The present invention provides a topical composition comprising dantrolene and/or azumolene and one or more of a magnesium releasing compound and a compound which reacts with calcium ions under temperatures of 30 to 40 °C and pH levels of 6 to 9. There is also provided a method of treating, alleviating or preventing muscle pain, muscle spasm and/or prolonged muscle contraction in a patient comprising the topical administration of such a composition.
The present invention relates to products, compositions, methods and uses which are useful in the prevention, alleviation or treatment of muscle pain and muscle spasm in a human or animal body. There is also provided products, compositions, methods and uses which are useful in the prevention, alleviation or treatment of muscles adopting or going into a latched state as encountered in myofascial pain. This treatment is suitable for use in restless leg syndrome, post-traumatic injury muscle pain such as whiplash and all forms of chronic and acute muscle spasm and pain. The products, compositions, methods and uses of the present invention generally provide topical relief.

BACKGROUND TO THE INVENTION
Muscle pain is a very common condition which is typically overlooked, misdiagnosed and left untreated. According to some estimates, up to 50% of all visits made by patients to doctors are related to issues surrounding pain. About 50% of those visits may be attributed to conditions associated in whole or in part with muscle pain, muscle spasm or muscle groups adopting a "latched state". These contracted muscle fiber groups are also known as trigger points and contraction knots. Muscle pain, also known as myofascial pain, is not generally accepted as a common cause of pain, and accordingly, few of those patients are diagnosed or treated appropriately. Most chronic pain is diagnosed as neuropathic pain, considered originating from dysfunctional sensory nerves.

Within the field of myofascial pain, controversy still surrounds the initiation of these chronic contracted states of muscle that result in pain. Whether there is one common pathway or more, muscle overload relative to blood (energy) supply seems to be at the root of the problem. Acute extreme muscle contraction, sustained contraction or repetitious muscle contraction result in muscle overload that outstrips the energy supply and appears to precipitate the crisis. As such, decreased/impaired blood supply due to systemic or local factors will also play a role.

Sustained contractions of sarcomeres markedly increase metabolic demands, at the same time squeezing shut the capillary network that supplies the energy and oxygen needs of the cells. Contraction of more than 30-50% of maximum effort will cause circulation in that contracted muscle to fail.
At the point of energy failure, the muscle cells involved encounter an energy crisis with insufficient ATP production from the mitochondria, resulting in loss of control of calcium homeostasis within the cell. The calcium pump that returns calcium back to the storage site (sarcoplasmic reticulum) is dependent on an adequate supply of energy in the form of adenosine triphosphate (ATP) from mitochondria within the cell. Further, this calcium pump is thought to be more sensitive to low ATP levels than the contractile mechanism of the cell. Therefore, the calcium pump fails first, exposing the contractile elements to increasing calcium concentration which increases contractile activity.

The role of intracellular calcium has been studied in strenuous exercise and injury. Resulting muscle damage and creatine kinase release were found to be associated with an intracellular mechanism involving the mobilization of calcium rather than direct damage to the sarcolemma, where the calcium is stored. Further, the calcium channels that trigger release of calcium from the sarcoplasmic reticulum are voltage gated and connected to the neuromuscular junction by the T-tubule that is capable of being depolarized. Sustained depolarization of the postjunctional membrane and T-tubule is one mechanism that might account for a tonic contraction increasing the release of calcium from the sarcoplasmic reticulum.

The loss of calcium homeostasis in myofibers and the resulting increase in free cytosolic calcium is a major step in the cascade of events that results in cellular damage after exercise. Excess intracellular calcium activates phospholipase A2 and calcium-dependent proteases - enzymes that break down muscle.

Investigations have revealed that muscle contracted into a taught band/ trigger point (generally considered to be in a latched state) appears to have no blood flow but a surrounding hyperemic state appears to exist. Oxygen levels at the border of the indurated muscle segment increase before falling precipitously to almost zero at the center of the induration. More recent work has confirmed a corresponding pH drop to as low as 4.0 at the site of low oxygen tension.

An acid milieu in muscle alone, without injury, is sufficient to cause profound changes in the properties of nociceptors, axons and the dorsal horn (spinal cord) neurons i.e. the whole pain pathway back to the spinal cord. Bradykinin levels are also increased locally within the acidic
cells. In response to this pain, the corresponding dorsal root ganglion produces increased tachykinins - substance P (SP) and calcitonin gene-related peptide (CGRP). Both of these extremely potent neuropeptides increase the sensitivity of the nociceptor nerve ending. SP and CGRP are transported antidromically down the pain nerve where they are released into the muscle fiber from the nociceptor nerve ending. Besides increasing sensitivity of the nerve endings, SP increases blood flow to the tissue by direct capillary vasodilatation, probably accounting for the area of hyperemia found surrounding a trigger point in muscle. Tachykinin production decreases rapidly following movement of the muscle fibers.

Most of the myofascial pain syndromes encountered in humans today are currently misdiagnosed by the medical establishment. Many diagnoses in medicine are made based on their response to certain treatments, rather than first obtaining diagnostic proof of a condition. This is the way most chronic pain conditions are diagnosed today owing to the fact that there is no way of proving or quantifying myofascial pain other than clinical examination. As such, some of the very common diagnoses that the inventor believes are directly related to myofascial pain have been attributed to central nervous system disorders.

