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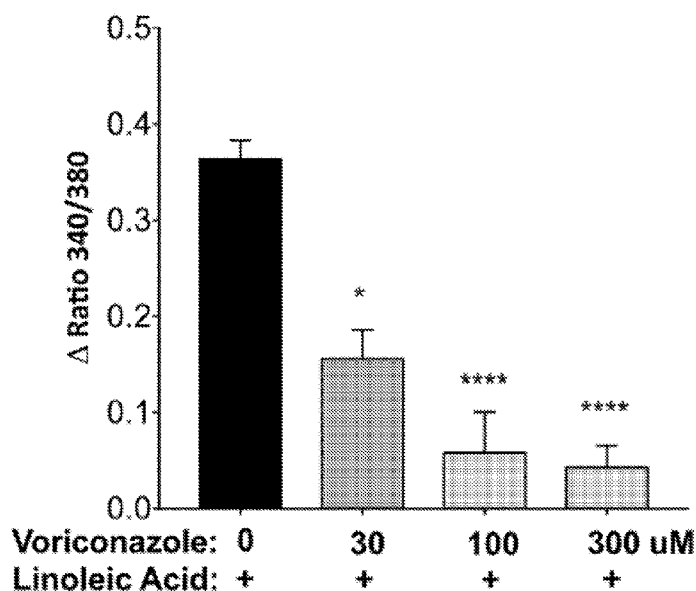


FIG. 1

(57) Abstract: Disclosed herein are pharmaceutical compositions comprising voriconazole, alone or in combination with a local anesthetic, and one or more pharmaceutically acceptable carriers, useful for alleviating pain or hyperalgesia.

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TOPICAL VORICONAZOLE FOR THE TREATMENT OF PAIN

BACKGROUND OF THE INVENTION

Many pain conditions are poorly managed by currently available analgesics. For example, injuries to the skin such as burns, sunburns, physical injury, infections or inflammation affect more than ten million people annually in the United States alone. Importantly, poor pain control is known to increase the risk for long term adverse outcomes. For example, surveys indicate that about one-half of patients with a burn injury have inadequate pain management. The mucosa of the mouth, nose, eyes and vagina also acts as an integument. Like skin, pain in the mucosa is also poorly managed. For example, infections, burning mouth syndrome, and vulvodynia affect more than five million people in the United States each year.

Currently available analgesics for treating pain in the integument (e.g., opiates, local anesthetics) have limited efficacy and are often associated with considerable adverse effects. In addition to burn pain, there are many other pain states (e.g., inflammatory pain, neuropathic pain, cancer pain, herpes zoster pain, etc.) for which currently available analgesics exhibit limited activity, even with repeated dosing.

SUMMARY

Disclosed here are pharmaceutical compositions comprising voriconazole and one or more pharmaceutically acceptable carriers, wherein the compositions are in a unit dosage form comprising 0.3 mg/ml to 3.5 mg/ml of voriconazole.

Disclosed herein are methods of alleviating pain or hyperalgesia in a patient in need thereof, the methods comprising topically administering to the patient, a therapeutically effective amount of voriconazole and one or more pharmaceutically acceptable carriers.

Disclosed herein are pharmaceutical compositions comprising voriconazole and one or more pharmaceutically acceptable carriers, wherein the compositions are formulated for topical administration, and wherein the compositions are in a unit dosage form comprising 150 μ M of voriconazole.

5 Disclosed herein are pharmaceutical compositions comprising voriconazole and one or more pharmaceutically acceptable carriers, wherein the compositions comprise liposomal beads or is formulated as a gel, ointment, cream, lotion, serum, spray or emulsion.

Disclosed herein are pharmaceutical compositions comprising voriconazole and one or more pharmaceutically acceptable carriers, wherein the composition is formulated for topical
10 administration, and wherein the composition is in a unit dosage form comprising 0.3 mg/ml to 3.5 mg/ml of voriconazole.

Other features and advantages of the present compositions and methods are illustrated in the description below, the drawings, and the claims.

15 **BRIEF DESCRIPTION OF THE DRAWINGS**

FIG. 1 shows that voriconazole inhibits linoleic acid-induced activation of capsaicin-sensitive neurons.

FIG. 2 shows that voriconazole blocks inflammatory pain.

FIG. 3 shows that voriconazole dose-dependently produces analgesia in inflammatory
20 pain.

FIG. 4 shows the voriconazole does not produce hyperthermia, while casapzepine, a TRPV1 antagonist does.

FIG. 5 depicts a summary of activity of linoleic acid metabolites on transient receptor potential channels.

25 **DETAILED DESCRIPTION**

The present disclosure can be understood more readily by reference to the following detailed description of the invention, the figures and the examples included herein.

Before the present methods and compositions are disclosed and described, it is to be understood that they are not limited to specific synthetic methods unless otherwise specified, or
30 to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, example methods and materials are now described.

5 Moreover, it is to be understood that unless otherwise expressly stated, it is in no way intended that any method set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not actually recite an order to be followed by its steps or it is not otherwise specifically stated in the claims or descriptions that the steps are to be limited to a specific order, it is in no way intended that an order be inferred, in any
10 respect. This holds for any possible non-express basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, and the number or type of aspects described in the specification.

 All publications mentioned herein are incorporated herein by reference to disclose and
15 describe the methods and/or materials in connection with which the publications are cited. The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided herein can be different from the actual publication dates, which can
20 require independent confirmation.

DEFINITIONS

 As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

 The word "or" as used herein means any one member of a particular list and also includes
25 any combination of members of that list.

 Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps. In particular, in methods stated as comprising one or more steps or operations it is specifically
30 contemplated that each step comprises what is listed (unless that step includes a limiting term such as "consisting of"), meaning that each step is not intended to exclude, for example, other additives, components, integers or steps that are not listed in the step.

 Ranges can be expressed herein as from "about" or "approximately" one particular value, and/or to "about" or "approximately" another particular value. When such a range is expressed, a
35 further aspect includes from the one particular value and/or to the other particular value.

5 Similarly, when values are expressed as approximations, by use of the antecedent "about," or "approximately," it will be understood that the particular value forms a further aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint and independently of the other endpoint. It is also understood that there are a number of values disclosed herein and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then
10 "about 10" is also disclosed. It is also understood that each unit between two particular units is also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

As used herein, the terms "optional" or "optionally" mean that the subsequently described
15 event or circumstance may or may not occur and that the description includes instances where said event or circumstance occurs and instances where it does not.

As used herein, the term "sample" is meant a tissue or organ from a subject; a cell (either within a subject, taken directly from a subject, or a cell maintained in culture or from a cultured cell line); a cell lysate (or lysate fraction) or cell extract; or a solution containing one or more
20 molecules derived from a cell or cellular material (e.g. a polypeptide or nucleic acid), which is assayed as described herein. A sample may also be any body fluid or excretion (for example, but not limited to, blood, urine, stool, saliva, tears, bile) that contains cells or cell components. The term sample can also refer to a "cancer sample" or "sample of the cancer" or the like. The sample can be obtained via biopsy such as needle biopsy, surgical biopsy, etc. A cancer sample
25 includes, for example, a specimen of cancers, parts of a cancer, cancer cells derived from a cancer (including cancer cell lines derived from a cancer and are grown in cell culture) and also the cancer mass as a whole, cell lines, cells and/or tissue derived from a subject that are suspected of being cancerous or suspected of comprising cancerous cells. Thus, it is possible that the cancer sample may also comprise non-cancerous cells.

30 As used herein, the term "subject" refers to the target of administration, e.g., a human. Thus the subject of the disclosed methods can be a vertebrate, such as a mammal, a fish, a bird, a reptile, or an amphibian. The term "subject" also includes domesticated animals (e.g., cats, dogs, etc.), livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), and laboratory animals (e.g., mouse, rabbit, rat, guinea pig, fruit fly, etc.). In one aspect, a subject is a mammal. In another aspect, a
35 subject is a human. The term does not denote a particular age or sex. Thus, adult, child,

5 adolescent and newborn subjects, as well as fetuses, whether male or female, are intended to be covered.

As used herein, the term "patient" refers to a subject afflicted with a disease or disorder. The term "patient" includes human and veterinary subjects. In some aspects of the disclosed methods, the "patient" has been diagnosed with a need for treatment for cancer, such as, for
10 example, prior to the administering step. The term "cancer patient" can refer to a subject having a cancer described herein, including a subject diagnosed to suffer from a cancer, but also includes a subject, for example, during or after therapy.

As used herein, the term "comprising" can include the aspects "consisting of" and "consisting essentially of." "Comprising can also mean "including but not limited to."

15 "Inhibit," "inhibiting" and "inhibition" mean to diminish or decrease an activity, response, condition, disease, or other biological parameter. This can include, but is not limited to, the complete ablation of the activity, response, condition, or disease. This may also include, for example, a 10% inhibition or reduction in the activity, response, condition, or disease as compared to the native or control level. Thus, in an aspect, the inhibition or reduction can be a
20 10, 20, 30, 40, 50, 60, 70, 80, 90, 100%, or any amount of reduction in between as compared to native or control levels. In an aspect, the inhibition or reduction is 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, or 90-100% as compared to native or control levels. In an aspect, the inhibition or reduction is 0-25, 25-50, 50-75, or 75-100% as compared to native or control levels.

"Modulate", "modulating" and "modulation" as used herein mean a change in activity or
25 function or number. The change may be an increase or a decrease, an enhancement or an inhibition of the activity, function or number.

The terms "alter" or "modulate" can be used interchangeable herein referring, for example, to the expression of a nucleotide sequence in a cell means that the level of expression of the nucleotide sequence in a cell after applying a method as described herein is different from
30 its expression in the cell before applying the method.

"Promote," "promotion," and "promoting" refer to an increase in an activity, response, condition, disease, or other biological parameter. This can include but is not limited to the initiation of the activity, response, condition, or disease. This may also include, for example, a 10% increase in the activity, response, condition, or disease as compared to the native or control
35 level. Thus, in an aspect, the increase or promotion can be a 10, 20, 30, 40, 50, 60, 70, 80, 90,

5 100%, or more, or any amount of promotion in between compared to native or control levels. In an aspect, the increase or promotion is 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, or 90-100% as compared to native or control levels. In an aspect, the increase or promotion is 0-25, 25-50, 50-75, or 75-100%, or more, such as 200, 300, 500, or 1000% more as compared to native or control levels. In an aspect, the increase or promotion can be greater than 100 percent
10 as compared to native or control levels, such as 100, 150, 200, 250, 300, 350, 400, 450, 500% or more as compared to the native or control levels.

