC of corresponding CT) with drugs alone and combined at the ratio employed in acute treatment in rats with neuropathic pain.

Figure 21. Time courses of the antihyperalgesic effect of a combination of Meloxicam + pregabalin in acute treatment, with Von Frey test in rats with chronic constriction injury (CCI). The combination Mel 1.0 mg/kg + Pgb 0.3 mg/kg showed no better effects than Pgb 0.3 alone.

Figure 22. Bars representing antihyperalgesic overall effects (AUC of corresponding CT) generated by drugs alone and combined at the ratio employed in acute treatment in rats with neuropathic pain.

Figure 23. Time courses of the antihyperalgesic effect of a combination of Meloxicam 3.2 + pregabalin 0.3 in acute treatment, with Von Frey test in rats with chronic constriction injury (CCI).

Figure 24. Bars representing the overall antihyperalgesic effects (AUC of corresponding CT) generated by drugs alone and combined at the ratio employed in acute treatment in rats with neuropathic pain.
Figure 25. Time courses of the antiallodynic effect of Pgb 0.3 mg/kg, Mel 0.1 mg/kg and the corresponding combination in acute treatment in rats with neuropathic pain. Data represent mean ± SD, n = 6.

Figure 26. Bars representing the overall antiallodynic effects generated by compounds administered alone and in combination, in acute treatment in rats with neuropathic pain.

Figure 27. Time courses of the antiallodynic effect of Pgb 0.3 mg/kg, Mel 0.3 mg/kg and the corresponding combination in acute treatment in rats with neuropathic pain. Data represent mean ± SD, n = 6.

Figure 28. Bars representing the overall antiallodynic effects generated by compounds administered alone and in combination, in acute treatment in rats with neuropathic pain.

Figure 29. Time courses of the antiallodynic effect of Pgb 0.3 mg/kg, Mel 1.0 mg/kg and the corresponding combination in acute treatment in rats with neuropathic pain. Data represent mean ± SD, n = 6.

Figure 30. Bars representing the antiallodynic overall effects generated by compounds administered alone and in combination, in acute treatment in rats with neuropathic pain.
Figure 31. Time courses of the antiallodynic effect of Pgb 0.3 mg/kg, Mel 3.2 mg/kg and the corresponding combination in acute treatment in rats with neuropathic pain. Data represent mean ± SD, n = 6.

Figure 32. Bars representing the overall antiallodynic effects generated by compounds administered alone and in combination, in acute treatment in rats with neuropathic pain.

Figure 33. Time courses of the antihyperalgesic effect of a combination of Meloxicam 0.1 mg/kg + pregabalin 0.3 mg/kg in chronic treatment (2 administrations/day/7 days), with Von Frey test in rats with chronic constriction injury (CCI). The combination produced a very poor antihyperalgesic effect throughout the observation period.

Figure 34. Bars representing overall antihyperalgesic effects generated by the combination, and comparison with the effects generated by single compounds, for chronic treatment in rats with neuropathic pain.

Figure 35. Time courses of the antihyperalgesic effect of a combination of Meloxicam 0.3 mg/kg + pregabalin 0.3 mg/kg in chronic treatment (2 administrations/day/7 days) in rats with chronic constriction injury (CCI).

Figure 36. Bars representing the global antihyperalgesic effects generated by the combination, and global effects
produced by individual agents for chronic treatment in rats with neuropathic pain.

Figure 37. Time courses of the antihyperalgesic effect of a combination of Meloxicam 1.0 mg/kg + pregabalin 0.3 mg/kg in chronic treatment (2 administrations/day/7 days) in rats with chronic constriction injury (CCI).

Figure 38. Bars that have global antihyperalgesic effects generated by the combination, and the global effects of the individual agents for chronic treatment in rats with neuropathic pain.

Figure 39. Time courses of the antihyperalgesic effect of a combination of Meloxicam 3.2 mg/kg + pregabalin 0.3 mg/kg in chronic treatment (2 administrations/day/7 days) in rats with chronic constriction injury (CCI).

Figure 40. Bars showing global antihyperalgesic effects generated by the combination, and the global effects of individual agents for chronic treatment in rats with neuropathic pain.

Figure 41. Time courses of the antiallodynic effect of Pgb 0.3 mg/kg, Mel 0.1 mg/kg and the corresponding combination for chronic treatment in rats with neuropathic pain. Data represent mean ± SD, n = 6.

Figure 42. Bars representing the overall antiallodynic effects generated by compounds administered alone and in
combination, in chronic treatment (14 administrations) in rats with neuropathic pain.

Figure 43. Time courses of the antiallodynic effect of Pgb 0.3 mg/kg, Mel 0.3 mg/kg and the corresponding combination for chronic treatment in rats with neuropathic pain. Data represent mean \( \pm \) SD, \( n = 6 \).

Figure 44. Bars representing the overall antiallodynic effects generated by compounds administered alone and in combination, for chronic treatment in rats with neuropathic pain.

Figure 45. Time courses of the antiallodynic effect of Pgb 0.3 mg/kg, Mel 1.0 mg/kg and the corresponding combination for chronic treatment in rats with neuropathic pain. Data represent mean \( \pm \) SD, \( n = 6 \).

Figure 46. Bars representing the overall antiallodynic effects generated by compounds administered alone and in combination, for chronic treatment in rats with neuropathic pain.

Figure 47. Time courses of the antiallodynic effect of Pgb 0.3 mg/kg, Mel 3.2 mg/kg and the corresponding combination for chronic treatment in rats with neuropathic pain. Data represent mean \( \pm \) SD, \( n = 6 \).

Figure 48. Bars representing the overall antiallodynic effects generated by compounds administered alone and in
combination, for chronic treatment in rats with neuropathic pain.

Figure 49. DRC of antihyperalgesic effects of Mel alone and Mel + Pgb 0.3 in acute treatment. Improvement of effects is apparent when Mel small doses are associated with Pgb, giving evidence of interaction of effect enhancement in treatment of hyperalgesia in neuropathic pain.

Figure 50. DRC of antiallodynic effects of Mel alone and Mel + 0.3 Pgb. Improvement effects of small doses of Mel when associated with 0.3 Pgb in treatment of allodynia in neuropathic pain is detected.

Figure 51. DRC of antihyperalgesic effects of Mel alone and Mel + Pgb 0.3 in chronic treatment. There is an effect improvement when Mel is associated with Pgb, giving evidence of interaction in the treatment of hyperalgesia in neuropathic pain.

Figure 52. DRC of antiallodynic effects of Mel alone and Mel + Pgb 0.3 in chronic administration. Improving antiallodynic effects of small doses of Mel are showed when associated with 0.3 Pgb, in treatment of neuropathic pain.

Figure 53. Bars showing global antiallodynic effects generated by Mel 0.1 and 0.3 Pgb and change effect when Mel 0.1 is combined with 0.3 Pgb in chronic treatment; and comparison of these effects from the combination with those
generated by Mel 10 mg/kg alone chronic, in rats with neuropathic pain.

**DETAILED DESCRIPTION OF THE INVENTION**

The present invention refers to a pharmaceutical combination of a γ-aminobutyric acid (GABA) analogue antihyperalgesic, antiallodynic agent, and a non-steroidal type anti-inflammatory agent, (NSAID), which showed a surprising synergistic effect, and pharmaceutical compositions comprising such a combination as well as pharmaceutically acceptable excipients or vehicles. This combination and pharmaceutical compositions showed usefulness to prevent and/or treat pain caused by different neuropathic etiologies.

A preferred embodiment of the present invention relates to a pharmaceutical combination comprising pregabalin or a pharmaceutically acceptable thereof, and Meloxicam or a pharmaceutically acceptable salt thereof, which showed an effective synergistic effect; and pharmaceutical compositions comprising such a combination as well as pharmaceutically acceptable excipients or vehicles, formulated to be administered by oral or parenteral route in a single dosage unit. Both the combination and the pharmaceutical compositions of the present invention proved to be effective
in the prevention and/or treatment of neuropathic pain caused by several etiologies, such as diabetic neuropathy, neuropathy after herpes zoster appearance, trigeminal nerve neuralgia, HIV, pain of the phantom member after an amputation, neuropathic pain of lumbar and dorsal region.

An assessment of the antihyperalgesic and antiallodynic effect of the present invention by oral administration of pregabalin, Meloxicam, and a combination of pregabalin + Meloxicam was conducted in order to assess the relief of neuropathic pain induced by chronic constriction of sciatic nerve (CCI) in rodents.