Whiplash is a non-medical term describing injury to the neck and shoulders as the result of sudden, usually traumatic, acceleration-deceleration of the neck. Whiplash injury is the most common nonfatal car accident injury and is commonly associated with rear-end motor vehicle accidents, but can be caused by almost any acceleration/deceleration traumatic injury to the head and neck. In the UK almost 50,000 people make motor vehicle insurance claims for whiplash injuries every year. Overall there is an estimated 3.8 new cases per 1000 people annually. After whiplash injury only about 11.5% of those affected return to work a year after the injury and 35.4% after 20 years. As such, about 6.2% of the population have ongoing (late) whiplash syndrome.

Whiplash is generally described by a sudden event (for instance 33 milliseconds or less) where the head and neck are subject to severe acceleration and deceleration forces that strain, contuse and/or tear the soft tissue structures of the neck, especially connective tissue, muscle and possibly nerves. The longitudinal ligaments are acutely affected with tearing and bleeding found throughout the structures. Avulsion fractions have also been described. Although pain may onset immediately and coup-contra-coup brain injuries may occur, the most common pattern of injury occurs when the whiplash pain starts to onset about 3-5 days
after the injury and becomes permanent, long after the ligament, bone and brain injuries have healed.

The chronic pain of whiplash has remained an enigma for many years and standard teaching has the brain injury as the major cause of the chronic pain. One study looking at 1000 cases over a four year period published in 2012 implicates the trapezius muscle, damaged through eccentric muscle contraction during the acute injury. No indication as to new treatment interventions and modalities was offered, save the usual physiotherapy and massage.

Restless legs syndrome (RLS) is currently thought to be a central neurological (brain and spinal cord) disorder, characterized by an urge to move the affected limbs to reduce the uncomfortable sensations felt. It may start at any age, with 45% of patients having their first symptoms before the age of 20 years. More than 60% of cases are familial. There are no specific tests to diagnose this condition and although many different treatments have been tried, only the Parkinson's treatment dopamine agonists Ropinirole (Requip) 2005 and Rotigotine (Neupro) 2012 and the antiepileptic gabapentin 2011 have been approved by the FDA for RLS.

RLS symptoms gradually worsen with age. RLS affects an estimated 7 - 10% of the general population in North America and Europe, and is twice as common in women as it is in men. Around one third of sufferers experience daily or severe symptoms. Currently, as with most myofascial pain syndrome, there is no effective treatment for this condition.

Chronic low back pain is another very common condition associated with myofascial pain for which there is frequently no effective remedy.

Dantrolene is a known muscle relaxant. Its skeletal relaxant muscle properties stem from the selective depressive action on the intrinsic muscle cellular mechanisms of excitation-contraction coupling. It is currently used as a treatment for malignant hyperthermia (MH), a rare, potentially fatal condition triggered by the volatile general anaesthetic agents and the muscle relaxant succinylcholine in MH susceptible patients. It is also used as a skeletal muscle relaxant, in particular in the management of neuroleptic malignant syndrome and chronic severe muscle spasticity.
Dantrolene is believed to act by binding to the ryanodine receptor and decreasing intracellular calcium concentration in skeletal muscle with no effect on smooth or cardiac muscle cells. It is suitable for relieving muscle spasticity resulting from neuromuscular disease including stroke, brain and spinal cord injury, cerebral palsy and multiple sclerosis. It has few adverse effects related to the nervous system.

Dantrolene is highly lipid soluble, making the intravenous preparation difficult to formulate and dissolve in preparation for use. Currently, the intravenous formulation is prepared in ampoules containing 20mg of lyophilized dantrolene sodium together with mannitol 3g and sufficient sodium hydroxide to yield a pH of 9.5 when dissolved in 60ml of water, providing a final concentration of 0.03% solubilized dantrolene.

In human volunteers, the intravenous administration of 2.4 mg/kg of dantrolene produced blood levels of 10 micromoles (4.2 micrograms/ml) with a 75% reduction in muscle twitch response and 42% reduction in grip strength. Thereafter the elimination half life is 12 hours, with a steady blood level being maintained for about 5 hours. Residual feelings of weakness may last for up to 48 hours. Following ingestion by mouth, only about 70% of the dantrolene gets into the systemic circulation, with peak levels being reached in 6 hours. There is a great variation in the plasma concentrations achieved relative to the oral dose between patients, in particular where the patients are children.

Dantrolene is metabolized in the liver and excreted in both bile and urine. Significant adverse indications have been reported in connection with the systemic administration of dantrolene including central nervous system effects encompassing speech and visual disturbances, headache, insomnia, precipitation or exacerbation of seizures, GI effects and respiratory depression. The major adverse reactions that have been documented with dantrolene have all resulted from chronic oral administration. The most important adverse event is hepatic dysfunction. This varies in severity from slight elevation in liver enzyme levels (1.8%) to fatal hepatic injury (0.35%). Researchers in the U.S.A. have reported 122 cases of hepatic dysfunction related to dantrolene until 1987, of which 27 were fatal. The dantrolene dosage in the fatal cases was 582 mg/day administered for 13.8+/- 12 months. The exact mechanism of hepatic induced dysfunction has not yet been established.
STATEMENT OF INVENTION

Myofascial pain is commonly misdiagnosed and misunderstood as neurological disease, including when associated with conditions such as whiplash, restless leg syndrome and chronic low back pain. The present invention provides the use of the pharmaceutically active compound dantrolene to specifically treat abnormal muscle calcium homeostasis - providing a resolution of the symptoms and an understanding of the source of the pain. In particular, the present invention provides the prophylactic use of dantrolene for muscles or muscle groups which have not yet entered, or have not yet fully entered their latched state but have experienced a stress such as a blow or a sudden change of direction and are thus likely to enter into the latched state. Such muscles or muscle groups are associated with syndromes such as whiplash.