As used herein, the term “determining” can refer to measuring or ascertaining a quantity or an amount or a change in activity. For example, determining the amount of a disclosed polypeptide in a sample as used herein can refer to the steps that the skilled person would take to
15 measure or ascertain some quantifiable value of the polypeptide in the sample. The art is familiar with the ways to measure an amount of the disclosed polypeptides and disclosed nucleotides in a sample.

As used herein the terms “administration,” “administering,” or the like, when used in the context of providing a pharmaceutical or nutraceutical composition to a subject generally refers
20 to providing to the subject one or more pharmaceutical, “over-the-counter” (OTC) or nutraceutical compositions in combination with an appropriate delivery vehicle by any means such that the administered compound achieves one or more of the intended biological effects for which the compound was administered. By way of non-limiting example, a composition may be administered by parenteral, subcutaneous, intravenous, intracoronary, rectal, intramuscular, intra-
25 peritoneal, transdermal, or buccal routes of delivery. In an aspect, the compositions disclosed herein can be administered by direct injection or local delivery. Alternatively, or concurrently, administration may be by the oral route. The dosage administered will be dependent upon the age, health, weight, and/or disease state of the recipient, kind of concurrent treatment, if any, frequency of treatment, and/or the nature of the effect desired. The dosage of pharmacologically
30 active compound that is administered will be dependent upon multiple factors, such as the age, health, weight, and/or disease state of the recipient, concurrent treatments, if any, the frequency of treatment, and/or the nature and magnitude of the biological effect that is desired.

As used herein, the term “agonist” generally refers to a type of ligand or drug that binds and alters the activity of a receptor.

5 As used herein, the term “antagonist” generally refers to a type of receptor ligand which binds a receptor but which does not alter the activity of the receptor; however when used with an agonist, prevents the binding of the agonist to the receptor hence the effect of the agonist.

 As used herein, the term “allodynia” generally refers to pain from stimuli which are not normally painful. The pain may occur other than in the area stimulated. Allodynia may
10 generally refer to other pain.

 As used herein, the term “antinociception” generally refers to a reduction in pain sensitivity.

 As used herein, terms such as “pharmaceutical composition,” “pharmaceutical formulation,” “pharmaceutical preparation,” or the like, generally refer to formulations that are
15 adapted to deliver a prescribed dosage of one or more pharmacologically active compounds to a cell, a group of cells, an organ or tissue, an animal or a human. Methods of incorporating pharmacologically active compounds into pharmaceutical preparations are widely known in the art. The determination of an appropriate prescribed dosage of a pharmacologically active compound to include in a pharmaceutical composition in order to achieve a desired biological
20 outcome is within the skill level of an ordinary practitioner of the art. A pharmaceutical composition may be provided as sustained-release or timed-release formulations. Such formulations may release a bolus of a compound from the formulation at a desired time, or may ensure a relatively constant amount of the compound present in the dosage is released over a given period of time. Terms such as “sustained release” or “timed release” and the like are
25 widely used in the pharmaceutical arts and are readily understood by a practitioner of ordinary skill in the art. Pharmaceutical preparations may be prepared as solids, semi-solids, gels, hydrogels, liquids, solutions, suspensions, emulsions, aerosols, powders, or combinations thereof. Included in a pharmaceutical preparation may be one or more carriers, preservatives, flavorings, excipients, coatings, stabilizers, binders, solvents and/or auxiliaries that are, typically,
30 pharmacologically inert. It will be readily appreciated by an ordinary practitioner of the art that, pharmaceutical compositions, formulations and preparations may include pharmaceutically acceptable salts of compounds. It will further be appreciated by an ordinary practitioner of the art that the term also encompasses those pharmaceutical compositions that contain an admixture of two or more pharmacologically active compounds, such compounds being administered, for
35 example, as a combination therapy.

5 As used herein the term “pharmaceutically acceptable salts” includes salts prepared from
by reacting pharmaceutically acceptable non-toxic bases or acids, including inorganic or organic
bases, with inorganic or organic acids. Pharmaceutically acceptable salts may include salts
derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous,
lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, etc. Examples
10 include the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from
pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and
tertiary amines, substituted amines including naturally occurring substituted amines, cyclic
amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N’-
dibenzylethylenediamine, diethylamine, 2-dibenzylethylenediamine, 2-diethylaminoethanol, 2-
15 dimethylaminoethanol, emanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine,
glucamine, glucosamine, histidine, hydrabamine, isopropylarnine, lysine, memylglucamine,
morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine,
triethylamine, trimemylamine, tripropylamine, tromethamine, etc. Examples for
pharmaceutically acceptable salts can be acetate, adipate, alginate, citrate, aspartate, benzoate,
20 benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate,
cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate,
hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-
hydroxy-ethane- sulfonate, lactate, maleate, mandelate, methansulfonate, nicotinate, 2-
naphthalene- sulfonate, oxalate, palmate, pectinate, persulfate, 2-phenylpropionate, picrate,
25 pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate, mesylate, and
undecanoate.

 The terms “reducing,” “inhibiting” and “ameliorating,” as used herein, when used in the
context of modulating a pathological or disease state, generally refers to the prevention and/or
reduction of at least a portion of the negative consequences of the disease state. When used in
30 the context of an adverse side effect associated with the administration of a drug to a subject, the
term(s) generally refer to a net reduction in the severity or seriousness of said adverse side
effects.

 As used herein, the term “treat” generally refers to an action taken by a caregiver that
involves substantially inhibiting, slowing or reversing the progression of a disease, disorder or

5 condition, substantially ameliorating clinical symptoms of a disease disorder or condition, or substantially preventing the appearance of clinical symptoms of a disease, disorder or condition.

Terms such as “in need of treatment,” “in need thereof,” “benefit from such treatment,” and the like, when used in the context of a subject being administered a pharmacologically active composition, generally refers to a judgment made by an appropriate healthcare provider that an individual or animal requires or will benefit from a specified treatment or medical intervention. Such judgments may be made based on a variety of factors that are in the realm of expertise of healthcare providers, but include knowledge that the individual or animal is ill, will be ill, or is at risk of becoming ill, as the result of a condition that may be ameliorated or treated with the specified medical intervention.

10 By “therapeutically effective amount” is meant an amount of a drug or pharmaceutical composition that will elicit at least one desired biological or physiological response of a cell, a tissue, a system, animal or human that is being sought by a researcher, veterinarian, physician or other caregiver.

As used herein the term "dermatologically acceptable vehicle" denotes one that can be suitable for topical application to the keratinous tissue. The vehicle can be in a wide variety of forms, including, but not limited to, oil-in-water emulsions, water-in-oil emulsions, water-in-silicone emulsions, silicone -in- water emulsions, water-in-oil -in- water, and oil-in-water-in-oil emulsions, and oil-in-water-in-silicone emulsions. Suitable surfactants include anionic, cationic, amphoteric, zwitterionic and non-ionic, including those listed in U.S. Patent No. 6,197,319. The International Cosmetic Ingredient Dictionary and Handbook (10th Edition, 2004), published by the Cosmetic, Toiletries & Fragrance Association, describes a wide variety of non-limiting cosmetic and dermatopharmaceutical ingredients commonly used in the skin care industry. Examples of these ingredients include: antioxidants, anti-inflammatory agents, anti-acne agents, antimicrobial agents, astringents, humectants, moisturizers, pH adjusters, skin bleaching/lightening agents, skin soothing/healing agents and agents that help decrease the appearance of signs of aging.

As used herein, the term "unit dosage form" refers to a single dosage form containing a quantity of the active ingredient and the diluent or carrier, said quantity being such that one or more predetermined units are normally required for a single therapeutic administration. In the case of multi-dose forms, such as liquid-filled bottles, said predetermined unit will be one

5 fraction such as a half or quarter of the multiple dose form. It will be understood that the specific dose level for any patient will depend upon a variety of factors including the indication being treated, therapeutic agent employed, the activity of therapeutic agent, route of administration severity of the indication, patient health, age, sex, weight, diet, and pharmacological response, the specific dosage form employed and other such factors.

10 Prior to the instant disclosure, it was a common finding that transient receptor potential cation channel subfamily V member 1 (TRPV1) antagonists produced the side-effect of hyperthermia which largely stopped development of these compounds as analgesic drugs. As disclosed herein, by going “up-stream” and inhibiting formation of the endogenous agonists to TRPV1 unexpectedly produces analgesia without production of hyperthermia.

15 **Methods and Compositions**

Mechanistically, injury to skin or mucosa is a type of tissue damage where exposure to noxious stimulus (e.g., physical, chemical, thermal, radiation, microbiological) results in long lasting changes in the exposed tissue (e.g., skin or mucosa). The studies performed in humans and in animals demonstrated that these changes in the damaged tissue are at least in part responsible for the development and maintenance of ongoing pain or hyperalgesia. The injured tissue generates various inflammatory mediators that sensitize ion channels such as transient receptor potential vanilloid 1 or TRPV1 to evoke ongoing pain and hyperalgesia. Other important pain conditions include inflammatory, neuropathic, infection, cancer and the like.

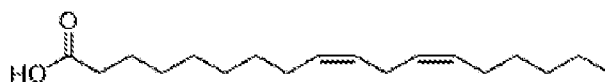
25 TRPV1, also known as the capsaicin receptor, plays a pivotal role in burn injury and other important pain conditions by evoked hyperalgesia and allodynia such that the mice deficient in TRPV1 protein show little to no hyperalgesia in these models. The key role played by TRPV1 in the development of thermal hyperalgesia and possibly mechanical hyperalgesia in various pain models is well established in animal and human studies. Signaling cascades initiated by a variety of inflammatory mediators may sensitize TRPV1 and contribute to inflammatory hyperalgesia. Given the importance of TRPV1 in inflammatory pain, burn pain and cancer pain, including other various pain states, antagonists against TRPV1 may be used for treating pain and/or inflammatory conditions. However, recent studies have demonstrated some serious on-target side effects of TRPV1 antagonists that may exclude their clinical use. These

5 data necessitate additional research in findings ways to block TRPV1 activation without using the antagonists.

A variety of endogenous molecules have been shown to activate TRPV1 and they include but are not limited to anandamide, N-arachidonoyl-dopamine, N-oleoyldopamine, oxidized metabolites of linoleic or arachidonic acid, polyamines etc. Such endogenous TRPV1 ligands
10 may be generated during inflammation and contribute to constitutive activation of TRPV1. Barring a few reports, the role of these endogenous TRPV1 ligands in physiological or pathological pain is not known. Interestingly, TRPV1 may be activated by stimuli such as protons and noxious heat. The mechanism by which heat activates TRPV1 is not completely understood although several hypotheses have been proposed. Heat may generate endogenous
15 TRPV1-stimulating ligands in the heat-exposed tissue and thus initiates noxious pain sensation. In tissues exposed to heat for longer durations, the endogenous TRPV1 ligands may be constitutively synthesized and activate TRPV1 to produce ongoing pain sensation in the absence of heat. A similar pathway may exist for inflammatory or other pain conditions as well.