Male Wistar rats were used [Crl: (WI) fBR], with a body weight of 120-140 g at the beginning of the pilot phase, which weighed 160-180 g upon drug delivery. The animals remained in polycarbonate boxes under controlled conditions of temperature and light, with 12-hour light/darkness cycles and water and food intake ad limitum. All experiments were conducted during the light phase. The number of experimental animals was placed at a minimum, n = 6 for determinations of desired effects (anti-hyperalgesia and anti-allodynia), and n = 10 per experimental point for determination of fatality effects.

A neuropathic pain CCI model was firstly standardized. Rats were anesthetized and the dissection of the sciatic
nerve of the right thigh by an incision was immediately performed, dissecting the muscle biceps femoris to locate the most proximal part to the trifurcation of the sciatic nerve and applying four loose ties with silk thread. At the end of the surgery, muscle was sutured with absorbable thread and skin with silk thread. Falsely operated rat (Sham) surgery was performed in the same way but without linking the sciatic nerve.

The degree of hyperalgesia and allodynia in rats subject to sciatic nerve surgery was determined using Von Frey test and the acetone test. These determinations were made a day before the surgery, and a time course of 180 minutes 7 days after surgery was performed for both control (saline) and for orally administered compounds in the study, both alone and combined, to reveal hyperalgesia and allodynia that were present. Then a hyperalgesia and allodynia time course, but now in rats with chronic treatment (1 Administration every 12 hours) making determinations of hyperalgesia and allodynia 30 minutes after administration of treatment in study conducted in the morning and in the following period: 0, 1, 3, 5 and 7 days (in total 14 administrations).
Von Frey Test (mechanical hyperalgesia).

Rats were placed on a metal mesh in an acrylic box transparent where they remained at least 10 minutes before the test for adaptation. Response to a touch stimulus in the surface plant of the right thigh with 15 g Von Frey filament was determined. The stimulus was applied 10 times at intervals of 3 seconds approximately and percentage response was obtained (% response = number of replies/10 X 100) (Tal and Bennett, 1994; Hama and Borsook, 2005; Xiao et al. 2007). With a 15-gram Von Frey filament, controls (Sham and non-surgical) presented some nociceptive response; therefore, in this case the response is deemed of hyperalgesia.

Acetone test (cold allodynia).

At the end of Von Frey test, rats were left at rest on the metal mesh and after a period of 5-10 min, 0.1 mL of acetone was applied on the surface of the hind legs with a syringe with flexible plastic tip, underneath a metal grid. A stopwatch time (seconds) recorded that the animal remained with the limb removed from surface during 60 s after exposure to acetone. Response time of the right thigh is measured, three replications were made with an interval of at least 2 minutes each (Choi et al., 1994; Street et al., 2002; Dowdall et al., 2005).
Once experimental methodologies to be used were standardized, group experimental design was developed and the experiments to be carried out.

- Different groups of animals with neuropathic pain (sciatic nerve ligation) were established, each group consisting of 6 animals. Effects of mechanical hyperalgesia were evaluated on these animals (Von Frey 15 g filaments) and cold allodynia (acetone test), both as reflection of the degree of neuropathic pain affecting the animals, before and after acute and chronic treatments.

- A CCI animal control group was established followed by 31 days in order to observe the time course of hyperalgesia and allodynia development, and to determine the permanence in time of hyperalgesia and allodynia.

- A SHAM control group was established having only a dissection without performing surgery or ligation of sciatic nerve, to demonstrate that neuropathic pain alone is present if done right on the sciatic nerve ligation.

- A control group named CCI-VEH that does have sciatic nerve surgery or ligation, but not drug treatment was established.

An analysis of anti-nociceptive (antihyperalgesia and antiallodynia) effects of combining Meloxicam + pregabalin in neuropathic pain animals was requested for this study.
Initially the ranges of useful doses in laboratory animals were determined to analyze and determine the preclinical useful dose. As known in pharmacology, it is necessary to determine and meet the range of effective dose or that to form the dose-response curve of desired effects and toxic effects, then to design the combinations that will be analyzed.

To determine the dose-response curve (DRC) of the individual drugs (Meloxicam and pregabalin), single doses of pregabalin (Pgb) of 0.1, 0.3, 1.0, 3.2 and 10 mg/kg were orally administered, and Meloxicam 0.1, 0.3, 1.0, 3.2, 10 and 31.6 mg/kg, orally, then the antinociceptive effect of Von Frey and acetone hyperalgesia and allodynia tests respectively was assessed, 30, 60, 90, 120 and 180 minutes post-administration to obtain the time course (CT) of the acute administration of these drugs. Findings are presented below. Figure 1 shows the effects determined in control groups, where the response of hyperalgesia is apparent (response close to 100% in rats who have surgery (CCI-VEH "○"), and there is evidence of a lack of vehicle antihyperalgesic effect.) While the rats which were not linked (SHAM '●') show a small nociceptive response to stimulation with 15 g filament, the response is very close to zero, but they actually show some degree of response, which
shows that there is whether pain or nociception with a 15 g Von Frey filament, and that rats present hyperalgesia after CCI surgery. Mean ± standard error is plotted.

Fig. 2 shows the CT of antihyperalgesic effects generated by each of pregabalin evaluated doses (PGB or Pgb) in rats with neuropathic pain. The response percentage generated by different doses is evaluated. The X axis shows the time in minutes with determinations in time 0, 30, 60, 90, 120 and 180 minutes after oral administration of each dose. Y axis shows that animals had virtually 100% of hyperalgesia response at beginning, but after administration of each dose, hyperalgesia decreased in a dose-dependent manner. Mean and standard error are plotted for 6 animals in each point. An antihyperalgesic effect generated by Pgb is apparent as the dose increases. Also observed that while the Pgb 0.1 mg/kg (●) dose virtually generates no antihyperalgesic effects, the 10 mg/kg (□) dose produces maximum antihyperalgesic effect.

Figure 3 presents the global antihyperalgesic effects, through 180 minutes in the form of bars corresponding to the area under the curve (AUC) of the antihyperalgesic effects shown in the CT above.

Figure 4 shows the DRC of antihyperalgesic effects developed by oral pregabalin in rats with neuropathic pain
caused by chronic constriction injury using Von Frey (15 g filament) test. Being the time course of 3 h, a maximum control area under the curve (AUC) was established as a value of 300 units of area (ua). With this value, the corresponding values of antihyperalgesic effects were calculated.

Maximum effect is reached with a 10 mg/kg pregabalin dose, producing 235.83 ± 4.86 units of area (ua). Effective doses are reported in table 1.

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFFECTIVE</td>
</tr>
<tr>
<td>ANTIHYPALGESIC (PREGABALIN)</td>
</tr>
<tr>
<td>ED_{50}</td>
</tr>
<tr>
<td>ED_{90}</td>
</tr>
</tbody>
</table>

As to the allodynia cold acetone test, Figure 5 shows the effects determined in control groups, wherein the allodynic response is apparent (response close to 25 seconds) in rats who have surgery (CCI-VEH "\*"), and there is evidence of a lack of antiallodynic effect of vehicle. While rats which were not linked (SHAM) showed no nociceptive response (limb removal in seconds) upon being stimulated with acetone (data not shown). Mean ± standard error is plotted.

Figure 6 shows the CT found with each individual dose of Pgb. The "X" axis shows times where antiallodynic effect generated by PGB in each dose was assessed, while Y axis
shows the allodynia developed in animals, expressed in accumulated seconds of limb removal. Mean ± standard error is plotted. 10 mg/kg is seen as the most effective dose.

Figure 7 presents more clearly the dose-dependent relationship of pregabalin antiallodynic effect by calculating AUC of CT shown in Figure 6.

Figure 8 shows the DRC of the antiallodynic effects which developed oral pregabalin in rats with neuropathic pain caused by chronic constriction injury using acetone test to produce cold allodynia. Being 3 h the time course, a value of 90 ua was established as control maximum area under the curve (AUC). With this value, the corresponding values of antiallodynic effects were calculated.

Maximum effect is reached with a 10 mg/kg pregabalin dose, producing 70.96 ± 1.54 units of area (ua). Effective doses are reported in table 2.