The methods and compositions of the present invention provide an alternate route of delivery to known systemic administrations. The topical compositions of the present invention bypass the first pass hepatic extraction of dantrolene by the liver (30% or more) improving the bioavailability of the dantrolene, making dosing more reliable and less toxic to the liver of the patient. In addition, topical delivery of the composition of the present invention directly to the site of action (muscle or muscle group affected) increases the delivery of dantrolene to the muscle affected, even and especially in the face of decreased blood flow to the muscle(s) involved.

According to a first aspect of the present invention, there is provided a topical composition comprising dantrolene and/or azumolene.

Compositions of dantrolene for systemic administration are known. Such compositions are generally suitable for oral or intravenous administration and commonly comprise doses of around 100 to 600 mg/day dantrolene. As noted above, dantrolene absorption is erratic and is associated with significant adverse effects including a significant incidence of liver injury and necrosis.

The products, compositions and methods of the present invention allow an alternative route of entry to the body, bypassing the first pass hepatic extraction of dantrolene by the liver. A reduction of around 30% is associated with the first pass hepatic extraction of systemically active dantrolene administrations. The products, compositions and methods of the present
invention improve the bioavailability of the dantrolene as well as reducing the associated adverse effects, including associated liver toxicity. The dosing of the compositions of the present invention is more reliable than known dantrolene formulations.

The products, compositions and methods of the present invention allow topical delivery of dantrolene and/or azumolene directly to the site of action, increasing the delivery of dantrolene and/or azumolene to the muscle affected, even and especially in the face of decreased blood flow to the muscle(s) involved.

The products and compositions of the present invention allow the topical administration of dantrolene and/or azumolene providing a focused muscle relaxant effect on the particular muscle group or area in need thereof. The necessary dose of dantrolene/azumolene and associated side effects are reduced accordingly. The composition of the present invention allows the action of dantrolene/azumolene to take effect more quickly than known dantrolene compositions and this provides an important advantage. In addition the products and compositions of the present invention ensure that a predictable amount of dantrolene/azumolene is absorbed from each application of the products and compositions.

According to a further aspect of the present invention there is provided a topical composition comprising dantrolene and/or azumolene and one or more compounds to improve calcium control in and around the affected area. The compound(s) generally react with excess free calcium in the affected area. Suitable compounds include sodium thiosulfate, vitamin K2 and vitamin D.

According to a further aspect of the present invention there is provided a topical composition comprising dantrolene and/or azumolene and one or more magnesium releasing compounds.

According to a further aspect of the present invention there is provided a method of treating or alleviating muscle pain (in particular myofascial pain), muscle spasm and/or prolonged muscle contraction in a patient suffering therefrom comprising the topical administration in a therapeutically effective amount of the composition described herein.
In particular there is provided a method of treating whiplash or alleviating the symptoms associated therewith comprising the topical administration in a therapeutically effective amount of the composition described herein.

According to a further aspect of the present invention there is provided a method of treating abnormal muscle calcium homeostasis in a patient suffering therefrom comprising the topical administration in a therapeutically effective amount of the composition described herein.

According to a further aspect of the present invention there is provided a method of preventing muscle pain (in particular myofascial pain), muscle spasm and/or prolonged muscle contraction in a patient likely to suffer therefrom comprising the topical administration in a therapeutically effective amount of the composition described herein.

In particular, there is provided a method of preventing muscle pain in a patient likely to suffer therefrom comprising the topical administration in a therapeutically effective amount of the composition described herein.

In particular, the method of preventing muscle pain, muscle spasm and/or prolonged muscle contraction in a patient involves the topical administration of the composition described herein before the muscle has fully entered a latched state. Such a prophylactic method is useful in connection with syndromes such as whiplash where a patient has suffered a stress, for instance a sudden change in direction, but the muscles have not yet entered or have not yet fully entered a latched state.

According to a further aspect of the present invention, there is provided the composition as described herein for use in the diagnosis of a source of pain.

This invention also contemplates topical anesthesia of a potential source of pain for diagnostic purposes. Specifically, the topical composition of the present invention is administered to a patient suffering from pain where the origin of the pain is not precisely known. This administration reliably blocks pain from a potential source for a temporary period of time. This allows differentiating this source of pain from pain emanating from other sources such as surrounding organs.
According to a further aspect of the present invention there is provided the composition as described herein for use in therapy.

According to a further aspect of the present invention there is provided the composition as described herein for use in the prevention, treatment or alleviation of muscle pain (in particular myofascial pain), muscle spasm and/or prolonged muscle contraction.

According to one embodiment, the muscle pain, muscle spasm and/or prolonged muscle contraction is a symptom of, or is associated with whiplash pain, chronic lower back pain or restless leg syndrome.

According to one embodiment, there is provided a method of treating a patient suffering from whiplash or alleviating the symptoms associated therewith, comprising the topical administration in a therapeutically effective amount of a topical composition comprising dantrolene and/or azumolene to the area of the patient affected. Generally the composition is any of those disclosed herein.