In some embodiments, heat injury to organs such as skin or mucosa results in generation
20 of oxidized linoleic acid metabolites. These metabolites represent a novel family of endogenous TRPV1 ligands. These ligands activate TRPV1 expressed by sensory nerve terminals in the damaged tissue. The opening of TRPV1 leads to generation of action potentials and the pain sensation in the somatosensory cortex.

In some embodiments, metabolites of linoleic acid have been identified as TRPV1
25 agonists. Linoleic acid is also known by its IUPAC name *cis, cis*-9,12-octadecadienoic acid. Linoleic acid has a structure:



In some embodiments, pharmacological interventions that can block the generation of the endogenous TRPV1 ligand in response to heat may be of therapeutic use. FIG. 5 depicts a
30 summary of activity of linoleic acid metabolites on various TRP channels and ways of interrupting activity of the metabolites on these channels. In addition, the measurement of linoleic acid metabolites may constitute a novel method for diagnosing pain or shock conditions, thereby guiding treatment selection.

5 In some embodiments, oxidized linoleic acid metabolites can be generated upon heat, cancer, bacterial infection in skin or other tissues. Oxidized linoleic acid metabolites include, but are not limited to, oxo linoleic acid metabolites, hydroxyl linoleic acid metabolites, and epoxy linoleic acid metabolites. Examples of oxo linoleic acid metabolites include, but are not limited to (10E,12Z)-9-oxooctadeca-10,12-dienoic acid (9-oxoODE, 9-KODE) and (9Z,11E)-13-oxooctadeca-9,11-dienoic acid (13-oxoODE, 13-KODE). Examples of hydroxyl linoleic acid metabolite include, but are not limited to: 9-hydroxyoctadecadienoic acid (9-HODE); 13-hydroxyoctadecadienoic acid (13-HODE); 9(10)-dihydroxy-octadec-12-enoic acid (9,10-DiHOME); and 12,13-dihydroxy-9Z-octadecenoic acid (12,13-DiHOME). Examples of epoxy linoleic acid metabolites include, but are not limited to: (12Z)-9,10-epoxyoctadecenoic acid (9(10)-EpOME) and 12,13-epoxyoctadec-9Z-enoic acid (12(13)-EpOME). It is believed that oxidized linoleic acid metabolites may function as endogenous TRPV1 agonists.

In some embodiments, the blockade of synthesis or immunoneutralization of oxidized linoleic acid metabolites results in decreased activation of pain sensing neurons *in vitro* and results in thermal and mechanical antinociception *in vivo*. Immunoneutralization of oxidized linoleic acid metabolites may be accomplished by the use of one or more antibodies that bind to at least one oxidized linoleic acid metabolite. Antibodies for oxidized linoleic acids may be formed using the procedure of Spindler et al. (Spindler et al. "Significance and immunoassay of 9- and 13-hydroxyoctadecadienoic acids." *Biochem Biophys Res Commun.* 1996; 218:187-191), which is incorporated herein by reference.

25 TRPV1 is an example of a heat-sensitive channel in the body. In some embodiments, other members of the family, TRPA1, TRPV3 and TRPV4 can be activated by warm temperatures. Therefore, the linoleic acid metabolites were screened against these channels. In some embodiments, 12,13-EpOME and 9,10-DiHOME can be TRPA1, TRPV3 and TRPV4 agonists respectively.

30 In some embodiments, intrathecal application of nordihydroguaiaretic acid (NDGA) or neutralizing antibodies against 9-HODE and 13-HODE may be an effective way to block inflammatory allodynia. Thus compounds such as NDGA and neutralizing antibodies may have two different sites of action in the treatment of thermal and mechanical allodynia. NDGA is a lipoxygenase (LOX) inhibitor and an antioxidant. LOX inhibitors may be administered sufficiently to substantially attenuate the catalytic effect of enzymes such as EC 1.13.11.34 (aka:

5 arachidonate 5-lipoxygenase) in order to treat pain, shock, and/or inflammatory conditions. In some embodiments, LOX inhibitors other than NDGA may be administered.

In some embodiments, a method of treating a pain, shock and/or inflammatory conditions may include administering a cytochrome P-450 (CYP) enzyme inhibitor sufficient to substantially inhibit and/or reduce the catalytic effect of multiple P450 isozymes capable of synthesizing oxidized linoleic acid metabolites (OLAMs). In some embodiments, the CYP inhibitor may be administered intravenously, orally, topically (for burns or wounds), directly into the central nervous system (e.g., epidural), or any other method described herein or that will be known to those skilled in the art.

In some embodiments, a method of treating a pain, shock and/or inflammatory conditions may include administering a cytochrome P-450 (CYP) isoenzyme inhibitor sufficient to substantially inhibit or reduce the catalytic effect of enzyme EC 1.14.14.1 (aka: CYP2C9 and CYP2C19).

Examples of CYP inhibitors include, but are not limited to; ketoconazole, micronazole, fluconazole, benzbromarone, sulfaphenazole, valproic acid, amiodarone, cimetidine, fenofibrate, fluvastatin, lovastatin, fluvoxamine, sertraline, isoniazid, probenecid, sulfamethoxazole, teniposide, voriconazole, and zafirlukast. Voriconazole, for example, is metabolized by cytochrome P450 isozymes, CYP2C9, CYP3A4 and CYP2C19. In some embodiments, the CYP inhibitor may be administered intravenously, orally, topically (for burns, wounds, infections or other pain disorders), directly into the central nervous system (e.g., epidural), or any other method described herein or that will be known to those skilled in the art.

In one embodiment, cytochrome P450 inhibitors that block the formation of linoleic acid metabolites may be used as analgesic drugs. In some embodiments, a method of treating a pain, shock, and/or inflammatory condition may include administering an antioxidant sufficient to substantially inhibit and/or reduce the catalytic effect of relevant metabolic enzymes in the Linoleate pathway. In some embodiments, antioxidant inhibitors of relevant metabolic enzymes in the Linoleate pathway may include Nordihydroguaiaretic acid (NDGA), Vitamin E and/or Vitamin E derivatives (e.g., water soluble Vitamin E derivative). NDGA may function at least in part as a therapeutic agent due to its strong antioxidant characteristics.

Recent research has indicated that activation of TRPV1 by 9-HODE may have other roles in the body depending upon the expression of TRPV1. TRPV1 in the spinal cord may play an

5 important role in maintenance of thermal and mechanical allodynia in inflammatory or other pain conditions. Depolarization of the spinal cord may lead to the release of 9-HODE and activation of TRPV1. 9-HODE in the spinal cord may lead to development of mechanical allodynia. Similar to heated skin, depolarized spinal cord (with high potassium) may release compound(s) that have TRPV1 agonist activity. Depolarized spinal cord superfusate may contain significantly
10 higher amounts of 9-HODE. Moreover, activation of TRPV1 in the spinal cord by capsaicin (positive control) or by 9-HODE results in tactile allodynia that is completely reversible by a TRPV1 antagonist. Thus, in some embodiments, the role of 9-HODE and similar linoleic acid oxidation products extends beyond heat-nociception.

In some embodiments, a method may include treating shock and/or inflammation. The
15 therapy used to treat any one case of shock depends upon the cause of the patient's hypoperfusal disorder, however, a disruption in cellular membrane integrity, leading to the release and oxidation of linoleic acid metabolites from stressed cells, is a process common to many if not most cases of shock. These oxidized linoleic acid metabolites have paracrine and/or endocrine effects that act to worsen the symptoms of shock. A method as described herein may
20 effectively delay the multi-organ failure associated with Refractory (Irreversible) shock. This therapeutic method may be used in many, if not most cases of shock and save many lives.

In some embodiments, given the role of these metabolites in various other diseases (e.g., arthritis, pulmonary edema and shock), similar methods and antibodies may be used in treating these conditions.

25 Any suitable route of administration may be employed for providing a subject with an effective dosage of the compositions (e.g., antibodies, compounds) described herein. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

30 The compositions may include those compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (aerosol inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and
35 prepared by any of the methods well-known in the art of pharmacy.

5 In practical use, compositions may be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, 10 such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations 15 being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

The pharmaceutical preparations may be manufactured in a manner which is itself known 20 to one skilled in the art, for example, by means of conventional mixing, granulating, dragee-making, softgel encapsulation, dissolving, extracting, or lyophilizing processes. Thus, pharmaceutical preparations for oral use may be obtained by combining the compositions with solid and semi-solid excipients and suitable preservatives, and/or co-antioxidants. Optionally, the resulting mixture may be ground and processed. The resulting mixture of granules may be 25 used, after adding suitable auxiliaries, if desired or necessary, to obtain tablets, softgels, lozenges, capsules, or dragee cores.

Suitable excipients may be fillers such as saccharides (e.g., lactose, sucrose, or mannose), sugar alcohols (e.g., mannitol or sorbitol), cellulose preparations and/or calcium phosphates (e.g., tricalcium phosphate or calcium hydrogen phosphate). In addition binders may be used such as 30 starch paste (e.g., maize or corn starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone). Disintegrating agents may be added (e.g., the above-mentioned starches) as well as carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof (e.g., sodium alginate). Auxiliaries are, above all, flow-regulating agents 35 and lubricants (e.g., silica, talc, stearic acid or salts thereof, such as magnesium stearate or

5 calcium stearate, and/or polyethylene glycol, or PEG). Dragee cores are provided with suitable coatings, which, if desired, are resistant to gastric juices. Soft gelatin capsules ("softgels") are provided with suitable coatings, which, typically, contain gelatin and/or suitable edible dye(s). Animal component-free and kosher gelatin capsules may be particularly suitable for the embodiments described herein for wide availability of usage and consumption. For this purpose, 10 concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol (PEG) and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures, including dimethylsulfoxide (DMSO), tetrahydrofuran (THF), acetone, ethanol, or other suitable solvents and co-solvents. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as 15 acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, may be used. Dye stuffs or pigments may be added to the tablets or dragee coatings or soft gelatin capsules, for example, for identification or in order to characterize combinations of active compound doses, or to disguise the capsule contents for usage in clinical or other studies.

In some embodiments, compositions (e.g., antibodies) will typically be formulated in 20 such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml.

For the prevention or treatment of disease, the appropriate dosage of the composition will depend on the type of disease to be treated, as defined above, the severity and course of the disease, whether the compositions are administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the composition, and the 25 discretion of the attending physician. The composition is suitably administered to the patient at one time or over a series of treatments.

Depending on the type and severity of the disease, about 0.015 to 15 mg/kg of composition (e.g., antibodies) is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. For 30 repeated administrations over several days or longer, depending on the condition, the treatment is repeated until a desired suppression of disease symptoms occurs. However, other dosage regimens may be useful.