**TABLE 2**

<table>
<thead>
<tr>
<th>EFFECTIVE DOSE ANTLALLODYNIC (PREGABALIN)</th>
<th>MEAN (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED&lt;sub&gt;50&lt;/sub&gt;</td>
<td>0.43</td>
</tr>
<tr>
<td>ED&lt;sub&gt;90&lt;/sub&gt;</td>
<td>2.80</td>
</tr>
</tbody>
</table>

Figure 9 shows the CT of antihyperalgesic effects generated by Meloxicam (Melox or Mel) evaluated in rats with
neuropathic pain. "X" axis shows the time in minutes with
determinations in time 0, 30, 60, 90, 120 and 180 minutes
after oral administration of each dose. "Y" axis shows that
animals had hyperalgesia after stimulation with Von Frey
filaments, but after Meloxicam administration hyperalgesia
was decreasing. Mean and standard error of at least 6 animals
in each point are plotted. An antihyperalgesic effect
generated by Meloxicam is apparent as the dose increases, and
also noted that while 0.1, 0.3, 1.0 Meloxicam (●) and 3.2 (■)
mg/kg doses practically do not generate antihyperalgesic
effects the 31.6 mg/kg dose produces maximum antihyperalgesic
effect.

Figure 10 presents antihyperalgesic global effects
through 180 minutes in the form of bars corresponding to the
area under the curve (AUC) of antihyperalgesic effects shown
in above CT.

Figure 11 shows a DRC of antihyperalgesic effects
developed by oral Meloxicam in rats with neuropathic pain
caused by chronic constriction injury using Von Frey (15 g
filament) test. With a 3 h time course, a value of 300 units
of area (ua) was determined as the maximum control possible
area under the curve (AUC). With this value, the
corresponding values of antihyperalgesic effects were
calculated.
Maximum effect is reached with a Meloxicam dose from 31.6 mg/kg, producing an effect of 227.5 ± 25.67 units of area (ua).

As to the allodynia cold acetone test, Figure 12 shows the CT found with each individual Meloxicam dose. The "X" axis shows times in which the antiallodynic effect generated by Melox in each dose was evaluated, while "Y" shows allodynia developed in animals, expressed in accumulated seconds from limb removal. Mean ± standard error is plotted. 31.6 mg/kg is seen as the most effective dose.

Figure 14 shows a DRC of the antiallodynic effects developed by oral Meloxicam in rats with neuropathic pain caused by chronic constriction injury using acetone test to produce cold allodynia. Being the time course of 3 h, a value of 90 ua was determined as the maximum possible control area under the curve (AUC), and with this value the corresponding values of antiallodynic effects were calculated.

Maximum effect is reached with a 31.6 mg/kg Mel dose producing 65.70 ± 3.56 units of area (ua).

With obtained data both from pregabalin and Meloxicam a timely analysis of the antinociceptive efficacy of these 2 drugs for neuropathic pain was conducted, and this analysis showed only a trend of pregabalin greater efficacy (no statistical difference) in terms of antihyperalgesic and
antiallodynic effects than Meloxicam. This is reflected in table 3.

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>MORE EFFECTIVE DOSE (po)</th>
<th>ANTIHYPERALGESIC EFFECT</th>
<th>RELATIVE EFFECTIVENESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin</td>
<td>10 mg/kg</td>
<td>235.83 ± 4.86</td>
<td>100%</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>31.62 mg/kg</td>
<td>227.50 ± 25.67</td>
<td>96.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>ANTIHYPERALGESIC EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin</td>
<td>70.96 ± 1.54</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>65.70 ± 3.56</td>
</tr>
</tbody>
</table>

It may be then established that under experimental conditions in rats with neuropathic pain, in terms of antihyperalgesic and antiallodynic effects, Meloxicam and pregabalin showed similar efficacy. This can be seen graphically in figures 15 and 16.

As to drug potency in short, being Pregabalin DRC more in left side on “X” axis, pregabalin proved to be more powerful than Meloxicam, both for antihyperalgesic and antiallodynic effects, accurately calculating potency using their respective ED$_{50}$:
In antihyperalgesic effects: Pregabalin was 4.3 times more potent than Meloxicam, even though both exhibited similar antihyperalgesic efficacy.

In antiallodynic effects: Pregabalin was 7.0 times more potent than Meloxicam, although both exhibited similar antiallodynic efficacy.

ANTINOCICEPTIVE EFFICACY (ANTIHYPERALGESIA AND ANTIALLODYNIA) IN NEUROPATHIC PAIN, MELOXICAM AND PREGABALIN IN COMBINATION.

Compounds in the following dosages used in clinical practice were assessed: Meloxicam 7.5 to 15 mg with pregabalin 75 to 150 mg, orally administered. But in preclinical practice as noticed from previously presented DRC in rat, active or effective Meloxicam dose ranges from 1.0 to 31.6 mg/kg orally, while in the case of oral pregabalin dose in rat ranges from 0.1 to 10 mg/kg.

Taking into account that a better synergistic interaction may be present in pharmacology by decreasing doses and not necessarily by an increase thereof, it was decided to analyze combinations comprising 2 smaller doses of Meloxicam and 2 still lower doses, making a total of 4 Meloxicam doses: 0.1, 0.32, 1.0 and 3.2 mg/kg, and to analyse their effects in combination with the pregabalin dose following that one starting to show pharmacological effects.
and which also showed little pharmacological activity development, so the selected dose was 0.3 mg/kg pregabalin. That above in order to be able to detect possible antihyperalgesic and antiallodynic enhancement effects, when generated and being able to avoid generation of side effects by significantly decreasing the dose to be used in combinations.

**Analysis of antihyperalgesic effects of compounds alone and in combination in acute administration.**

Under these experimental conditions the results showed similar antinociceptive (antihyperalgesic) effects when Pgb 0.3 mg/kg (♦) was administered alone, and a combination comprising a small Meloxicam dose: Mel 0.1 + Pgb 0.3 (■). This may be seen in Figure 17 showing time courses (CT) obtained in neuropathic rats by administering them each compound alone and in combination. “X” axis shows time (min) used to determine the time course of acute effects for 180 minutes from administrations, while “Y” axis shows the antihyperalgesic effects (%) that generate each of the drugs alone or in combination. Mean ± standard error of n = 6 rats with neuropathic pain were plotted. Meloxicam in doses of 0.1 mg/kg (▴) is noticed not to generate antihyperalgesic effects along the evaluated time course (180 min), while Pgb 0.3
mg/kg (3) generates a small antihyperalgesic effect through the assessment time, as well as the combination Mel 0.1 + Pgb 0.3 mg/kg (3).

Figure 18 presents a bar chart to show with areas under the curve (AUC) of the corresponding time courses, coverage through time of antihyperalgesic effects. "X" axis shows administered treatment, while "Y" axis shows the degree of hyperalgesia as AUC demonstrated after the treatment. A large AUC should remind that high hyperalgesia and low antihyperalgesic effect are present, while a small AUC points out that there is little hyperalgesia, therefore, a great antihyperalgesic effect after treatment. This combination ratio results show that animals receiving 0.1 Mel still show high hyperalgesia, while groups of rats receiving both 0.3 Pgb and Mel 0.1 + 0.3 Pgb showed less hyperalgesia; therefore, more antihyperalgesic effects with treatment in acute form.

Figure 19 shows time courses (CT) obtained in neuropathic rats administered with another different combination ratio of Meloxicam 0.3 mg/kg + pregabalin 0.3 mg/kg. Again in this and subsequent graphs of time course, axis "X" shows time (min) used to determine the time course of acute effects for 180 minutes from administrations, while "Y" axis shows antihyperalgesic effects (%) generated by each
drug alone or in combination. Mean ± standard error of n = 6 rats with neuropathic pain were plotted. Meloxicam at a 0.3 mg/kg (▲) dose did not generate antihyperalgesic effects, while Pgb 0.3 mg/kg (◆) generated a small antihyperalgesic effect through assessment time, and the combination (Mel 0.3 + Pgb 0.3 mg/kg) produces greater antihyperalgesic effects reaching its maximum effect at 120 min (■).

Figure 20 presents a bar graph to demonstrate antihyperalgesic effects with areas under the curve (AUC) of corresponding time courses. Results from this combination ratio show that animals receiving Mel 0.3 have still high hyperalgesia, while groups of rats receiving the combination Mel 0.3 + Pgb 0.3 mg/kg showed less hyperalgesia; therefore, more antihyperalgesic effects with treatment in acute form.

Figure 21 shows time courses (CT) obtained by administering another different combination ratio: Meloxicam 1.0 mg/kg + pregabalin 0.3 mg/kg. It should be noticed that Meloxicam in a 1.0 mg/kg (▲) dose begins to generate antihyperalgesic effects along the evaluated time course. Pgb 0.3 mg/kg (◆) generates a small antihyperalgesic effect, as the combination Mel 1.0 + Pgb 0.3 mg/kg (■). Even though a combination of figures 19 and 20 used less Meloxicam (0.3 mg/kg), generated a better interaction than when Meloxicam dose is up to 1 mg/kg.
Figure 22 shows the bar graph to demonstrate antihyperalgesic effects with areas under the curve (AUC) of corresponding time courses. Results with this combination ratio show that animals receiving the combination showed better effects than Meloxicam alone, but very similar to those showed by Pgb alone.