According to a further aspect of the present invention there is provided a method of treating a patient suffering from restless leg syndrome or alleviating the symptoms associated therewith, comprising the topical administration in a therapeutically effective amount of a topical composition comprising dantrolene and/or azumolene to the area of the patient affected. Generally the composition is any of those disclosed herein.

According to a further aspect of the present invention there is provided the use of the composition as described herein in the manufacture of a medicament for the prevention, treatment or alleviation of muscle pain (in particular myofascial pain), muscle spasm and/or prolonged muscle contraction.

According to a further aspect of the present invention, there is provided a kit of parts for use in the prevention, treatment or alleviation of muscle pain, muscle spasm and/or prolonged muscle contraction, said kit of parts comprising the composition as described herein and an applicator device such as a spatula.
Definitions

Dantrolene (sodium, l-{[5-(p-paraphenyl) furfurylidene] amino} hydantoin), is pharmacologically the most active member of a long series of l-{(5 aryl furfurylidene) amino} hydantoin syntheses for their muscle relaxant properties. Dantrolene has the IUPAC name l-{[5-(4-nitrophenyl)-2-mryl]methylideneamino}imidazolidine-2,4-dione, and the chemical structure:

![Chemical structure of Dantrolene](image)

Dantrolene is available from JHP Pharmaceuticals LLC under the trade name Dantrolen ® in Europe and Dantrium ® in the US.

Azumolene is an analogue of dantrolene having improved water solubility. Azumolene has the structure:

![Chemical structure of Azumolene](image)

The term "latched state" is used to refer to a muscle or group of muscles in a contracted state, with reduced associated blood flow. In some cases, the blood flow may be substantially or completely precluded. A muscle in a latched state may undergo necrosis over time.

By an "effective" amount or "therapeutically effective amount" is meant an amount of one or more active substances which, within the scope of sound medical judgment, is sufficient to provide a desired effect without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

All numerical values provided incorporate 10% less than and 10% more than the numerical value provided.
Composition
According to a first aspect of the present invention, there is provided a topical composition comprising dantrolene and/or azumolene. This will generally be applied directly over the muscles affected and is expected to provide a therapeutic effect at much lower systemic levels of the drug than that provided by systemic administration which must rely on blood transport to the poorly or unperfused muscle.

The composition of the present invention is provided topically, thus bypassing the first pass hepatic extraction of dantrolene by the liver (30% or more) and improving the bioavailability of dantrolene, making dosing more predictable and reliable and less toxic to the liver.

Even in the face of decreased blood flow to the muscle(s) affected, the delivery of dantrolene and/or azumolene associated with the composition of the present invention is maintained. This is particularly advantageous as blood flow is decreased to muscles in a latched state.

The amount of dantrolene and/or azumolene in the composition is dependent on many factors including whether the composition will be used in treatment/alleviation or prevention of muscle pain, muscle spasm or prolonged muscle contraction, the severity of the condition, the age, weight and gender of the patient.

The composition generally comprises from at least 0.1% to no more than 20 wt % dantrolene.

The composition generally comprises from at least 0.1% to no more than 20 wt % azumolene.

The composition generally comprises from at least 0.1% to no more than 20 wt % dantrolene and azumolene combined.

This will generally be used at 1-10cc, typically 1-5cc topically per application and is expected to provide 30mg or less per dose, generally 5-25mg per dose. This is significantly less than the dose required for effective systemic administration.

According to one embodiment, the topical composition of the present invention comprises less than 50% of the amount of dantrolene in known dosing of dantrolene suitable for systemic administration, typically less than 25%, generally around 20% of the amount of
dantrolene in known dosing of dantrolene suitable for systemic administration.

According to one embodiment, a unit dose of the composition of the present invention comprises less than 25 mg dantrolene, generally 5 to 20 mg dantrolene.

Alternatively, a unit dose of the composition of the present invention comprises less than 25 mg azumolene, generally 5 to 20 mg azumolene.

Generally a unit dose of the composition of the present invention comprises less than 25 mg dantrolene and azumolene combined, generally 5 to 20 mg dantrolene and azumolene combined.

Where there is insufficient blood supply to a muscle, this leads to a reduction in the pH levels of that tissue. The pH of the composition is optimized to maximize the absorption of dantrolene into the human or animal body. Generally the pH of the composition is also optimized to help reverse any drop in pH caused by a reduction in the blood flow.

According to one embodiment of the present invention, the composition has a pH of at least 6, generally at least 7, typically around 7 to 8.

Topical administration of the composition of the present invention generally raises the pH of the area of the human or animal body to which the composition has been administered to at least 6, generally at least 7.

The active compounds (in particular dantrolene) and other ingredients may form suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. It is possible to add, if necessary, an adjuvant chosen from antioxidants, surfactants, other preservatives, film-forming, keratolytic or comedolytic agents, perfumes, flavorings and colourings. Antioxidants such as t-butylhydroquinone, butylated hydroxyanisole, butylated hydroxytoluene and [alpha]-tocopherol and its derivates can be added. Preservatives can typically be added to help maintain the shelf life of the dosage form/composition of the present invention.
Generally, the composition is in the form of a pharmaceutical formulation of the therapeutic compounds of the invention comprising a solvent or diluent. Solvents or diluents may include acid solutions, dimethylsulphone, N-(2-mercaptobutanoyl) glycine, 2-nonyl-1,3-dioxolane and ethyl alcohol. Preferably the solvent/diluent is an acidic solvent, for example, acetic acid, citric acid, boric acid, lactic acid, propionic acid, phosphoric acid, benzoic acid, butyric acid, malic acid, malonic acid, oxalic acid, succinic acid or tartaric acid.