According to another embodiment of the invention, the effectiveness of the composition in preventing or treating disease may be improved by administering the composition serially or 35 in combination with another agent that is effective for those purposes, such as another antibody

5 directed against a different epitope or neutralizing a different protein than the first composition, or one or more conventional therapeutic agents such as, for example, alkylating agents, folic acid antagonists, anti-metabolites of nucleic acid metabolism, antibiotics, pyrimidine analogs, 5-fluorouracil, purine nucleosides, amines, amino acids, triazol nucleosides, corticosteroids, calcium, retinoids, lipoxygenase and cyclooxygenase inhibitors, fumaric acid and its salts, 10 analgesics, psychopharmaceuticals, local anesthetics, spasmolytics, and beta-blockers. Such other agents may be present in the composition being administered or may be administered separately. The composition may be suitably administered serially or in combination with radiological treatments, whether involving irradiation or administration of radioactive substances.

15 Voriconazole (α R, β S)- α -(2,4-Difluorophenyl)-5-fluoro- β -methyl- α -(1*H*-1,2,4-triazol-1-yl-methyl)-4-pyrimidineethanol) is considered an azole antifungal that works by blocking fungal cell wall growth. It is approved for the treatment of invasive aspergillosis and other fungal infections. As disclosed herein, voriconazole can be useful in the treatment of pain or hyperalgesia. As described herein, voriconazole can be administered to a patient in need thereof 20 to alleviate or reduce pain or hyperalgesia. The compositions disclosed herein can be useful in alleviating or reducing pain or hyperalgesia associated with thermal injury and burns. In an aspect, the compositions disclosed herein can be useful in alleviating or reducing pain or hyperalgesia associated with sunburns, inflammation, infection or mucosal injury. In an aspect, the infection can be a viral infection. In an aspect, the viral infection can be herpes zoster. In an 25 aspect, the mucosal injury can be burning mouth syndrome or vulvodynia. In an aspect, voriconazole can be Vfend[®].

Pharmaceutical Compositions

Disclosed herein, are pharmaceutical compositions. The pharmaceutical compositions 30 can comprise voriconazole and one or more pharmaceutically acceptable carriers. In an aspect, the composition can be in a unit dosage form. In an aspect, the composition comprises 0.3 mg/ml to 3.5 mg/ml of voriconazole. In an aspect, the composition comprises 0.03 to 1% w/w of voriconazole. In an aspect, the composition comprises 0.3 mg/ml, 0.35 mg/ml, 0.4 mg/ml, 0.45 mg/ml, 0.5 mg/ml, 0.55 mg/ml, 0.6 mg/ml, 0.65 mg/ml, 0.7 mg/ml, 0.75 mg/ml, 0.8 mg/ml, 0.85 35 mg/ml, 0.9 mg/ml, 0.95 mg/ml, 1 mg/ml, 1.5 mg/ml, 2 mg/ml, 2.5 mg/ml, 3 mg/ml or 3.5 mg/ml

5 of voriconazole or any concentration in between. In an aspect, the composition can comprises 0.005%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5% or 5% w/w voriconazole or concentration in between. In an aspect, the composition comprises 10 μ M to 1,000 μ M of voriconazole. In an aspect, the composition comprises 10 μ M to 300 μ M of voriconazole. In an
10 aspect, the composition comprises 150 μ M of voriconazole. In an aspect, the composition comprises 10 to 20%, 20 to 30%, 30 to 40%, 40 to 50%, 50 to 60%, 60 to 70%, 70 to 80% or 90 to 100% of 1 mM concentration of voriconazole. In an aspect, the composition can be made with or comprise 0.0001 mg to 1 g voriconazole. The compositions can be formulated for administration by any of a variety of routes of administration, and can include one or more
15 physiologically acceptable excipients, which can vary depending on the route of administration. As used herein, the term “excipient” means any compound or substance, including those that can also be referred to as “carriers” or “diluent.” Preparing pharmaceutical and physiologically acceptable compositions is considered routine in the art, and thus, one of ordinary skill in the art can consult numerous authorities for guidance if needed. In some aspects the pharmaceutical
20 compositions can include a dermatologically acceptable vehicle.

The pharmaceutical compositions as disclosed herein can be prepared for oral or parenteral administration. Pharmaceutical compositions prepared for parenteral administration include those prepared for intravenous (or intra-arterial), intramuscular, subcutaneous, intraperitoneal, transmucosal (e.g., intranasal, intravaginal, or rectal), or transdermal (e.g.,
25 topical) administration. Aerosol inhalation can also be used to deliver the compositions disclosed herein. Thus, compositions can be prepared for parenteral administration that includes components of the compositions disclosed herein, dissolved or suspended in an acceptable carrier, including but not limited to an aqueous carrier, such as water, buffered water, saline, buffered saline (e.g., PBS), and the like. One or more of the excipients included can help
30 approximate physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents, wetting agents, detergents, and the like. Where the compositions include a solid component (as they may for oral administration), one or more of the excipients can act as a binder or filler (e.g., for the formulation of a tablet, a capsule, and the like). Where the compositions are formulated for application to the skin or to a mucosal surface, one or more of

5 the excipients can be a solvent or emulsifier for the formulation of a cream, an ointment, a paste and the like.

The pharmaceutical compositions can be sterile and sterilized by conventional sterilization techniques or sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation, which is encompassed by the present disclosure, can be
10 combined with a sterile aqueous carrier prior to administration. The pH of the pharmaceutical compositions typically will be between 3 and 11 (e.g., between about 5 and 9) or between 6 and 8 (e.g., between about 7 and 8). The resulting compositions in solid form can be packaged in multiple single dose units, each containing a fixed amount of the above-mentioned agent or agents, such as in a sealed package of tablets or capsules. The composition in solid form can
15 also be packaged in a container for a flexible quantity, such as in a squeezable tube designed for a topically applicable cream, paste or ointment.

In an aspect, the pharmaceutical compositions can be formulated for topical administration. In an aspect, the composition can be formulated as a solid dosage form. In an aspect, the composition comprises liposomal beads or is formulated as a gel, ointment, cream,
20 lotion, serum, spray or emulsion. In an aspect, the spray formulation can be a topical spray, a pump spray, a nasal spray or an intra-mouth spray. In an aspect, the composition can be formulated as a transdermal patch. In an aspect, the composition can be formulated for sustained or extended release.

In an aspect, the pharmaceutical composition comprises 10 μM to 300 μM of
25 voriconazole. In an aspect, the pharmaceutical composition comprises 150 μM of voriconazole.

In an aspect, the pharmaceutical composition disclosed herein can comprise voriconazole and one or more pharmaceutically acceptable carriers, wherein the composition can be formulated for topical administration, and wherein the composition can be in a unit dosage form comprising 150 μM of voriconazole. In an aspect, the composition can be formulated for topical
30 administration, wherein the composition can be in a unit dosage form comprising 0.3 mg/ml to 3.5 mg/ml of voriconazole. In an aspect, the composition comprises 0.03 to 1% w/w of voriconazole. In an aspect, the composition can be formulated as a solid dosage form. In an aspect, the composition can comprise liposomal beads or is formulated as a gel, ointment, cream, lotion, serum, spray or emulsion. In an aspect, the composition can be formulated for extended
35 release. In an aspect, the composition can comprise 10 μM to 300 μM of voriconazole.

5 In an aspect, the pharmaceutical composition disclosed herein can comprise voriconazole and one or more pharmaceutically acceptable carriers, wherein the composition comprises liposomal beads or is formulated as a gel, ointment, cream, lotion, serum, spray or emulsion. In an aspect, the composition can be administered topically. In an aspect, the composition can be formulated for topical administration, wherein the composition can be in a unit dosage form
10 comprising 0.3 mg/ml to 3.5 mg/ml of voriconazole. In an aspect, the composition can be formulated as a solid dosage form. In an aspect, the composition can comprise liposomal beads or is formulated as a gel, ointment, cream, lotion, serum, spray or emulsion. In an aspect, the composition can be formulated for extended release. In an aspect, the composition can comprise 10 μ M to 300 μ M of voriconazole. In an aspect, the composition can comprise 150 μ M of
15 voriconazole.

In an aspect, the pharmaceutical compositions described herein can further comprise one or more additional active agents. In an aspect, the composition can further comprise one or more local anesthetics. In an aspect, the local anesthetic can be, for example, but not limited to lidocaine, benzocaine, or articaine. In an aspect, the concentration of lidocaine can be about 1 to
20 2%. In an aspect, the concentration of benzocaine can be about 4 to 20%. In an aspect, the concentration of articaine can be about 2-5%. In an aspect, the concentration of ropivacaine can be about 0.2 to 1%. In an aspect, the composition can be formulated for topical administration. In an aspect, the composition can be formulated for sustained or extended release.

25 **Topical Formulations**

Disclosed herein are formulations comprising one or more of the compositions disclosed herein suitable for topical application to skin or mucosa.

The compositions can be made into a wide variety of product types that are for topical administration or use and include, but are not limited to, solutions, lotions, creams, gels, sticks,
30 sprays, colloids, ointments, cleansing liquid washes, solid bars, pastes, foams, powders, mousses, wipes, patches, wound dressing, adhesive bandages, hydrogels, and films. Make-up, such as foundations, mascaras, and lipsticks also form suitable compositions. These product types may comprise several types of acceptable topical carriers including, but not limited to solutions, emulsions (e.g., microemulsions and nanoemulsions), gels, solids and liposomes. Certain non-
35 limitative examples of such carriers are set forth herein below. Other suitable carriers can be

5 formulated by those of ordinary skill in the art.

Sprays. As used herein, the term "sprays" can refer to "spray-on" formulations. Spray formulations, such as those in pressurized containers or pumps, can contain ingredients of traditional semisolid formulations plus propellants and/or diluents. The propellants and diluents can improve the ease of application of the formulation. A spray formulation for drug delivery
10 can comprise one or more active agents as disclosed herein, a non-volatile solvent system comprising at least one non-volatile solvent, a solidifying agent, and a propellant. The formulation can have an initial viscosity suitable to be expelled out of a pressurized container or manual pump container and applied onto a skin (or mucosa) surface as a layer, and further, the formulation can also be capable of forming a solidified layer on the skin (or mucosa) surface
15 after evaporation of at least a portion of the propellant. In an aspect, a spray formulation for dermal drug delivery can comprise spraying onto a skin surface an adhesive, solidifying formulation. The formulation can comprise a drug, a non-volatile solvent system that can be flux-enabling for the drug, a solidifying agent, and a propellant. The formulation can have an initial viscosity suitable to be expelled out of a pressurized container and applied onto a skin
20 surface as a layer. Additional steps include solidifying the formulation to form a solidified layer on the skin surface by at least partial evaporation of the propellant, and dermally delivering the drug from the solidified layer to the skin surface at a therapeutically effective rate over a sustained period of time.