Figure 23 shows time courses (CT) obtained by administering another different combination ratio: Meloxicam 3.2 mg/kg + pregabalin 0.3 mg/kg. Meloxicam in 3.2 mg/kg (▲) doses generates poor antihyperalgesic effects over the evaluated time course. On the other hand, Pgb 0.3 mg/kg (♦) generates a small antihyperalgesic effect, the combination Mel 3.2 + Pgb 0.3 mg/kg (■) generated hardly a better antihyperalgesic effect.

Figure 24 shows a bar chart showing with areas under the curve (AUC), the corresponding time courses of antihyperalgesic effects. Results with this combination ratio showed that animals receiving Mel 3.2 expressed little antihyperalgesic effects. The group receiving the combination Mel 3.2 + 0.3 Pgb showed similar antihyperalgesic effects than those produced by 0.3 pregabalin in acute administration.
Analysis of antiallodynic effects of compounds alone and in combination in acute administration.

Below are presented the results found as to antiallodynic effects of these different combination ratios in acute administration. Figure 25 and those following showed in the "X" axis the time in minutes to build the time course for 180 minutes, while in "Y" axis showed the allodynia evaluated by the time from limb removal before a cold acetone stimulus in neuropathic rats. A combination Mel 0.1 + 0.3 Pgb is apparent to produce better effect than Meloxicam alone or pregabalin alone in acute administration and over 180 min.

Figure 26 and following bar charts showed in "X" axis the administered treatment and in "Y" axis allodynia (AUC of time course). Given that the larger AUC, the higher allodynia effect and the lower antiallodynic effect is, the effects of Meloxicam 0.1 and 0.3 Pgb are noticed in the figure to be very similar, but the combination showed higher antiallodynic effects.

Figure 27 shows the results found in terms of antiallodynic effects of a combination Mel 0.3 + Pgb 0.3 mg/kg. Although CTs are very similar, a slight better effect with the combination is present.

Figure 28 shows AUC bars from allodynia in rats treated with compounds alone and combined. A better antiallodynic
effect is clearer with a combination Mel 0.3 + Pgb 0.3 mg/kg than with individual compounds.

Figure 29 shows the results found in terms of antiallodynic effects of the combination Mel 1.0 + Pgb 0.3 mg/kg. The CT show that while Mel 1.0 mg/kg did not generate adequate antiallodynic effects, Pgb 0.3 mg/kg had slightly better effects, and that the corresponding combination also produced a slight better time course.

Figure 30 shows AUC bars from allodynia in rats treated with compounds alone and combined: Mel 1.0 + Pgb 0.3 mg/kg. Antiallodynic effect is better with the combination than with individual compounds which evidence a slight antiallodynic effect.

Figure 31 shows the results found in terms of antiallodynic effects of a combination Mel 3.2 + Pgb 0.3 mg/kg. The CT showed that antiallodynic effect of Mel alone and Pgb alone is very similar, but the combination generates better antiallodynic effects.

Figure 32 shows AUC bars from allodynia in rats treated with compounds alone and combined: Mel 3.2 + Pgb 0.3 mg/kg. There is clearly a better effect with the combination.

**Analysis of antihyperalgesic effects of compounds alone and combined in chronic administration.**
Due to the results and antihyperalgesic and antiallodynic effects detected with a combination of Meloxicam and pregabalin in acute and single administration, a research protocol began to detect the effect of combinations but under repeated or chronic treatment (14 administrations in total). Thus, different groups of rats with neuropathic pain (n = 6 each) were given orally each of the combinations and individual components with a frequency of 2 times a day for 7 days, conducting assessments of antihyperalgesic and antiallodynic effects every 2 days, 30 minutes after morning administration. In order to perform a comparison of such effects of the combination with its individual components in chronic treatment, other 6 groups of rats with neuropathic pain were administered also 14 times with Mel (0.1, 0.32, 1.0 or 3.2 mg/kg) or Pgb at doses that formed the combination and were assessed at the same time. Thus, the results were as follows. Following figures of time course show time post-administration for 7 days as “X” axis, and % hyperalgesia as “Y” axis. Figure 33 shows the antihyperalgesic effects generated with the combination Mel 0.1 CT + Pgb 0.3 mg/kg in chronic treatment: 0.3 Pgb generated better antihyperalgesic effect than Mel 0.1 or a combination, which virtually generated no effect over time.
The combination created a very poor antihyperalgesic effect through the whole treatment.

Figure 34 shows in a bar graph the overall antihyperalgesic effects generated by individual compounds and in combination. The antihyperalgesic effect of the combination in chronic administration is lower than the effect generated by Pgb alone.

When antihyperalgesic effects of the combination Mel 0.3 + 0.3 Pgb and Pgb 0.3 alone in chronic treatment were analyzed a similar behavior was observed. Figure 35 shows CT during 7 days of antihyperalgesic effects of the combination (♦), and the comparison with the effects generated by component individual administration of the association: Pgb 0.3 (▲) and Mel 0.3 (■).

Figure 36 bar graph shows antihyperalgesic global effects generated by individual compounds and in combination. Antihyperalgesic effect of the combination and Pgb 0.3 alone is similar in chronic administration, and better than those produced by Meloxicam 0.3 mg/kg alone.

Figure 37 shows that combining Meloxicam 1.0 + pregabalin 0.3 (♦) mg/kg produces very similar effects to Pgb 0.3, but better effects than Mel 1.0 (■ antihyperalgesic).

Figure 38 bar graph shows overall antihyperalgesic effects generated by individual compounds and in combination
Mel 1.0 + 0.3 Pgb. Chronic administration is similar to the antihyperalgesic effect of the combination and Pgb 0.3 and better than Meloxicam 1 mg/kg.

Figure 39 shows that combination Meloxicam 3.2 + 0.3 pregabalin (△) mg/kg produced only a trend of better antihyperalgesic effects than produced by Pgb 0.3 (▲).

Figure 40 bar graph shows global antihyperalgesic effects generated by individual compounds and combination Mel 3.2 + 0.3 Pgb. In chronic administration, antihyperalgesic effect of the combination and Pgb 0.3 alone is similar.

Analysis of antiallodynic effects compounds alone and in combination in chronic administration.

Below are presented the results found for antiallodynic effects shown by the different combination ratios in chronic administration. Remember that chronic treatment was provided with individual compounds or in combination (4 different combinations), 14 administrations in total, giving oral treatments with a frequency of 2 times a day for 7 days, conducting assessments of antiallodynic effects every 2 days after morning administration. Figure 41 and following showed time post-administration during 7 days in "X" axis, while allodynia evaluated by time from limb removal to the cold acetone stimulus in neuropathic rats is shown in the "y"
axis. Neither Mel 0.1 mg/kg, nor Pgb 0.3 mg/kg generated antiallodynic effects, while combining Mel 0.1 + 0.3 Pgb produced clear antiallodynic effects.

Figure 42 and following bar figures showed the administered treatment in “X” axis and allodynia still present after administrations (AUC of corresponding time course) in “Y” axis. Since the larger is AUC the higher allodynia effect and the lower the antiallodynic effect is, the figure shows that antiallodynic effects of the combination were higher than those produced by Mel 0.1 or Pgb 0.3 mg/kg.

Figure 43 shows the results found in terms of antiallodynic effects of a combination Mel 0.3 + Pgb 0.3 mg/kg. The combination shows better and higher antiallodynic effects than Mel 0.3 or Pgb 0.3 mg/kg alone.

Figure 44 shows that Pgb 0.3 shows poor antiallodynic effects, Mel 0.3 showed higher antiallodynic effects to Pgb, but the combination Mel 0.3 + 0.3 Pgb generated better antiallodynic effects.

Figure 45 shows antiallodynic effects of the combination Mel 1.0 + Pgb 0.3 mg/kg. Again the combination continues to generate higher antiallodynic effects than Pgb 0.3 alone or Mel 1.0 alone.
Figure 46 evidences better antiallodynic effects of the combination Mel 1.0 + 0.3 Pgb than Pgb alone. However, Mel 1.0 mg/kg has also better antiallodynic effects than chronic Pgb 0.3.

Figure 47 shows antiallodynic effects of the combination Mel 3.2 + Pgb 0.3 mg/kg. This combination generated higher antiallodynic effects that those already generated by Pgb 0.3 or Mel 3.2 mg/kg.