The composition of the present invention generally also includes one or more pharmaceutically acceptable carriers, excipients, adjuvants, diluents, solubilizing or emulsifying agents. The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings or, as the case may be, an animal without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The sterile media employed in the preparation of suitable formulations are all readily obtainable by standard techniques well-known to those skilled in the art.

The form and physical properties of the composition depend on the method of administration. However, the composition is typically in the form of a gel, hydrogel, lotion, cream, ointment, foam or liquid including a solution or suspension.

**Composition Formulated for Application to the Skin**

According to one embodiment, the composition of the present invention is formulated for topical cutaneous application. The dantrolene contained within the composition is able to cross biological membranes such as the skin relatively well and is thus absorbed into the biological tissue, in particular muscle.

Forms chiefly conditioned for topical application to the skin take the form, for example, of creams, milks, gels, powders, dispersion or microemulsions, lotions thickened to a greater or lesser extent, impregnated pads, ointments or sticks, aerosol formulations (e.g. sprays or foams), soaps, detergents, lotions or cakes of soap. Other conventional forms for this purpose include wound dressings, coated bandages or other polymer coverings, ointments, creams, lotions, pastes, jellies, sprays, and aerosols. Thus, the therapeutic compounds of the invention
can be delivered via patches or bandages for dermal administration. Alternatively, the therapeutic compounds can be formulated to be part of an adhesive polymer, such as polyacrylate or acrylate/vinyl acetate copolymer. For long-term applications it might be desirable to use microporous and/or breathable backing laminates, so hydration or maceration of the skin can be minimized. The backing layer can be any appropriate thickness that will provide the desired protective and support functions. A suitable thickness will generally be from about 10 to about 200 microns.

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. The active compounds can also be delivered via iontophoresis, e.g., as disclosed in US Patent Nos. 4,140,122; 4,383,529; or 4,051,842 which are incorporated herein by reference. The percentage by weight of a therapeutic agent of the invention present in the topical formulation will depend on various factors, but generally will be from 0.01% to 95% of the total weight of the formulation, and typically 0.1-85% by weight.

Drops, such as eye drops or nose drops, may be formulated with one or more of the active compounds of the present invention in an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilizing agents or suspending agents. Liquid sprays can be pumped, or are conveniently delivered from pressurized packs. Drops can be delivered via a simple eye dropper-capped bottle, via a plastic bottle adapted to deliver liquid contents drop-wise, or via a specially shaped closure.

These formulations can contain pharmaceutically acceptable carriers, vehicles and adjuvants that are well-known in the art. It is possible, for example, to prepare solutions using one or more organic solvent(s) that is/are acceptable from the physiological standpoint, chosen, in addition to water, from solvents such as acetone, acetic acid, ethanol, isopropyl alcohol, dimethyl sulfoxide, glycol ethers such as the products sold under the name "Dowanol", polyglycols and polyethylene glycols, CI- C4 alkyl esters of short-chain acids, ethyl or isopropyl lactate, fatty acid triglycerides such as the products marketed under the name "Miglyol", isopropyl myristate, animal, mineral and vegetable oils and polysiloxanes.
According to one embodiment, the composition of the present invention provides lubricant properties. In particular, the composition may comprise a lubricant base.

**Typical Additional Active Compounds**

According to one embodiment, the composition of the present invention comprises one or more additional active compound such as one or more compound to improve blood supply to the affected area, one or more compound to control the pH of the affected muscle tissue, generally by increasing the pH by buffering H⁺ ions, one or more compound to improve calcium control in and around the affected area, one or more analgesic or anaesthetic, one or more anti-neuropathic and/or one or more anti-inflammatory compound.

According to one embodiment, the composition comprises one or more additional compounds to achieve a reduction in free calcium in the affected tissue, for instance muscle tissue (mopping up the excess free calcium). Suitable compounds include sodium thiosulfate, vitamin K₂ and vitamin D.

In particular the composition comprises one or more compounds which react with calcium ions in the tissue to which the composition is applied, in particular under the conditions typically found in human muscle tissue, generally under temperatures of 30 to 40 °C, pH of 6 to 9.

According to one embodiment there is provided a topical composition comprising dantrolene and/or azumolene and one or more of a compound which reacts with calcium ions under temperatures of 30 to 40 °C and pH levels of 6 to 9 and magnesium releasing compounds.

The compound which reacts with calcium ions improves calcium control in and around the affected area

According to one embodiment, the composition comprises one or more additional compounds to improve the blood supply to the affected muscle tissue. Suitable compounds include phosphodiesterase inhibitors (such as sildenafil, vardenafil etc.), magnesium releasing compounds useful in the relaxation of smooth muscle, in particular vascular smooth muscle, calcium channel blocker drugs, and alpha 2 antagonist compounds.
According to one embodiment, the composition comprises one or more additional compounds to achieve a reduction in free calcium in the affected tissue, and one or more additional compounds to improve the blood supply to the affected tissue.