The phrases "dermal drug delivery" or "dermal delivery of drug(s)" can include both
25 transdermal and topical drug delivery, and includes the delivery of drug(s) to, through, or into the skin. "Transdermal delivery" of drug can be targeted to skin tissues just under the skin, regional tissues or organs under the skin, systemic circulation, and/or the central nervous system.

"Volatile solvent system" refers to a single solvent or combination of solvents that are volatile, including water and solvents that are more volatile than water, but which have a boiling
30 point which is greater than 25° C.

"Non-volatile solvent system" can be a single solvent or mixture of solvents that are less volatile than water. It can also contain substances that are solid or liquid at room temperatures, such as pH or ion-pairing agents. After evaporation of the volatile solvent system, most of the non-volatile solvent system should remain in the solidified layer for an amount of time sufficient
35 to dermally delivery a given drug to, into, or through the skin of a subject at a sufficient flux for

5 a period of time to provide a therapeutic effect. In some aspects, in order to obtain desired permeability for an active drug and/or compatibility with solidifying agents or other ingredients of the formulation, a mixture of two or more non-volatile solvents can be used to form the non-volatile solvent system. In an aspect, the combination of two or more non-volatile solvents to form a solvent system provides a higher transdermal flux for a drug than the flux provided for
10 the drug by each of the non-volatile solvents individually. The non-volatile solvent system may also serve as a plasticizer of the solidified layer, so that the solidified layer is elastic and flexible.

“Adhesive solidifying formulation” or “solidifying formulation,” “sprayable solidifying formulation”, and the like, are used interchangeably and refer to a composition that has a viscosity suitable for application to a skin surface prior to evaporation of its volatile solvent(s),
15 and which can become a solidified layer after evaporation of at least a portion of the volatile solvent(s). The solidified layer, once formed, can be very durable. In an aspect, once solidified on a skin surface, the formulation can form a peel. The peel can be a soft, coherent solid that can be removed by peeling large pieces from the skin relative to the size of the applied formulation, and often, can be peeled from the skin as a single piece. The application viscosity is typically
20 more viscous than a water-like liquid, but less viscous than a soft solid. Examples of preferred viscosities include materials that have consistencies similar to pastes, gels, ointments, and the like, e.g., viscous liquids that flow but are not subject to spilling. Thus, when a composition is said to have a viscosity “suitable for application” to a skin surface, this means the composition has a viscosity that is high enough so that the composition does not substantially run off the skin
25 after being applied to skin, but also has a low enough viscosity so that it can be easily spread onto the skin. A viscosity range that meets this definition can be from about 100 cP to about 3,000,000 cP (centipoises), and more preferably from about 1,000 cP to about 1,000,000 cP.

In some aspects, it may be desirable to add an additional agent or substance to the formulation so as to provide enhanced or increased adhesive characteristics. The additional
30 adhesive agent or substance can be an additional non-volatile solvent or an additional solidifying agent. Non-limiting examples of substances which might be used as additional adhesion enhancing agents include copolymers of methylvinyl ether and maleic anhydride (Gantrez polymers), polyethylene glycol and polyvinyl pyrrolidone, gelatin, low molecular weight polyisobutylene rubber, copolymer of acrylsan alkyl/octylacrylamido (Dermacryl 79), and
35 various aliphatic resins and aromatic resins.

5 *Lotions, Creams, Gels, Ointments.* A lotion can be made from such a solution. Lotions typically comprise from about 1% to about 20% (e.g., from about 5% to about 10%) of an emollient(s) and from about 50% to about 90% (e.g., from about 60% to about 80%) of water.

Another type of product that can be formulated from a solution is a cream. A cream typically comprises from about 5% to about 50% (e.g., from about 10% to about 20%) of an
10 emollient(s) and from about 45% to about 85% (e.g., from about 50% to about 75%) of water.

Another type of product that can be formulated from a solution is an ointment. An ointment can comprise a simple base of animal or vegetable oils or semi-solid hydrocarbons. An ointment can comprise from about 2% to about 10% of an emollient(s) plus from about 0.1% to about 2% of a thickening agent(s). A more complete disclosure of thickening agents or viscosity
15 increasing agents useful herein can be found in Sagarin, *Cosmetics, Science and Technology*, 2nd Edition, Vol. 1, pp. 72-73 (1972) and the ICI Handbook pp. 1693-1697.

Another type of product that can be formulated from a solution is a serum. Generally serums can be thick liquids and are sometimes clear (but not always). Serums can be water-based.

20 Ointments can be a semisolid dosage form that can contain water, volatiles and hydrocarbons, waxes or polyethylene. Examples of ointment bases include but are not limited to hydrocarbon bases (e.g., hard paraffin, paraffin, microcrystalline wax and ceresine); absorption bases (e.g., wool fat, beeswax); water soluble bases (e.g., PEG 200, 300, 400, 600, 4000); and emulsifying bases (e.g., emulsifying wax, vegetables oils including coconut oil, sesame oil, olive
25 oil, almond oil and peanut oil). In some aspects, mixtures of PEG can be used. Preparation of ointments can be carried out by one of ordinary skill in the art including but not limited to the mechanical or trituration method and the fusion method.

Components of an ointment preparation comprising voriconazole can also include one or more water soluble bases (e.g., PEG 200, 300, 400, 600, 4000), methanol or mint oil, propylene glycol, one or more preservatives (e.g., methylparaben, propylparaben); and water q.s. (sufficient
30 water to make 100%). In an aspect, the one or more water soluble bases can be less than 20% w/w. In an aspect, the one or more water soluble bases can be 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70% w/w. In an aspect, the emulsifying base can be 0.2% to less than 2% w/w. In an aspect, the emulsifying base can be 2%, 2.5%, 3% w/w or more. In an aspect, the
35 compositions described herein can include one or more humectants. In an aspect, the humectant

5 can be propylene glycol. In an aspect, the propylene glycol can be less than 20% w/w. In an aspect, the propylene glycol can be 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70% w/w.

The topical compositions can be formulated as emulsions. If the carrier is an emulsion, from about 1% to about 10% (e.g., from about 2% to about 5%) of the carrier comprises an emulsifier(s). Emulsifiers can be nonionic, anionic or cationic. Suitable emulsifiers are disclosed
10 in, for example, in McCutcheon's Detergents and Emulsifiers, North American Edition, pp. 317-324 (1986), and the ICI Handbook, pp. 1673-1686.

Lotions and creams can be formulated as emulsions. Typically such lotions comprise from 0.5% to about 5% of an emulsifier(s). Such creams would typically comprise from about 1% to about 20% (e.g., from about 5% to about 10%) of an emollient(s); from about 20% to
15 about 80% (e.g., from 30% to about 70%) of water; and from about 1% to about 10% (e.g., from about 2% to about 5%) of an emulsifier(s).

Single emulsion preparations, such as lotions and creams, of the oil-in-water type and water-in-oil type are well known in the art. Multiphase emulsion compositions, for example the water-in-oil-in-water type, can also be useful. In general, such single or multiphase emulsions
20 contain water, emollients, and emulsifiers as ingredients.

Topical compositions can also be formulated as a gel (e.g., an aqueous, alcohol, alcohol/water, or oil gel using a suitable gelling agent(s)). Suitable gelling agents for aqueous gels include, but are not limited to, natural gums, acrylic acid and acrylate polymers and copolymers, and cellulose derivatives (e.g., hydroxymethyl cellulose and hydroxypropyl
25 cellulose). Suitable gelling agents for oils (such as mineral oil) include, but are not limited to, hydrogenated butylene/ethylene/styrene copolymer and hydrogenated ethylene/propylene/styrene copolymer. Such gels typically comprise between about 0.1% and 5%, by weight, of such gelling agents.

The topical compositions can also be formulated as a solid formulation.

30 *Liposomal Formulations.* In some aspects, the compositions described herein or components of the compositions described herein can be contained within a liposome. Examples of liposomes are unilamellar, multilamellar, and paucilamellar liposomes, which may or may not contain phospholipids. Such compositions can be prepared by first combining the compositions described herein or components of the compositions described herein with a phospholipid, such
35 as dipalmitoylphosphatidyl choline, cholesterol and water. An example of a method for

5 producing liposomes is described in Mezei & Gulasekharam, "Liposomes—A Selective Drug Delivery System for the Topical Route of Administration; Gel Dosage Form", Journal of Pharmaceutics and Pharmacology, Vol. 34 (1982), pp. 473-474. Those of skill in the art may make suitable modifications of the method described therein.

10 Epidermal lipids of suitable composition for forming liposomes may be substituted for the phospholipid. The liposome preparation can then be incorporated into one of the above carriers (e.g., a gel or an oil-in-water emulsion) in order to produce the liposomal formulation. Other compositions and uses of topically applied liposomes are described in Mezei, M., "Liposomes as a Skin Drug Delivery System", Topics in Pharmaceutical Sciences (D. Breimer and P. Speiser, eds.), Elsevier Science Publishers B. V., New York, N.Y., 1985, pp. 345-358, 15 PCT Patent Application No. WO96/31194, Niemiec, et al., 12 Pharm. Res. 1184-88 (1995), and U.S. Pat. No. 5,260,065.

In some aspects, the liposome can be nonionic. In one example, the liposome contains (a) glycerol dilaurate; (b) compounds having the steroid backbone found in cholesterol; and (c) fatty acid ethers having from about 12 to about 18 carbon atoms. In some aspects, the liposome 20 comprises glycerol dilaurate, cholesterol, polyoxyethylene-10-stearyl ether, and polyoxyethylene-9-lauryl ether. In some aspects, these ingredients are in a ratio of about 38:12:33:17.

The liposomes can be present in the topical composition in an amount, based upon the total volume of the composition, of from about 5 mg/ml to about 100 mg/ml such as from about 25 10 mg/ml to about 50 mg/ml.

Other Agents in the Formulations. The topical compositions disclosed herein can contain, in addition to the aforementioned components, a wide variety of additional oil-soluble materials and/or water-soluble materials.

30 Examples of humectants include glycerol, sorbitol, propylene glycol, ethylene glycol, 1,3-butylene glycol, polypropylene glycol, xylitol, malitol, lactitol, allantoin, acetamine MEA, oat protein, hyaluronic acid, and the like. They can be used either singly or in combination. Preservatives can also be included in the compositions. Preservatives are useful for substantially preventing microbial decomposition. Examples of preservatives include phenoxyethanol and parabens such as methyl-paraben, ethyl-paraben, and propyl-paraben; salicylic acid, 35 chlorhexidine hydrochloride, phenoxyethanol, sodium benzoate, methyl para-hydroxybenzoate,

5 ethyl para-hydroxybenzoate, propyl para-hydroxybenzoate, butyl para-hydroxybenzoate, isothiazolones and the like. Other examples of preservatives are listed on pages 1654-55 of the International Cosmetic Ingredient Dictionary and Handbook, eds. Wenninger and McEwen (CTFA, 7th ed., 1997), hereinafter referred to as the "Cosmetic Handbook." The composition can
10 5%, by weight) of preservative. Microbial contamination can also be eliminated by gamma irradiation or microfiltration, or by brief heat treatments that do not result in the elimination of protease inhibitory activity.