Figure 48 evidences in bar charts with the corresponding area under the curve that antiallodynic effects of a combination Mel 3.2 + Pgb 0.3 mg/kg in chronic treatment are better than compounds administered on an individual basis.

Having already all antihyperalgesic and antiallodynic effect data both of Meloxicam, pregabalin and all tested combinations of Meloxicam + pregabalin, all data may be grouped together and synergism DRC determined in order to analyze how these compounds interacted in neuropathic pain, to determine the importance of combining Mel with Pgb and to determine whether these compounds present interactions between them having potential therapeutic use.

Figure 49 shows the DRC of antihyperalgesic effects of Mel alone and DRC of Mel associated to Pgb 0.3 mg/kg acute treatment, and also the timely effect of Pgb 0.3 mg/kg is shown for the purpose of comparison. The DRC of "Mel Alone"
(▲) has the characteristic sigmoid shape in pharmacology and was obtained with 1.0, 3.2, 10.0 and 31.6 mg/kg po doses, reaching its maximum effect with a 31.6 mg/kg dose (227.5 ± 25.7 area units = ua). While the administration of a small Meloxicam dose but now together with Pgb at a 0.3 mg/kg dose produced increased antihyperalgesic effects (●), improving the almost zero effect of several small doses of "Mel alone" and demonstrating clear effects of antihyperalgesic synergism. To have a full analysis the effect generated only by Pgb in the 0.3 mg/kg dose (●) was included.

**Analysis of DRC antihyperalgesic effects**

The DRC obtained with "Meloxicam alone" has the shape of the perfect sigmoid described for drugs in the classical pharmacological literature. However, the DRC of Meloxicam in small doses administered simultaneously with pregabalin 0.3 mg/kg has an irregular shape and does not correspond to a classic sigmoid. But this is "normal" or usual when drugs are administered simultaneously and interaction effects are observed, where a dose-dependent relation for enhancement or addition effects is not followed. That is, when drug interaction occurs, this interaction does not increase as interaction doses are increased, having some combination ratios that can generate enhancement, while increasing or
decreasing said drug doses in combination can only provide a sum effect or even in some cases, infra-additive effects or antagonism type can be generated. Again, being this highlighted, it is known for some drugs that the association of small doses may lead to enhancement or sum, while the association of higher doses of the same drugs can produce only sum or no interaction or no modification of the original effect of one of the drugs, or even antagonism (Lopez-Muñoz, 1994; García-Hernández et al., 2007). On the other hand, DRC may appear “irregular” where a dose in combination can produce enhancement, while a combination of lower or higher doses can produce much minor or no interaction effects. This is why DRC occurs irregularly when interacting Meloxicam with Pgb 0.3 mg/kg.

**Antihyperalgesic efficacy analysis.**

Some data can be analyzed from Figure 49 of antihyperalgesic effect synergism. While Mel 0.3 mg/kg administered individually produced an effect of $33.3 \pm 6.2$ ua, and Pgb 0.3 mg/kg alone produced an effect of $73.3 \pm 14.4$ ua, that same dose of Mel (0.3 mg/kg) associated with Pgb 0.3 produced an effect of $148.3 \pm 10.9$ ua. That means that with a combination of correct doses of these compounds, enhancement of antihyperalgesic effects may occur by using small doses of both drugs, which may even reduce the possibility of side
effects. It should be also noted that Meloxicam in doses of 
10 mg/kg produced an antihyperalgesic effect of 175.0 ± 15.3 
ua, and this same effect can be produced using a combination 
of Mel 0.3 mg/kg + Pgb 0.3 mg/kg producing an effect of 148.3 
± 10.9 ua. In other words, it is possible to generate the 
same effect produced by Meloxicam 10 mg/kg, using 33.3 times 
less (the Meloxicam dose goes from 10 mg/kg to 0.3 mg/kg) 
Meloxicam dose by combining it with a small Pgb dose (0.3 
mg/kg).

Moreover, given that there is an interaction between 
Meloxicam and pregabalin, combination efficacy may be 
increased or added to have better results, which is 
therapeutically useful. Usefulness of such studies is 
precisely to demonstrate that a proper and positive 
interaction between compounds in study is possible, or 
ultimately, if there is not any interaction that leads an 
association of both drugs useless. Clinical practice should 
be discussed with these findings, as found doses in 
preclinical practice do not show a direct extrapolation to 
the clinical practice, but preclinical finding is important 
to make clinical practice analysis worthwhile.

It is important in clinical practice to remember that 
when drug combinations are used additive effects are at least 
provided, and whether desired effects are better enhanced.
But it will be a good result if by using combinations, a lower dose to be administered is possible and a maximum efficacy is obtained which was only previously possible by using higher doses.

**Analysis of the antihyperalgesic potency.**

A traditional analysis of pharmacological potency may be conducted since there is no classic sigmoid given by combinations, allowing determining an ED$_{50}$ of the combination. However, a fixed antihyperalgesic pharmacological effect may be defined obtained by Meloxicam alone and combined and thus the relative potency at that particular effect point is determined. Thus, Meloxicam 10 mg/kg produced the same effect as achieved with Meloxicam 0.3 mg/kg + pregabalin 0.3 mg/kg, so Meloxicam in combination was 33.3 times more potent than when Meloxicam was used alone. This data of relative potency should be clarified as determined at a 160 ua antihyperalgesia fixed effect.

It is clear that some DRC of Mel doses are displaced to left when associated with Pgb, i.e. lower doses of Mel associated with Pgb are required to produce the same effects as with Mel alone.

Another important aspect is the fact that we can detect the importance of combining these drugs after analyzing
various combination ratios and detect the range of results that could be generated, since having analyzed only one combination (as in many research articles, but not as proper), we would not have certainty of having selected the best combination or more correct doses and we could have fallen into an error of concluding that Mel + Pgb the association does not generate antihyperalgesic interaction.

This important behavior of a combination effect interaction is also evident by analyzing the antiallodynic effects after acute treatment. Figure 50 shows the DRC of antiallodynic effects of "Mel Alone" and found effects by administering "Mel associated with Pgb 0.3 mg/kg", and also shows the specific effect of Pgb 0.3. DRC of "Mel Alone" (■) shows the sigmoid feature obtained with 1.0, 3.2, 10.0 and 31.6 mg/kg po doses, reaching its maximum efficacy with a 31.6 mg/kg dose. While administration of the same Mel dose but now together with Pgb at a 0.3 mg/kg dose produced better effects with smaller Meloxicam doses (●). The effect developed by Pgb 0.3 mg/kg (▲) alone is also included.

With antiallodynic results generated by the combination, an analysis similar to that made for antihyperalgesic effects is possible to make. Again we should remember that the DRC of combinations do not follow the characteristic sigmoid form in
pharmacology, since the interaction type may be changed to the extent that combination ratios are changed.

In terms of efficacy, Mel 10 mg/kg dose produced an antiallodynic effect of 52.2 ± 6.2 au, whereas with Mel 0.1 mg/kg + Pgb 0.3 mg/kg produced an effect of 45.0 ± 5.5 au. In other words, a similar antiallodynic effect occurred; however, a dose 100 times lower of Meloxicam is being used in the combination. This has therapeutic advantages, since we know that producing the same efficacy with fewer doses also leads to the possibility of generating fewer side effects.

In addition, there was also a change of pharmacological potency combinations in terms of antiallodynic effects determined after acute treatment. If again we establish a comparison of potency with Meloxicam doses alone or in combination in an arbitrary manner, required to produce an effect of 50 ua of antiallodynic effects, then Meloxicam in combination showed a potency 100 times higher than when Meloxicam is administered alone to generate an effect of 50 ua. Therefore, Mel 0.1 associated to Pgb 0.3 is 100 times more powerful than Mel alone (10 mg/kg dose).

In the case of chronic treatments with a total of 14 administrations, interaction also happens when Mel is associated with Pgb. Figure 51 shows DRC of antihyperalgesic effects after chronic treatment, and Figure 52 shows the DRC
of antiallodynic effects after chronic treatment with Mel Alone and Mel associated to Pgb 0.3 mg/kg. Again we see phenomena as those explained above (in figures 49 and 50) as to the form of interaction DRCs, in terms of efficacy changes, and potency changes.