According to one embodiment, the composition comprises dantrolene, one or more compounds which react with excess free calcium in the affected tissue and/or one or more magnesium releasing compound.

Typically the analgesic may also provide anti-inflammatory properties such as NSAIDs, including ibuprofen.

In addition, the composition may comprise sufficient alkaline compound to increase the pH of the composition to 7 to 8. Suitable alkaline compounds include bicarbonate of soda.

The ratio of the dantrolene/azumolene to other active ingredient administered according to the invention may be at least 1:4 to 4:1.

The abovementioned active agents may be administered as free or fixed combinations. Free combinations may be provided as combination packages containing all the active agents in free combinations.

The compounds of the present invention may be administered in the form of pharmaceutically acceptable salts. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., US, 1985, p. 1418, the disclosure of which is hereby incorporated by reference; see also Stahl et al, Eds, "Handbook of Pharmaceutical Salts Properties Selection and Use", Verlag Helvetica Chimica Acta and Wiley-VCH, 2002. The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical
judgment, suitable for use in contact with the tissues of human beings or, as the case may be, an animal without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

There is also provided the product described above for therapeutic use.

Method of Treatment

According to a further aspect of the present invention there is provided a method of treating abnormal muscle calcium homeostasis in a patient suffering therefrom comprising the topical administration in a therapeutically effective amount of the composition described herein.

According to a further aspect of the present invention there is provided a method of treating or alleviating muscle pain (in particular myofascial pain), muscle spasm and/or prolonged muscle contraction in a patient suffering therefrom comprising the topical administration in a therapeutically effective amount of the composition described herein.

Typically there is provided a method of treating or alleviating the symptoms associated with one or more of whiplash and restless leg syndrome.

According to a further aspect of the present invention there is provided a method of preventing muscle pain, muscle spasm and/or prolonged muscle contraction in a patient likely to suffer therefrom comprising the topical administration in a therapeutically effective amount of a composition comprising dantrolene and/or azumolene. Typically the composition is any as described herein.

Typically there is provided a method of preventing muscle pain, in particular that associated with whiplash.

According to one aspect of the present invention, there is provided a method of treating a patient suffering from whiplash or alleviating the symptoms associated therewith, comprising the topical administration in a therapeutically effective amount of the composition described herein to the area of the patient affected.
In particular, there is provided a prophylactic method of preventing or minimizing the onset of the symptoms of whiplash, comprising the topical administration of the composition described herein to muscles or muscle groups which have been the subject of a stress (such as a sudden change in direction), wherein said muscles or muscle groups have not yet entered a latched state.

According to one aspect of the present invention, there is provided a method of treating a patient suffering from restless leg syndrome or alleviating the symptoms associated therewith, comprising the topical administration in a therapeutically effective amount of the composition described herein to the area of the patient affected.

Typically the condition is associated with whiplash, restless leg syndrome, chronic lower back pain, strokes, paraplegia, cerebral palsy or multiple sclerosis.

According to one embodiment, the muscle has adopted a "latched state" where the muscle is in the contracted state with blood flow to the muscle restricted or precluded.

As noted above, the method of the present invention may be used to prevent muscle pain, muscle spasm and/or prolonged muscle contraction. This is commonly used where a patient has undergone an impact or a stress or strain injury which is likely to result in direct or indirect muscle injury, pain, spasm or contraction. For instance, where tissue damage has occurred and the surrounding muscle may contract in an attempt to stabilize the surrounding area.

Typical impacts include sports injuries, blows to the head (for instance from a falling object or from assault), sudden changes in direction (for instance from a child being shaken, roller coasters, minor bike or car accidents, slips or falls and major traffic or car accidents). Additionally or alternatively, the tissue damage may have been caused through a chronic stress or strain injury including a repetitive strain injury.

Tissue damage may have occurred to for instance, bones, ligaments, tendons, muscle, nerves and/or cartilage.
According to one embodiment, the condition is restless leg syndrome. Alternatively the condition may be whiplash.

Alternatively or additionally, the method of the present invention may be used to treat muscle pain, muscle spasm and/or prolonged muscle contraction.

The condition(s) to be treated and/or used as indicators for the need for a method of prevention to be adopted may be associated with tenderness in the affected area(s), in particular along the back of the neck and shoulders, swelling (in particular swelling of the neck), muscle spasms in the posterior cervical spine (back of the neck), anterior cervical spine (front of the neck) and/or in the trapezius muscles (back of the shoulders), difficulty extending or rotating the head, headache, difficulty concentrating, sleep disturbances, fatigue, jaw tightness and difficulty chewing and/or nerve irritation, including vision disturbance and tinnitus.

According to a further aspect of the present invention, there is provided the composition as described herein for use in the diagnosis of a source of pain.

This invention also contemplates topical anesthesia of a potential source of pain for diagnostic purposes. Specifically, the topical composition of the present invention is administered to a patient suffering from pain where the origin of the pain is not precisely known. This administration reliably blocks pain from a potential source for a temporary period of time. This allows differentiating this source of pain from pain emanating from other sources such as surrounding organs.

According to one embodiment, the composition of the present invention provides topical relaxation of the muscle within less than 30 minutes of administration, generally within less than 10 minutes of administration, typically within around 5 minutes of administration.