Examples of surface active agents include sodium alkyl sulfates, e.g., sodium lauryl sulfate and sodium myristyl sulfate, sodium N-acyl sarcosinates, e.g., sodium N-lauroyl
15 sarcosinate and sodium N-myristoyl sarcosinate, sodium dodecylbenzenesulfonate, sodium hydrogenated coconut fatty acid monoglyceride sulfate, sodium lauryl sulfoacetate and N-acyl glutamates, e.g., N-palmitoyl glutamate, N-methylacyltaurin sodium salt, N-methylacylalanine sodium salt, sodium α -olefin sulfonate and sodium dioctylsulfosuccinate; N-alkylaminoglycerols, e.g., N-lauryldiaminoethylglycerol and N-myristyldiaminoethylglycerol, N-
20 alkyl-N-carboxymethylammonium betaine and sodium 2-alkyl-1-hydroxyethylimidazoline betaine; polyoxyethylenealkyl ether, polyoxyethylenealkylaryl ether, polyoxyethylenelanolin alcohol, polyoxyethyleneglyceryl monoaliphatic acid ester, polyoxyethylenesorbitol aliphatic acid ester, polyoxyethylene aliphatic acid ester, higher aliphatic acid glycerol ester, sorbitan aliphatic acid ester, Pluronic™ type surface active agent, and polyoxyethylenesorbitan aliphatic
25 acid esters such as polyoxyethylenesorbitan monooleate and polyoxyethylenesorbitan monolaurate.

Examples of the binder or thickener include cellulose derivatives such as alkali metal salts of carboxymethylcellulose, methyl cellulose, hydroxyethyl cellulose and sodium
30 carboxymethylhydroxyethyl cellulose, alkali metal alginates such as sodium alginate, propylene glycol alginate, gums such as carrageenan, xanthan gum, tragacanth gum, caraya gum and gum arabic, and synthetic binders such as polyvinyl alcohol, polysodium acrylate and polyvinyl pyrrolidone. Thickening agents that can be added to the compositions to alter viscosity include other polymers such as polyacrylates (e.g., polyacrylamide). Other examples of viscosity
35 modifying agents are listed on pages 1692-97 of the Cosmetic Handbook. To achieve the appropriate viscosity, compositions of the present invention may comprise from about 0.01% to

5 about 20%, by weight (e.g., from about 0.1% to about 5%, by weight) of a thickening agent. Coloring agents and fragrances can also be included in the compositions disclosed herein. In some aspects, the compositions further comprise a second active agent in addition to voriconazole. An "active agent" is a compound (e.g., a synthetic compound or a compound
10 isolated from a natural source or a natural extract) that has a therapeutic effect on the skin, including, but not limiting to, anti-microbial agents, anti-inflammatory agents, anti-mycotic agents, anti-parasite agents, external analgesics, sunscreens, photoprotectors, antioxidants, keratolytic agents, detergents/surfactants, moisturizers, nutrients, vitamins, energy enhancers, astringents, deodorants, firming agents, anti-callous agents, and agents for skin conditioning. The compositions disclosed herein can be applied prior to, concurrently with or after other active
15 ingredients or compositions to enhance their effect.

Antioxidants and/or chelating agents can be used to increase shelf life and stability of the disclosed compositions. Antioxidants can be added both for formulation stabilization and for biological efficacy. Antioxidant compounds and their derivatives include, but are not limited to, water-soluble antioxidants such as sulfhydryl compounds and their derivatives (e.g., sodium
20 metabisulfite and N-acetyl-cysteine), lipoic acid and dihydrolipoic acid, resveratrol, acetyl-cysteine (Iniferine®) or lactoferrin, and ascorbic acid and ascorbic acid derivatives (e.g., ascorbyl palmitate and ascorbyl polypeptide). Oil-soluble antioxidants suitable for use in the compositions include, but are not limited to, butylated hydroxytoluene, retinoids (e.g., retinol and retinyl palmitate), tocopherols (e.g., tocopherol acetate), tocotrienols, and ubiquinone. Natural
25 extracts containing antioxidants suitable for use in the disclosed compositions, include, but not limited to, extracts containing flavonoids and isoflavonoids and their derivatives (e.g., genistein and diadzein), extracts containing resveratrol and the like. Examples of such natural extracts include grape seed, green tea, pine bark, propolis, and legume extracts. Other examples of antioxidants can be found on pages 1612-13 of the Cosmetic Handbook. The compositions
30 disclosed herein can comprise the antioxidant in an amount of from about 0.001% to about 20%, by weight (e.g., from about 0.01% to about 10% by weight) of the composition.

In an aspect, at least one oil-soluble antioxidant can be in the disclosed compositions. The antioxidants can be utilized in a stabilizing effective amount and may range in total from about 0.001 to 10% based on the weight of the total composition, preferably from about 0.005 to
35 about 5%. The oil-soluble antioxidants which are useful in the compositions include butylated

5 hydroxytoluene (BHT), ascorbyl palmitate, butylated hydroxyanisole (BHA), phenyl- α -naphthylamine, hydroquinone, propyl gallate, nordihydroguaiaretic acid, and mixtures thereof as well as any other known oil-soluble antioxidant compatible with the other components of the disclosed compositions.

10 A water-soluble antioxidant can be present in the water phase of the compositions described herein. The water-soluble antioxidants can include ascorbic acid, sodium metabisulfite, sodium bisulfite, sodium thiosulfite, sodium formaldehyde sulfoxylate, isoascorbic acid, thioglycerol, thiosorbitol, thiourea, thioglycolic acid, cysteine hydrochloride, 1,4-diazobicyclo-(2,2,2)-octane and mixtures thereof as well as any other known water-soluble antioxidant compatible with the other components of the disclosed compositions.

15 Chelating agents can also be useful in assisting the stabilization of the disclosed compositions. Examples of chelating agents include EDTA and derivatives thereof (e.g., disodium EDTA and dipotassium EDTA), Iniferine®, lactoferrin, and citric acid. The disclosed compositions can comprise the chelating agent in an amount of from about 0.001% to about 20%, by weight (e.g., from about 0.01% to about 10% by weight) of the composition.

20 Various irritancy mitigants can be added to the disclosed compositions. Irritancy mitigants such as α -bisabolol, panthenol, allantoin, ginkgo biloba, stearyl glycerethinic acid (licorice extract), tea tree oil, butchers' broom, calendula, ginseng and the like can be added. Other ingredients can include agents that assist in protecting the skin from aging, such as sunscreens, anti-oxidant vitamins such as ascorbic acid, vitamin B, biotin, pantothenic acid, 25 vitamin D, vitamin E and vitamin C, and sodium bisulfite. Yeast extract, ginkgo biloba, bisabolol, panthenol, alpha hydroxy acids and oligosaccharides such as melibiose are among other ingredients which assist in preventing aging of the skin by such means as irritation mitigation, oxidation mitigation, healing, affecting retinoid metabolism and inhibiting the production of elastase.

30 The disclosed compositions can also contain compounds that enhance the feel of the composition on the skin of the user. Examples of such compounds include, but are not limited to, oils, silicones (e.g., siloxane polymers such as dimethicone) and skin-conditioning agents such as emollients, and humectants.

Anti-inflammatory agents can also be used in the compositions disclosed herein.
35 Examples of steroidal anti-inflammatory agents, include but are not limited to, corticosteroids

5 such as hydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, beclomethasone dipropionate, clobetasol valerate, desonide, desoxycorticosterone acetate, dexamethasone, dichlorisone, deflorasonediacetate, diflucortolone valerate, fluadronolone, fluclarolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocionide, fluocortine butylester, fluocortolone, flupredidene (flupredylidene) acetate, 10 flurandronolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenalone acetonide, medrysone, amciafel, amcinafide, betamethasone and its esters, chlorprednisone acetate, clocortelone, clescinalone, dichlorisone, difluprednate, flucoronide, flunisolid, fluoromethalone, fluperolone, 15 fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortamate, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone and mixtures thereof may be used. Hydrocortisone or natural extracts with similar activity can be used.

Nonsteroidal anti-inflammatory agents can also be employed in the disclosed 20 compositions, such as salicylates, acetic acid derivatives, fenamates, propionic acid derivatives and pyrazoles or mixtures thereof. Other synthetic and natural anti-inflammatory agents can also be used.

It can be readily appreciated that a transdermal route of administration can be enhanced by use of a dermal penetration enhancer, e.g., such as enhancers described in U.S. Pat. No. 25 5,164,189, U.S. Pat. No. 5,008,110, and U.S. Pat. No. 4,879,119, issued Nov. 7, 1989 to Aruga et al. In some aspects, the disclosed compositions can be delivered in a controlled release system, such as using a transdermal patch, liposomes, or other modes of administration. In some aspects, polymeric materials can be used [see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Press: Boca Raton, Fla. (1974); Controlled Drug Bioavailability, Drug Product 30 Design and Performance, Smolen and Ball (eds.), Wiley: New York (1984); Ranger and Peppas, J. Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J. Neurosurg. 71:105 (1989)].

The concentration or amount of the voriconazole used to prepare or be present in any of the formulations described herein can vary.

35 In an aspect, voriconazole can be less than 5% w/w. In an aspect, voriconazole can be

5 more than 5% w/w. In an aspect, voriconazole can be between 3% and 5% w/w. In an aspect, voriconazole can be between 5% and 10% w/w. In an aspect, the composition can comprise about 0.03% w/w to 1% w/w of voriconazole. In an aspect, voriconazole can be 0.03% to 3% w/w. In an aspect, the concentration of voriconazole can range between 0.03% to 5% w/w.

In an aspect, for oral formulations, the concentration of voriconazole can be about 1 mM.

10 In an aspect, the concentration of voriconazole can be about 0.5 mM to 1 mM.

In an aspect, for topical solutions, the concentration of voriconazole can be 0.3 mg/ml, 0.35 mg/ml, 0.4 mg/ml, 0.45 mg/ml, 0.5 mg/ml, 0.55 mg/ml, 0.6 mg/ml, 0.65 mg/ml, 0.7 mg/ml, 0.75 mg/ml, 0.8 mg/ml, 0.85 mg/ml, 0.9 mg/ml, 0.95 mg/ml, 1 mg/ml, 1.5 mg/ml, 2 mg/ml, 2.5 mg/ml, 3 mg/ml or 3.5 mg/ml of voriconazole or any concentration in between. In an aspect, the
15 concentration of voriconazole can be about 0.05 mM to 1 mM. In an aspect, the concentration of voriconazole can be about 0.5 mM to 1 mM.