In terms of antihyperalgesic efficacy after chronic treatments, a chronic treatment may be established with Meloxicam in small doses, as Mel 0.3 mg/kg (see Figure 51) produced as antihyperalgesic effect 173.3 ± 23.1 ua, but this same dose increased its effectiveness when combined with Pgb 0.3 to produce 327.5 35.0 ± ua. Again by moving the DRC of the combination to the left is indicated that antihyperalgesic potency increased with the combination. An issue that limits a use evaluation of the combination in these conditions is that Pgb 0.3 mg/kg alone produced an effect of 296.7 ± 27.9 ua.

A similar behavior in terms of DRC, efficacy and potency was detected by analyzing the antiallodynic effects which produced Mel alone and combined with Pgb 0.3 mg/kg administered chronically in rats with neuropathic pain (Figure 52).

Given that is outstanding in terms of antiallodynic effects after chronic treatments, it may be determined that small doses such as Mel 0.1 mg/kg (see Figure 53) produced an
antiallodynic effect 34.4 ± 12.3 ua in chronic treatment, but
this dose increased its effect when combined with Pgb 0.3 to
produce 106.4 ± 11.0 ua. In other words, Mel 0.1 effect in
chronic treatment increased 309% when combined with Pgb. That
same effect could be also obtained with Mel, but at 100 times
higher doses, as Mel 10 mg/kg chronic produced an effect of
127.3 ± 19.4 ua (see Figure 53). Additionally, toxic effects
were not detected with these combinations.

SUMMARY OF RESULTS.

In neuropathic pain induced by chronic constriction of
sciatic nerve in rat (CCI),

1) Both Meloxicam and pregabalin showed antihyperalgesic
and antiallodynic efficacy in acute administration.

2) In antihyperalgesic efficacy, pregabalin was as
effective as Meloxicam.

3) In antiallodynic efficacy, pregabalin was as
effective as Meloxicam.

4) By comparing the respective DRC of antihyperalgesic
and antiallodynic effects, pregabalin was more powerful than
Meloxicam. By antihyperalgesic effects and using ED$_{50}$:
Pregabalin was 4.3 times more potent than Meloxicam, while in
antiallodynic effects: Pregabalin was 7.0 times more potent
than in rat by oral Meloxicam.
5) In acute administration, with 180 minutes post-treatment assessment, the association of Mel with Pgb showed interaction, and some of the combination ratios showed antihyperalgesic and antiallodynic activity additive effects as well as enhancement effects in neuropathic pain.

6) In chronic administration (14 administrations), the overall effects of antihyperalgesic action of some combinations showed better effect than when Pgb was administered, but most combinations showed no better effect than that generated by Pgb.

7) As to antiallodynic effects in chronic administration (14 administrations), the overall effects of some combinations showed better effect than when administered Pgb alone. The efficacy of small Meloxicam doses increased.

8) Overall, the association of Meloxicam + pregabalin shows potential therapeutic use in neuropathic pain, showing in some combination ratios better enhancement effects than when some of the combination components are individually administered.

9) The usefulness of this type of study is to provide information that Meloxicam and pregabalin in certain combination ratios can have a proper interaction, and that therefore, they may have a positive interaction in clinical
practice, then being necessary to conduct the relevant studies.

The present invention also includes the formulation of pharmaceutical compositions comprising a synergistic combination of pregabalin or a pharmaceutically acceptable salt thereof in a therapeutically effective amount, and Meloxicam or a pharmaceutically acceptable salt thereof in a therapeutically effective amount, in addition to one or more pharmaceutically acceptable excipients or vehicles.

Pharmaceutical compositions comprising the synergistic pharmaceutical combination of the present invention together with pharmaceutically acceptable excipients or vehicles are formulated to be supplied in a single dosage unit.

Such pharmaceutical compositions can be formulated to be administered by oral, enteral, parenteral, topical, transdermal, intranasal, ophthalmic route or any other route of administration. Suitable routes of administration to the present invention, in a preferred but not restricted manner are oral and parenteral.

Pharmaceutical forms or appropriate dosage units for the present invention, including but not limited to, are selected from capsules, tablets, capsules, powders, granulates, lyophilized, drops; injectable solutions, suspensions or
emulsions. Preferred pharmaceutical forms for present invention are capsules and tablets.

Pharmaceutical compositions of the present invention can also be made in release-controlled or modified (prolonged, delayed or slow) pharmaceutical forms.

Pharmaceutically acceptable excipients or vehicles used in the present invention, by way of example but not limited to, are selected from the group consisting of binding agents, solubilizers, lubricants, disintegrants, surfactants, granulating agents, dispersants, coating, glidants, non-stick agents, adsorbents, emulsifiers, solvents, thinners, preservatives, flavors, sweeteners, colorants, or any other necessary for the formulation of such pharmaceutical compositions.

Formulations comprising a pharmaceutical combination of present invention may include exemplarily but not limited to, one or more of the following excipients or vehicles: methylcellulose, carboxymethylcellulose, hydroxypropyl cellulose, ethylcellulose, starches from corn, potato and rice; polyvinylpyrrolidone (PVP), sodium and potassium alginate, propylene glycol (PEG), gelatin, acacia gum, tragacanth gum, xanthan gum, pectin, xylitol, sorbitol, maltitol; vitamin E polyethylene glycol succinate, sodium lauryl sulfate, pyrrolidone, poloxamer, polysorbate,
povidone, derivatives from castor oil, cyclodextrins, hypromellose, lecithin; talc, sodium, magnesium, calcium or zinc stearates, stearic acid, polyethylene glycols, sodium acetate, stearyl fumarate, sodium benzoate; crospovidone, croscarmellose sodium, hydroxypropylmethyl-cellulose, alginic acid; phospholipids, benzalkonium chloride, glycercyl monooleate; sodium, magnesium or calcium carbonate; chitosan, copovidone, hydroxyethyl-cellulose, hydroxyethylmethylcellulose, maltodextrins, sodium, magnesium, zinc oxides; colloidal silicon dioxide, magnesium silicate; aluminum hydroxide, aluminum oxide, kaolin, calcium silicate; carbomer, glycercyl monooleate, lanolin, linoleic acid, triethanolamine; water, alcohol (benzyl ethyl, isopropyl), isotonic saline, glycerin, monoethanolamine, mineral and vegetable oils (corn, castor, almonds, cotton, sesame, soya, sunflower), benzyl benzoate, dipropylene glycol; lactose, dextrose, sucrose, mannitol, glucose, calcium dibasic and tribasic phosphate, sodium phosphate, calcium sulfate, kaolin, microcrystalline cellulose, sodium chloride; saccharin, aspartame, maltose, sucralose, sucrose, acesulfame potassium, inulin, fructose, citric acid, fumaric acid, methionine, monosodium glutamate, maltol, and/or any other excipient or vehicle that is necessary for the formulation of such pharmaceutical compositions.
The present invention can be also formulated in a case or sectioned packaging adapted to contain the active ingredients in two or more separate dosage units, i.e., drugs can be contained in various dosage forms, thus a first drug can be for example, in a pharmaceutical form in capsules, and the second drug in another different from the first pharmaceutical form, for example in injectable solution.

In the present invention, used dosage of the active ingredient pregabalin or pharmaceutically acceptable salts thereof ranges within a concentration range from 12.5 mg. to 300 mg, preferably administered therapeutically effective amount of 75 and 150 mg in a single daily dose.

Also, the Meloxicam active ingredient dosage or pharmaceutically acceptable salts thereof used in the present invention ranges within a concentration range from 5 mg to 20 mg, preferably a therapeutically effective amount of 7.5 and 15 mg in a single daily dose being administered.

The synergistic effect demonstrated with a combination of the present invention promotes its therapeutic efficacy and a dose decrease of used drugs with respect to known daily doses when individually administered, as well as a significant reduction of side effects.
EXAMPLES

Some examples of the present invention, considered as illustrative but not limitative are described below.

**EXAMPLE 1**

A combination of 75 mg of pregabalin and 15 mg of Meloxicam were mixed with polysorbate, mannitol, microcrystalline cellulose, magnesium stearate and colloidal silicon dioxide.

**EXAMPLE 2**

A combination of 75 mg of pregabalin and 15 mg of Meloxicam were mixed with castor oil, mannitol, lactose, stearyl fumarate and colloidal silicon dioxide.

**EXAMPLE 3**

A combination of 75 mg of pregabalin and 15 mg of Meloxicam were mixed with cyclodextrins, corn starch, lactose, talc and colloidal silicon dioxide.

**EXAMPLE 4**

A combination of 75 mg of pregabalin and 15 mg of Meloxicam were mixed with poloxamer, mannitol, corn starch, magnesium stearate and colloidal silicon dioxide.