The duration of the effects provided by the composition of the present invention depends on many factors including the type of tissue to which the composition is applied, the amount of composition applied thereto and the concentration of dantrolene in the composition.
Generally the composition provides topical relaxation of the muscle for at least 1 hour, typically at least 2 hours, suitably at least 3 hours.

The active agents of the present invention may be administered by any suitable route known to those skilled in the art, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment or prevention intended.

The amount of therapeutically active compound that is administered and the dosage regimen for treating a condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, as well as the pharmacokinetic properties of the individual treated, and thus may vary widely. The dosage will generally be lower if the compounds are administered for prevention rather than for treatment. Such treatments may be administered as often as necessary and for the period of time judged necessary by the treating physician. One of skill in the art will appreciate that the dosage regime or therapeutically effective amount of the inhibitor to be administrated may need to be optimized for each individual.

The active agents may be administered simultaneously or sequentially. According to one embodiment, the active agents are administered simultaneously.

The composition may be suitable for application to the skin of the patient to be treated. The active compounds in the composition are then absorbed into the muscle underlying the skin.

Where the composition is administered through dermal application, the total volume administered per application is generally 1 to 10 cc, typically 1 to 5 cc. The dose of dantrolene per application is dependent on the size of the affected area, but is generally 5 to 25 mg per topical application. The composition is generally applied to the affected tissue (or tissue proximal to the affected tissue) at least once a day. In cases of severe damage, the composition may be applied to the affected tissue (or tissue proximal to the affected tissue) up to five times a day.

The adverse effects associated with the systemic administration of dantrolene can be severe. The method of the present invention provides the topical administration of dantrolene
resulting in lower dosage requirements, and thus less risk of severe adverse effects. In addition, the effect of the dantrolene is exhibited more quickly through topical administration, and the amount of dantrolene absorbed into the muscle of interest can be predicted with greater accuracy than for systemic administrations. The bioavailability of dantrolene from the topical administration associated with the present invention is more reliable and predictable than the bioavailability of dantrolene from known systemic routes of administering dantrolene.

The method of the present invention provides a focused method of exploiting the beneficial effects of dantrolene whilst limiting the associated dosage required and the risk of adverse effects.

Generally the effects of the dantrolene are limited to within 15 cm of the site of administration of the composition, typically 10 cm or less, suitably 5 cm or less, more suitably around 1 cm from the site of administration of the composition.

Generally, where the composition of the present invention is administered through dermal application, the dantrolene contained within the composition remains within 5 cm of the site of application, typically within 1 cm.

Typically, where the composition of the present invention is administered through dermal application a dose of 5 to 25 mg of dantrolene is administered per application.

Where the composition of the present invention is administered to tissue proximal to the affected muscle/the muscle to be treated, the composition may be absorbed through the proximal tissue relatively quickly. The rate of absorption depends on the type of tissue.

The active agents of the method of the present invention may be administered simultaneously or sequentially. Where the active agents are administered sequentially, the administration of all of the active agents is generally within 10 minutes, typically within 5 minutes.

According to one embodiment, the active compounds may be administered via different routes. For instance, the dantrolene may be administered via topical dermal application and the additional active compounds may be administered via topical injection.
The method of the present invention may be undertaken whenever required. The active agents may be administered at least once daily, generally at least three times daily, and typically up to five times daily.

The duration of the course of treatment depends on the condition to be treated and its severity.

Where the condition to be treated is associated with whip lash, a course of treatment will generally last up to two weeks. However, where the condition to be treated is associated with an ongoing medical condition such as multiple sclerosis, strokes, paraplegia or cerebral palsy, a course of treatment is generally ongoing, generally lasting at least six months, for example up to several years.

The patient is generally a human although in some embodiments, an animal may be treated.

**Kit of Parts**

According to a further aspect of the present invention, there is provided a kit of parts for use in the prevention, treatment or alleviation or diagnosis of a source of muscle pain, muscle spasm and/or prolonged muscle contraction, said kit of parts comprising the composition as described herein and an applicator device such as a spatula.

The kit of parts may comprise the active agents in dosage units containing a particular amount of the active agent. The dosage units may comprise one or more active agents.

Generally the kit includes instructions for use, for example the nature of administration.

Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be
understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith.

Throughout the description and claims of this specification, the words "comprise" and "contain" and variations of the words, for example "comprising" and "comprises", mean "including but not limited to", and are not intended to (and do not) exclude other moieties, additives, components, integers or steps. All documents referred to herein are incorporated by reference.

Various modifications and variations of the described aspects of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes of carrying out the invention which are obvious to those skilled in the relevant fields are intended to be within the scope of the following claims.
CLAIMS

1. A topical composition comprising dantrolene and/or azumolene and one or more of a magnesium releasing compound and a compound which reacts with calcium ions under temperatures of 30 to 40 °C and pH levels of 6 to 9.

2. The composition as claimed in claim 1 comprising 0.1 to 20 wt % dantrolene.

3. The composition as claimed in either one of claims 1 and 2 wherein a unit dose of the composition comprises 5 to 20 mg dantrolene.

4. The composition as claimed in any preceding claim, having a pH of 7 to 8.

5. The composition as claimed in any preceding claim formulated for topical cutaneous application.

6. The composition of claim 5 in the form of creams, milks, gels, powders, dispersion or microemulsions, lotions, impregnated pads, ointments or sticks, aerosol formulations (e.g. sprays or foams), soaps, detergents, cakes of soap, wound dressings, coated bandages or other polymer coverings, ointments, pastes or jellies.