In an aspect, the concentration of voriconazole for a transdermal delivery can be between 0.03% and 5% w/w. In an aspect, the concentration of voriconazole for a transdermal delivery can be 5% w/w. In an aspect, the concentration of voriconazole for direct application to a wound
20 or injury or as applied to any of the methods disclosed herein can be between 0.03% and 5% w/w. In an aspect, the concentration of voriconazole for direct application to a wound or injury or as applied to any of the methods disclosed herein can be about 0.03%.

In an aspect, for intra-mouth spray formulations, the concentration of voriconazole can be 0.3 mg/ml, 0.35 mg/ml, 0.4 mg/ml, 0.45 mg/ml, 0.5 mg/ml, 0.55 mg/ml, 0.6 mg/ml, 0.65 mg/ml,
25 0.7 mg/ml, 0.75 mg/ml, 0.8 mg/ml, 0.85 mg/ml, 0.9 mg/ml, 0.95 mg/ml, 1 mg/ml, 1.5 mg/ml, 2 mg/ml, 2.5 mg/ml, 3 mg/ml or 3.5 mg/ml of voriconazole or any concentration in between.

In an aspect, for intranasal spray formulations, the concentration of voriconazole can be 0.3 mg/ml, 0.35 mg/ml, 0.4 mg/ml, 0.45 mg/ml, 0.5 mg/ml, 0.55 mg/ml, 0.6 mg/ml, 0.65 mg/ml, 0.7 mg/ml, 0.75 mg/ml, 0.8 mg/ml, 0.85 mg/ml, 0.9 mg/ml, 0.95 mg/ml, 1 mg/ml, 1.5 mg/ml, 2
30 mg/ml, 2.5 mg/ml, 3 mg/ml or 3.5 mg/ml of voriconazole or any concentration in between.

In an aspect, for any of the spray formulations disclosed herein, the concentration of voriconazole can be about 0.01 mM to 1 mM. In an aspect, the concentration of voriconazole can be about 0.1 mM to 1 mM.

In an aspect, for gel formulations, the concentration of voriconazole can be 0.3 mg/ml,
35 0.35 mg/ml, 0.4 mg/ml, 0.45 mg/ml, 0.5 mg/ml, 0.55 mg/ml, 0.6 mg/ml, 0.65 mg/ml, 0.7 mg/ml,

5 0.75 mg/ml, 0.8 mg/ml, 0.85 mg/ml, 0.9 mg/ml, 0.95 mg/ml, 1 mg/ml, 1.5 mg/ml, 2 mg/ml, 2.5 mg/ml, 3 mg/ml or 3.5 mg/ml of voriconazole or any concentration in between. In an aspect, the concentration of voriconazole can be about 0.05 mM to 1 mM. In an aspect, the concentration of voriconazole can be about 0.5 mM to 1 mM.

10 In an aspect, for ointment formulations, the concentration of voriconazole can be 0.3 mg/ml, 0.35 mg/ml, 0.4 mg/ml, 0.45 mg/ml, 0.5 mg/ml, 0.55 mg/ml, 0.6 mg/ml, 0.65 mg/ml, 0.7 mg/ml, 0.75 mg/ml, 0.8 mg/ml, 0.85 mg/ml, 0.9 mg/ml, 0.95 mg/ml, 1 mg/ml, 1.5 mg/ml, 2 mg/ml, 2.5 mg/ml, 3 mg/ml or 3.5 mg/ml of voriconazole or any concentration in between. In an aspect, the concentration of voriconazole can be about 0.01 mM to 1 mM. In an aspect, the concentration of voriconazole can be about 0.1 mM to 1 mM.

15 **Methods of Treatment**

Disclosed herein, are methods of treating a patient with pain. The method comprising: (a) identifying a patient in need of treatment; and (b) administering to the patient a therapeutically effective amount of the pharmaceutical composition described herein, and a pharmaceutically acceptable carrier.

Disclosed herein, are methods of treating a patient with hyperalgesia. The method comprising: (a) identifying a patient in need of treatment; and (b) administering to the patient a therapeutically effective amount of the pharmaceutical composition described herein, and a pharmaceutically acceptable carrier.

25 Disclosed herein are methods of alleviating pain or hyperalgesia in a patient in need thereof. The method can comprise topically administering to the patient, a therapeutically effective amount of voriconazole and one or more pharmaceutically acceptable carriers. In an aspect, the method can comprise the administration of any of the compositions disclosed herein.

In an aspect, the patient can be diagnosed with pain or hyperalgesia prior to the administering step.

30 In an aspect, the compositions disclosed herein can be administered on an as-needed basis. In an aspect, any of the compositions disclosed herein can be used to in any of the methods disclosed herein. In an aspect, any of the compositions disclosed herein can be administered 1, 2, 3 or 4 or more times a day. In an aspect, the compositions disclosed herein can be administered topically 1, 2, 3, 4 or more times a day. In an aspect, the total daily dose of

voriconazole can range from 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 mg or more or any value in between. In an aspect, the total daily dose of voriconazole administered topically can range from 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 mg or more or any value in between. In an aspect, the total daily dose of voriconazole can be about 100 mg.

In an aspect, the pain or hyperalgesia can be associated with pain in the skin or mucosa. In an aspect, the pain or hyperalgesia can be associated with injury, infection, thermal injury, radiation, cancer or other causes. In an aspect, pain or hyperalgesia can be associated with sunburns, inflammation, viral infection or mucosal injury. In an aspect, the viral infection can be herpes zoster. In an aspect, the mucosal injury can be burning mouth syndrome or vulvodynia. As disclosed herein, injury can be to skin or mucosa. Further, injury to the skin or mucosa can be a type of tissue damage where exposure to noxious stimulus (e.g., physical, chemical, thermal, radiation, microbiological) results in long lasting changes in the exposed tissue (e.g., skin or mucosa).

In an aspect, the administration of any of compositions described herein can reduce one or more of the symptoms of any of the diseases, disorders or conditions disclosed herein. In an aspect, the administration of any of compositions described herein can reduce one or more of the symptoms of pain or hyperalgesia. In an aspect, the one or more of the symptoms can be reduced for a period of at least 15 minutes to about 30 minutes. In an aspect, the one or more of the symptoms can be reduced for a period of at least 1 hour. In an aspect, the one or more of the symptoms can be reduced for a period of at least three hours.

In an aspect, the methods described herein can further comprise administering a second active agent. In an aspect, the method further comprises administering one or more local anesthetics. In an aspect, the local anesthetic can be lidocaine, benzocaine or articaine. In an aspect, the method can comprise administering voriconazole and one or more local anesthetics simultaneously as single dosage unit. In an aspect, the method can comprise administering voriconazole and one or more local anesthetics as separate compositions simultaneously or sequentially. In an aspect, the single dosage unit can be formulated for topical administration.

The pharmaceutical compositions described above can be formulated to include a therapeutically effective amount of voriconazole. Therapeutic administration encompasses prophylactic applications. Based on genetic testing and other prognostic methods, a physician in

5 consultation with their patient can choose a prophylactic administration where the patient has a clinically determined predisposition or increased susceptibility (in some cases, a greatly increased susceptibility) to pain or hyperalgesia.

In an aspect, the methods disclosed herein can be used to treat or prevent pain or hyperalgesia associated with dermal tissue, subdermal tissue, muscosal membranes or any
10 combination thereof.

The pharmaceutical compositions described herein can be administered to the subject (e.g., a human patient) in an amount sufficient to delay, reduce, or preferably prevent the onset of pain or hyperalgesia. Accordingly, in some aspects, the patient can be a human patient. In therapeutic applications, compositions can be administered to a subject (e.g., a human patient)
15 already with or diagnosed with pain or hyperalgesia in an amount sufficient to at least partially improve a sign or symptom or to inhibit the progression of (and preferably arrest) the symptoms of the condition, its complications, and consequences. An amount adequate to accomplish this is defined as a "therapeutically effective amount." A therapeutically effective amount of a pharmaceutical composition can be an amount that achieves a cure, but that outcome is only one
20 among several that can be achieved. As noted, a therapeutically effective amount includes amounts that provide a treatment in which the onset or progression of the pain or hyperalgesia is delayed, hindered, or prevented, or the pain or a symptom of the pain or hyperalgesia is ameliorated. One or more of the symptoms can be less severe. Recovery can be accelerated in an individual who has been treated.

25 In some aspects, the pain or hyperalgesia can be associated with a burn or thermal injury. In other aspects, the pain or hyperalgesia can be within the patient's skin.

In some aspects, the pain or hyperalgesia can be within the patient's mucosa. Mucosa is a membrane that lines various cavities of the body and covers the surface of internal organs. It can be continuous with the skin. Examples of mucosa continuous with the skin at various body
30 openings, include but are not limited to eyes, ears, inside the nose, inside the mouth, lip, the urethral opening and the anus. Additional examples of mucosa include but are not limited to bronchial mucosa and the lining of vocal folds; endometrium (mucosa of the uterus); esophageal mucosa; gastric mucosa; intestinal mucosa; nasal mucosa; olfactory mucosa; oral mucosa; penile mucosa; vaginal mucosa; frenulum of tongue; tongue; and anal canal.

35 Disclosed herein, are methods of treating a patient having pain. The pain can be from

5 any cause. In some aspects, the pain is due to burns or a thermal injury.

Amounts effective for the uses described herein can depend on the severity of the pain or hyperalgesia and the weight and general state and health of the subject, but generally range from about 0.3 mg/ml to about 3.5 mg/ml of an equivalent amount of voriconazole per dose per subject. Suitable regimes for initial administration and booster administrations are typified by an
10 initial administration followed by repeated doses at one or more hourly, daily, weekly, or monthly intervals by a subsequent administration. For example, a subject can receive the composition disclosed herein one or more times per minute, hour, day or week, (e.g., 2, 3, 4, 5, 6, or 7 or more times per week).

The therapeutically effective amount of one or more of the therapeutic agents present
15 within the compositions described herein and used in the methods as disclosed herein applied to mammals (e.g., humans) can be determined by one of ordinary skill in the art with consideration of individual differences in age, weight, and other general conditions (as mentioned above).

In an aspect, voriconazole can be applied topically to at least one skin graft site.

In an aspect, the subject has a burn wound or thermal injury. In aspect, the subject has
20 sustained a burn wound or burn injury of less than 30% of their total body surface area or has a traumatic wound requiring a skin graft.