**EXAMPLE 5**
A combination of 75 mg of pregabalin and 7.5 mg of Meloxicam were mixed with cyclodextrins, corn starch, lactose, talc and colloidal silicon dioxide.

**EXAMPLE 6**

A combination of 75 mg of pregabalin and 7.5 mg of Meloxicam were mixed with poloxamer, mannitol, corn starch, magnesium stearate and colloidal silicon dioxide.

**EXAMPLE 7**

A combination of 75 mg of pregabalin and 7.5 mg of Meloxicam were mixed with polysorbate, mannitol, microcrystalline cellulose, magnesium stearate and colloidal silicon dioxide.

**EXAMPLE 8**

A combination of 75 mg of pregabalin and 7.5 mg of Meloxicam were mixed with castor oil, mannitol, lactose, stearyl fumarate and colloidal silicon dioxide.

**EXAMPLE 9**

A combination of 150 mg of pregabalin and 15 mg of Meloxicam were mixed with polysorbate, mannitol, microcrystalline cellulose, magnesium stearate and colloidal silicon dioxide.

**EXAMPLE 10**
A combination of 150 mg of pregabalin and 15 mg of Meloxicam were mixed with castor oil, mannitol, lactose, stearyl fumarate and colloidal silicon dioxide.

**EXAMPLE 11**

A combination of 150 mg of pregabalin and 15 mg of Meloxicam were mixed with cyclodextrins, corn starch, lactose, talc and colloidal silicon dioxide.

**EXAMPLE 12**

A combination of 150 mg of pregabalin and 15 mg of Meloxicam were mixed with poloxamer, mannitol, corn starch, magnesium stearate and colloidal silicon dioxide.

**EXAMPLE 13**

A combination of 150 mg of pregabalin and 7.5 mg of Meloxicam were mixed with cyclodextrins, corn starch, lactose, talc and colloidal silicon dioxide.

**EXAMPLE 14**

A combination of 150 mg of pregabalin and 7.5 mg of Meloxicam were mixed with poloxamer, mannitol, corn starch, magnesium stearate and colloidal silicon dioxide.

**EXAMPLE 15**

A combination of 150 mg of pregabalin and 7.5 mg of Meloxicam were mixed with polysorbate, mannitol, microcrystalline cellulose, magnesium stearate and colloidal silicon dioxide.
EXAMPLE 16

A combination of 150 mg of pregabalin and 7.5 mg of Meloxicam were mixed with castor oil, mannitol, lactose, stearyl fumarate and colloidal silicon dioxide.

The invention has been described sufficiently so that a person with average skill in the relevant technical subject can reproduce and achieve the results which refer in the present patent application. However, any person skilled in the art related to present invention may be able to make modifications not described in this application. Therefore, if for adapting such changes in a certain combination and/or pharmaceutical composition the matter claimed in the following claims is needed, such combination and/or pharmaceutical composition shall be included within the scope of the invention that concerns us.
NOVELTY OF THE INVENTION

Having described the present invention, it is considered as a novelty, and is therefore claimed as property the contents in the following:

CLAIMS

1. A pharmaceutical combination characterized by comprising pregabalin or a pharmaceutically acceptable salt thereof as antihyperalgesic, antiallodynic agent, γ-aminobutyric acid (GABA) analogue, and Meloxicam or a pharmaceutically acceptable salt thereof as a non-steroidal type anti-inflammatory agent, (NSAIDs), also having a synergistic effect.

2. A pharmaceutical composition characterized by comprising the synergistic combination of pregabalin and Meloxicam in accordance with claim 1, in a therapeutically effective amount from 12.5 mg to 300 mg and from 5 mg to 20 mg., respectively, as well as one or more pharmaceutically acceptable excipients or vehicles, which are formulated in a single dosage unit.

3. The pharmaceutical composition according to claim 2, characterized by Pregabalin being present in a concentration range from 12.5 mg to 300 mg, preferably in the
therapeutically effective amount of 75 and 150 mg administered as a single daily dose.

4. The pharmaceutical composition according to claim 2, characterized by Meloxicam being present at a concentration range from 5 mg to 20 mg, preferably in the therapeutically effective amount of 7.5 and 15 mg administered as a single daily dose.

5. The pharmaceutical composition according to claims 2 to 4, characterized by being formulated to be administered by oral, enteral, parenteral, topical, transdermal, intranasal, ophthalmic route, preferably by oral and parenteral route.

6. The pharmaceutical composition according to claims 2 to 5, characterized by being found in the pharmaceutical form of capsule, tablet, tablets, powders, granulates, drops, lyophilized, solutions, suspensions, emulsions, preferably in the form of capsules and tablets.

7. The pharmaceutical composition according to claims 2 to 6, further characterized by being formulated in controlled-release or modified (prolonged, delayed or slow) pharmaceutical forms.

8. The pharmaceutical composition according to claims 2 to 7, further characterized by pharmaceutically acceptable excipients or vehicles being selected from the group consisting of binding agents, solubilizers, lubricants,
disintegrants, surfactants, granulating agents, dispersants, coating agents, glidants, non-stick agents, adsorbents, emulsifiers, solvents, thinners, preservatives, flavorings, sweeteners, colorants, and/or any other necessary for the formulation.

9. The pharmaceutical composition in accordance with claims 2 to 8, further characterized by being formulated in a sectioned case or packaging adapted to contain the active ingredients in two or more separate dosage units to be administered as separate, consecutive or sequential form in various dosage forms.

10. The use of the pharmaceutical composition according to claims 2 to 9, for the manufacture of a drug useful for prevention and treatment of neuropathic pain caused by several etiologies, including diabetic neuropathy, neuropathy after herpes zoster appearance, trigeminal nerve neuralgia, HIV, pain of phantom member after an amputation, neuropathic pain of lumbar and dorsal region.

11. The use of the pharmaceutical combination in accordance with claim 1, for manufacturing a drug that is useful for prevention and treatment of neuropathic pain caused by several etiologies, including diabetic neuropathy, neuropathy after herpes zoster appearance, trigeminal nerve
neuralgia, HIV, pain of phantom member after an amputation, neuropathic pain of lumbar and dorsal region.
Figure 1

VON FREY TEST

Hyperalgesia (%) vs. Post-treatment time (min)

CCI-VSH
SHAM
Figure 2

VON FREY TEST
(Filament 15 g, CCl rat)

Hyperalgesia (%)

Post-treatment time (min)
Figure 3

VON FREY TEST
(Anti-hyperalgesic effect in CCI rats)

Hyperalgesia (AUC)

Pgb Dose (mg/kg po)

Pgb 0.1 mg/kg
Pgb 0.3 mg/kg
Pgb 1.0 mg/kg
Pgb 3.2 mg/kg
Pgb 10 mg/kg

0 50 100 150 200 250 300
Figure 4

PREGABALIN DRC
Rats with neuropathic pain
Figure 5

ACETONE TEST

Allodynia (withdrawal in sec)

Post-treatment time (min)

Saline
Figure 7

COLD ALLODYnia
Anti-alloodynic effect

Allodynia (AUC)

0 10 20 30 40 50 60 70 80 90 100

0.1 0.3 1 3.2 10

PGB Dose (mg/kg po)
Figure 8

PREGABALIN DRC
Rats with neuropathic pain
Figure 9

VON FREY TEST (Rat)

Hyperalgesia (%) vs Post-administration time (min)

- Melox 1.0 mg/kg
- Melox 3.2 mg/kg
- Melox 10.0 mg/kg
- Melox 31.6 mg/kg
Figure 10
Figure 11

MELoxicam DRC

Anti-hyperalgesia (AUC) vs Dose (mg/kg pd)
Figure 12

ACETONE TEST

Allodynia (withdrawal in sec)

Post-administration time (min)

- Melox 1.0 mg/kg
- Melox 3.2 mg/kg
- Melox 10 mg/kg
- Melox 31.6 mg/kg
Figure 13

ACETONE TEST (CCI Rats)

Allodynia (AUC)

Melox 1.0 mg/kg  Melox 3.2 mg/kg  Melox 10 mg/kg  Melox 31.6 mg/kg
Figure 14

MELOXICAM DRC
Figure 15

MELODICAM AND PREGABALIN DRC (RAT)
Figure 16

MELOXICAM AND PREGABALIN DRC (RAT)

Anti-AlloDynia (AUC)

Dose (mg/kg po)

0.001 0.01 0.1 1 10 100 1000

Pregabalin
Meloxicam
Figure 17

VON FREY 15 g

Hyperalgesia (%)

Post-administration time (min)