7. The composition of any preceding claim comprising one or more compound to improve blood supply to an affected area to which the composition is applied, compound to control the pH of an affected area to which the composition is applied, analgesic or anaesthetic, anti-neuropathic and/or anti-inflammatory compound.

8. The composition of claim 1 comprising a compound which reacts with calcium ions wherein the compound is one or more of sodium thiosulfate, vitamin K2 and vitamin D.

9. The composition of either one of claims 7 and 8 comprising one or more phosphodiesterase inhibitors such as sildenafil and vardenafil; one or more magnesium releasing compound useful in the relaxation of smooth muscle, in
particular vascular smooth muscle; one or more calcium channel blocker drugs; and/or one or more alpha 2 antagonist compounds.

10. A method of treating or alleviating muscle pain, muscle spasm and/or prolonged muscle contraction in a patient suffering there from comprising the topical administration in a therapeutically effective amount of the composition as claimed in any one of claims 1 to 9.

11. The method as claimed in claim 10 wherein the muscle pain, muscle spasm and/or prolonged muscle contraction is associated with whip lash, chronic lower back pain, restless leg syndrome, stroke, paraplegia, cerebral palsy or multiple sclerosis.

12. The method as claimed in either one of claims 10 and 11 wherein the muscle pain, muscle spasm and/or prolonged muscle contraction is associated with whip lash.

13. The method as claimed in any one of claims 10 to 12 where the muscle is in a latched state.

14. A method of preventing muscle pain, muscle spasm and/or prolonged muscle contraction in a patient suffering there from comprising the topical administration in a therapeutically effective amount of a topical composition comprising dantrolene and/or azumolene.

15. The method as claimed in claim 14 wherein the composition is as claimed in any one of claims 1 to 9.

16. The method as claimed in either one of claims 14 and 15 wherein the method is undertaken after the patient has undergone an impact or a stress or strain injury which is likely to result in direct or indirect muscle injury, pain, spasm or contraction, but before the muscle has entered or fully entered the latched state.

17. The method as claimed in claim 16 wherein the impact or stress or strain injury is due to a sports injury, a blow to the head (for instance from a falling object or from assault), a sudden change in direction (for instance from a child being shaken, roller
coasters, traffic, bike or car accidents, slips or falls) or a chronic stress or strain injury including a repetitive strain injury.

18. A method of treating a patient suffering from whiplash or alleviating the symptoms associated therewith, comprising the topical administration in a therapeutically effective amount of a topical composition comprising dantrolene and/or azumolene to the area of the patient affected.

19. The method of claim 18 wherein the composition is as claimed in any one of claims 1 to 9.

20. A method of treating a patient suffering from restless leg syndrome or alleviating the symptoms associated therewith, comprising the topical administration in a therapeutically effective amount of a topical composition comprising dantrolene and/or azumolene to the area of the patient affected.

21. The method as claimed in claim 20 wherein the composition is as claimed in any one of claims 1 to 9.

22. A method of treating a patient suffering from chronic lower back pain or alleviating the symptoms associated therewith, comprising the topical administration in a therapeutically effective amount of the composition as claimed in any one of claims 1 to 9 to the area of the patient affected.

23. A method of treating abnormal muscle calcium homeostasis in a patient suffering therefrom comprising the topical administration in a therapeutically effective amount of the composition as claimed in any one of claims 1 to 9 to the area of the patient affected.

24. A method of diagnosing a source of pain comprising the topical administration in a therapeutically effective amount of the composition as claimed in any one of claims 1 to 9 to the area of the patient affected.

25. The method of any one of claims 10 to 24 wherein topical relaxation of the muscle is provided within less than 30 minutes of administration of the composition.
26. The method of any one of claims 10 to 25 wherein topical relaxation of the muscle is provided for at least 1 hour from administration of the composition.

27. The method of any one of claims 10 to 26 wherein the composition is administered to the patient from 1 to 5 times daily.

28. The method of any one of claims 10 to 27 wherein the effects of the dantrolene and/or azumolene are limited to within 15 cm of the site of administration of the composition.

29. The method of any one of claims 10 to 28 wherein the composition is administered through dermal application, and the dantrolene contained within the composition remains within 1 cm of the site of application.

30. The method of any one of claims 10 to 29 wherein the composition is administered through dermal application and 1 to 10 cc composition is topically applied per application.

31. The composition as claimed in any one of claims 1 to 9 for therapeutic use.

32. A kit of parts for use in the prevention, treatment or alleviation of muscle pain, muscle spasm and/or prolonged muscle contraction, said kit of parts comprising the composition as claimed in any one of claims 1 to 9 and an applicator device such as a spatula.
### INTERNATIONAL SEARCH REPORT

**International application No.**

PCT/GB2014/005224

#### A. CLASSIFICATION OF SUBJECT MATTER


ADD.

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

#### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

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

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

EPO-Internal, WPI Data, EMBASE, BIOSIS, FSTA

#### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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| * | Further documents are listed in the continuation of Box C. | X | See patent family annex. |

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* Special categories of cited documents:

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

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* "A" document member of the same patent family

Date of the actual completion of the international search

16 April 2014

Date of mailing of the international search report

29/04/2014

Name and mailing address of the ISA

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Peri s Antoli, Berta
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