- Pgb 0.3
- Mel 0.1 + Pgb 0.3 mg/kg
- Mel 0.1
Figure 18

![Graph showing the effect of different treatments on hyperalgesia (AUC)]

- **Pgb 0.3 mg/kg**
- **Meli 0.1 + Pgb 0.3 mg/kg**
- **Meli 0.1 mg/kg**
Figure 19

VON FREY 15 g

Hyperlgesia (%)

Post-administration time (min)

- Pgb 0.3
- Mel 0.3 + Pgb 0.3 mg/kg
- Mel 0.3
Figure 20

![Graph showing hyperalgesia (AUC) for different treatments: Pgb 0.3, Mel 0.3, Mel 0.3 + Pgb 0.3 (mg/kg).]
Figure 21

![Graph showing the effect of different treatments on hyperalgesia over time. The x-axis represents post-administration time in minutes (0 to 180), and the y-axis represents hyperalgesia (%). The graph compares the effects of Pgb 0.3, Mel 1 + Pgb 0.3 mg/kg, and Mel 1. The data points are displayed with error bars indicating variability.](image-url)
Figure 22

[Graph showing hyperalgesia (AUC) for different treatments: Pgb 0.3, Mel 1 + Pgb 0.3 mg/kg, and Mel 1.]
Figure 23

VON FREY 15 g

Hyperalgesia (%)

Post-administration time (min)

- Pgb 0.3
- Mel 3.2 + Pgb 0.3 mg/kg
- Mel 3.2
Figure 24

![Graph showing hyperalgesia (AUC) for different treatments]
Figure 25

ACETONE TEST

Allodynia (withdrawal sec)

Post-administration time (min)
Figure 26

Acetone (Acute)

Allodynia (AUC)

Treatment

- Pgb 0.3
- Mel 0.1
- Mel 0.1 + Pgb 0.3
Figure 27

ACETONE TEST

Allodynia (withdrawal sec)

0  10  20  30  40
0  30  60  90  120  150  180
Post-administration time (min)

Pgh 0.3
Mel 0.3
Mel 0.3 + Pgh 0.3
Figure 28

ACETONE (Acute)

![Graph showing Allodynia (AUC) for Pgb 0.3, Mel 0.3, and Mel 0.3 + Pgb 0.3 treatments.]

- Pgb 0.3
- Mel 0.3
- Mel 0.3 + Pgb 0.3
Figure 29

ACETONE TEST

Allodynia (withdrawal sec)

Post-administration time (min)
Figure 30

ACETONE (Acute)

Allodynia (AUC)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pgb 0.3</th>
<th>Mel 1</th>
<th>Mel 1 + Pgb 0.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>~60</td>
<td>~80</td>
<td>~50</td>
</tr>
</tbody>
</table>
Figure 31

ACETONE TEST

Allodynia (withdrawal sec)

Post-administration time (min)

- Pgb0.3
- Mel3.2
- Mel3.2 + Pgb0.3
Figure 32

ACETONE (Acute)

Allodynia (AUC)

Treatment

Pgb 0.3
Mel 3.2
Mel 3.2 + Pgb 0.3
Figure 33

Chronic Treatment

Hypergesia (%) vs. Post-administration time (days)

- Mel 0.1 + Pgb 0.3
- Mel 0.1
- Pgb 0.3
Figure 34

Chronic Treatment

![Bar chart showing hyperalgesia (AUC) for Mel 0.1 + Pgb 0.3, Mel 0.1, and Pgb 0.3 treatments.]
Figure 35

Chronic Treatment

Hyperalgesia (%) vs. Post-administration time (days)
Figure 36

Chronic Treatment

![Bar chart showing Hyperalgesia (AUC) for different treatments: Mel 0.3 + Pgb 0.3, Mel 0.3, and Pgb 0.3. The y-axis represents Hyperalgesia (AUC) ranging from 0 to 700, and the x-axis represents different treatments. The chart indicates that Mel 0.3 + Pgb 0.3 has a lower AUC compared to Mel 0.3 and Pgb 0.3.]
Figure 37

Chronic Treatment

Hyperalgesia (%) vs. Post-administration time (days)

- Mel 1 + Pgb 0.3
- Mel 1
- Pgb 0.3
Figure 38

Chronic Treatment

Hyperalgesia (AUC)

Mel 1 + Pgb 0.3  |  Mel 1  |  Pgb 0.3
Figure 39

Chronic Treatment

Hyperalgesia (%) vs. Post-administration time (days)

- Mel 3.2 + Pb 0.3
- Mel 3.2
- Pb 0.3
Chronic Treatment

![Bar graph showing hyperalgesia (AUC) for different treatments: Mel 3.2 + Pgb 0.3, Mel 3.2, Pgb 0.3. The graph displays higher hyperalgesia levels for Mel 3.2 compared to the other treatments.](image)
Figure 41

Chronic Treatment

- Mel 0.1 + Pg 0.3
- Mel 0.1
- Pg 0.3

Allodynia (withdrawal sec)

Post-administration time (days)
Figure 42

Chronic Treatment

Alloodynia (AUC)

- Mel 0.1 + Pgb 0.3
- Mel 0.1
- Pgb 0.3
Figure 43

Chronic Treatment

Allodynia (withdrawal sec)

Post-administration time (days)
Figure 44

Chronic Treatment

![Graph showing Allodynia (AUC) for Mel 0.3 + Pgb 0.3, Mel 0.3, and Pgb 0.3 treatments. The graph indicates a comparison of the pain response with error bars for each condition.](image-url)
Figure 45

Chronic Treatment

Allodynia (withdrawal sec) vs. Post-administration time (days)
Figure 46

Chronic Treatment

Allodynia (AUC)
Figure 47

Chronic Treatment

- Mel 3.2 + Pgb 0.3
- Mel 3.2
- Pgb 0.3

Allodynia (withdrawal sec)

Post-administration time (days)
Figure 48

Chronic Treatment

Allodynia (AUC)

Mel 3.2 + Pgb 0.3  Mel 3.2  Pgb 0.3
Figure 49

DRC OF MELOXICAM ALONE AND WITH PREGABALIN, 0.3 mg/kg

Anti-hyperalgesia (AUC)

0 100 200 300

0.01 0.1 1 10 100 1000 10000

Meloxicam (mg/kg po)

- Me
- Me + Pgb 0.3
- Pgb 0.3
Figure 50

DRC OF MELOXICAM ALONE AND WITH MELOXICAM + PREGABALIN 0.3 mg/kg
Figure 51

DRC OF MELOXICAM ALONE AND WITH PREGABALIN 0.3 mg/kg
(Cragnostic Treatment)
Figure 52

DRC OF MELOXICAM ALONE AND WITH PREGABALIN 0.3 mg/kg
(Chronic Treatment)
Figure 53

Anti-allodynic effect increase of Mel 0.1 when associated to Pgb 0.3
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<tr>
<td>X</td>
<td>SEIJI OHTORI ET AL: &quot;Efficacy of Combination of Meloxicam and Pregabalin for Pain in Knee Osteoarthritis&quot;, YONSEI MEDICAL JOURNAL, vol. 54, no. 5, 1 January 2013 (2013-01-01), page 1253, XP055214507, ISSN: 0513-5796, DOI: 10.3349/ymj.2013.54.5.1253 abstract page 1254, left-hand column, paragraph 1 - paragraph 2 page 1254, right-hand column, last paragraph - page 1255, left-hand column, paragraph 1 page 1255, right-hand column, last paragraph table 4</td>
<td>1-11</td>
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<tr>
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<td>SHIMIZU KAZUTAKA ET AL: &quot;Evaluation of Pregabalin Therapy in Peripheral Neuropathy&quot;, IMMUNOLOGY ENDOCRINE &amp; METABOLIC AGENTS IN MEDICINAL CHEMISTRY, vol. 13, no. 2, June 2013 (2013-06), pages 132-138, XP002744801, page 132, right-hand column, paragraph 1 figure 3 page 134, right-hand column, paragraph 2 page 136, right-hand column, paragraph 1</td>
<td>1,5,6,8, 10,11</td>
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<td>A</td>
<td>EMILIO BLANCO TARRIO ET AL: &quot;Effectiveness of Pregabalin as Monotherapy or Combination Therapy for Neuropathic Pain in Patients Unresponsive to Previous Treatments in a Spanish Primary Care Setting&quot;, CLINICAL DRUG INVESTIGATION, vol. 33, no. 9, 3 August 2013 (2013-08-03), pages 633-645, XP055214489, ISSN: 1173-2563, DOI: 10.1007/s40261-013-0116-7 page 633, right-hand column, paragraph 2 table 2</td>
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