Methods of Measuring Pain

Pain can be measured by any known method of measuring pain. For example, pain levels
25 can be reported by a patient using the Four Point Category Pain Scale at specific time points over 72 hours. This value can be compared, for instance, to a pre-operative baseline pain report. For example, a pre-operative measurement can be taken and compared to pain levels recorded over 72 hours post-skin graft procedure (e.g., 1, 3, 6, 9, 12, 24, 36, 48, 60 and 72 hours).

Subjects can complete a pre-operative pain assessment tool (e.g., Four Point Category
30 Pain Scale consisting of 0-3 numeric with corresponding adjectives), then complete the same instrument at 1, 3, 6, 9, 12, 24, 36, 48, 60 and 72 hours post-procedure.

Pain levels can also be reported by the patient using the Heft-Parker Pain Scale at specific time points over 72 hours. This value can be compared to pre-operative baseline pain report. For example, a pre-operative measurement can be taken and compared to pain levels recorded over
35 72 hours post-skin graft (1, 3, 6, 9, 12, 24, 36, 48, 60 and 72 hours).

5 Subjects can also complete a pre-operative pain assessment tool (e.g., Heft-Parker Pain Scale - 170mm), then complete the same instrument at 1, 3, 6, 9, 12, 24, 36,48, 60 and 72 hours post-procedure.

 Pain levels can also be reported by the patient using the Visual Analog Pain Scale at specific time points over 72 hours. This value can be compared to pre-operative baseline pain
10 report. For example, a pre-operative measurement can be taken and compared to pain levels recorded over 72 hours post-skin graft (e.g., 1, 3, 6, 9, 12, 24, 36,48, 60 and 72 hours).

 Subjects can also complete a pre-operative pain assessment tool (e.g., Visual Analog Pain Scale - 100mm), then complete the same instrument at 1, 3, 6, 9, 12, 24, 36,48, 60 and 72 hours post-procedure.

15 Cutaneous dialysate levels can be collected over time to measure and compare baseline vs. time point oxidized linoleic acid metabolites (OLAMs) levels. This value can be compared to pre-operative baseline cutaneous dialysate levels. For example, a pre-operative measurement can be taken and compared to post-operative measurements recorded over 72 hours post-skin graft (e.g., 1, 3, 6, 9, 12, 24, 36,48, 60 and 72 hours).

20 Microdialysates can also be collected from a CMA-70 probe and CMA-106 pump at 1, 2, 3, 6, 9,12, 24, 36, 48,60, and 72 hours post drug administration (e.g., voriconazole; +/- 20 minutes per time interval). The time point dialysates levels can be analyzed and compared to baseline.

 Additional outcome measures include but are not limited to measuring and comparing
25 skin graft donor site wounds for cosmetic healing using photographs at post-operative visits. For example, a post-operative visit can be between 30-45 days post-procedure. Digital photographs of the wounds can be taken at the post-opertive visit between 30-45 days after the skin graft procedure to assess the cosmetic appearance of the two wound sites.

 Dialysates can be collected before and/or after topical administration of the compositions
30 disclosed herein. Dialysates can be collected at the site of at least one skin graft site. In an aspect, dialysates can be collected over, for example, 12 hours post-skin graft and/or sterile water application for analysis of OLAM concentrations.

Articles of Manufacture

The compositions described herein can be packaged in a suitable container labeled, for example, for use as a therapy to treat or prevent pain or analgesia. Accordingly, packaged products (e.g., sterile containers containing the composition described herein and packaged for storage, shipment, or sale at concentrated or ready-to-use concentrations) and kits, including at least voriconazole as described herein and instructions for use, are also within the scope of the disclosure. A product can include a container (e.g., a vial, jar, bottle, bag, or the like) containing the composition described herein. In addition, an article of manufacture further may include, for example, packaging materials, instructions for use, syringes, buffers or other control reagents for treating or monitoring the condition for which prophylaxis or treatment is required. The product may also include a legend (e.g., a printed label or insert or other medium describing the product's use (e.g., an audio- or videotape)). The legend can be associated with the container (e.g., affixed to the container) and can describe the manner in which the compound therein should be administered (e.g., the frequency and route of administration), indications therefor, and other uses. The compositions can be ready for administration (e.g., present in dose-appropriate units), and may include a pharmaceutically acceptable adjuvant, carrier or other diluent. Alternatively, the compositions can be provided in a concentrated form with a diluent and instructions for dilution.

EXAMPLES

Example 1: Voriconazole Inhibits Linoleic Acid-Induced Activation of Capsaicin-Sensitive Neurons.

Mouse trigeminal ganglion neurons were cultured for 24h. Since TRPV1 is a cation channel, monitoring intracellular calcium (Ca^{2+}) levels provides a method to determine activation. Neurons were incubated with the calcium-sensing dye, Fura 2AM. The net changes in Ca^{+2} influx were calculated by subtracting the basal $[\text{Ca}^{+2}]_i$ (mean value collected for 60 s prior to the experiment) from the peak $[\text{Ca}^{+2}]_i$ value achieved after exposure to the test compounds. Ca^{2+} influxes above 50 nM were considered positive. This minimal threshold criterion was established by application of 0.1% DMSO as a vehicle. Ratiometric data were converted to $[\text{Ca}^{+2}]_i$ (in μM) by using the equation $[\text{Ca}^{+2}]_i = K^* (R - R_{\min}) / (R_{\max} - R)$, where R is the 340/380 nm fluorescence ratio.

5 Neurons were pretreated with either vehicle (calcium buffer) or 30 μ M, 100 μ M, or 300 μ M voriconazole for 15 min followed by addition of 100 nM linoleic acid with measurement of fluorescence at 340 nm and 380 nm. FIG. 1 shows that linoleic acid significantly increased calcium in capsaicin-sensitive neurons and this was blocked by increasing concentrations of voriconazole. At the end of the experiment, capsaicin 100 nM was added and neurons that were capsaicin sensitive were used in the analysis. Data were analyzed by one-way ANOVA. * $p < 0.05$ *** $p < 0.0001$.

FIG. 1 is significant as it demonstrates that voriconazole unexpectedly reduces linoleic acid-induced activation of a major class of pain neurons – the capsaicin-sensitive neurons.

15 **Example 2: Voriconazole Blocks Inflammatory Pain.**

Thermal baselines (plantar or Hargreaves test) were taken the day prior to complete Freund's adjuvant (CFA) injection in male rats. CFA intraplantar injection was given at 6:30 AM. Thermal testing was performed and recorded 3 hours after CFA injection. Vehicle or drug (voriconazole, 300 μ g/50 μ l was injected intraplantar and tested by blinded observers. Thermal testing was performed and recorded at 30, 60, 90, 120, 150 and 180 minutes after injection of drug. The results show that voriconazole significantly increases paw withdrawal latency compared to vehicle (FIG. 2; 2-way ANOVA. ** $p < 0.01$ *** $p < 0.001$).

FIG. 2 is significant because it shows that local injection of voriconazole into inflamed tissues blocks inflammatory pain.

25 **Example 3: Voriconazole Dose-Dependently Produces Analgesia in Inflammatory Pain.**

Thermal baselines (plantar or Hargreaves test) were taken the day prior to complete Freund's adjuvant (CFA) injection in male rats. CFA and voriconazole were administered by intraplantar injection into the hindpaw skin by blinded observers. Thermal testing was performed and recorded 3 hours after CFA injection. FIG. 3 shows that voriconazole increases paw withdrawal latency compared to vehicle.

FIG. 3 is significant as it demonstrates that increased doses of voriconazole produces increased magnitude of analgesia for inflammatory pain.

Example 4: Voriconazole Does Not Produce Hyperthermia, Whereas the TRPV1 Antagonist, Capsazepine Does.

Baseline rectal temperatures were taken in male rats by a blinded observer. Animals were then injected i.p. with either vehicle, voriconazole (100 mg/kg) or the TRPV1 antagonist, capsazepine, (5 mg/kg) and temperatures were recorded at 30, 60, 90, and 120 minutes after injection of drug. FIG. 4 shows that voriconazole does not produce hyperthermia. Two-way ANOVA, ** $p < 0.01$ *** $p < 0.001$.

FIG. 4 is significant because it demonstrates that a TRPV1 antagonist, capsazepine, produces hyperthermia, whereas voriconazole does not.

In this patent, certain U.S. patents, U.S. patent applications, and other materials (e.g., articles) may have been incorporated by reference. The text of such U.S. patents, U.S. patent applications, and other materials is, however, only incorporated by reference to the extent that no conflict exists between such text and the other statements and drawings set forth herein. In the event of such conflict, then any such conflicting text in such incorporated by reference U.S. patents, U.S. patent applications, and other materials is specifically not incorporated by reference in this patent.

Further modifications and alternative embodiments of various aspects of the invention will be apparent to those skilled in the art in view of this description. Accordingly, this description is to be construed as illustrative only and is for the purpose of teaching those skilled in the art the general manner of carrying out the invention. It is to be understood that the forms of the invention shown and described herein are to be taken as examples of embodiments. Elements and materials may be substituted for those illustrated and described herein, parts and processes may be reversed, and certain features of the invention may be utilized independently, all as would be apparent to one skilled in the art after having the benefit of this description of the invention. Changes may be made in the elements described herein without departing from the spirit and scope of the invention as described in the following claims.

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising voriconazole and one or more pharmaceutically acceptable carriers, wherein the composition is formulated for topical administration, and wherein the composition is in a unit dosage form comprising 0.3 mg/ml to 3.5 mg/ml of voriconazole.
2. The pharmaceutical composition of claim 1, wherein the composition is formulated as a solid dosage form.
3. The pharmaceutical composition of claim 0, wherein the composition comprises liposomal beads or is formulated as a gel, ointment, cream, lotion, serum, spray or emulsion.
4. The pharmaceutical composition of claim 0, wherein the composition is formulated as a transdermal patch.
5. The pharmaceutical composition of claim 1, wherein the composition is formulated for extended release.
6. The pharmaceutical composition of claim 1, wherein the composition comprises 10-300 μ M of voriconazole, preferably 150 μ M of voriconazole.
7. The pharmaceutical composition of claim 1, further comprising a local anesthetic.
8. The pharmaceutical composition of claim 7, wherein the local anesthetic is lidocaine, benzocaine, or articaine.
9. The pharmaceutical composition of claim 8, wherein the composition is formulated for topical administration.
10. The pharmaceutical composition of claim 8, wherein the composition is formulated for extended release.
11. A pharmaceutical composition comprising voriconazole and one or more pharmaceutically acceptable carriers, wherein the composition is in a unit dosage form comprising 0.3 mg/ml to 3.5 mg/ml of voriconazole.

12. The pharmaceutical composition of claim 11, wherein the composition is formulated for topical administration.
13. The pharmaceutical composition of claim 11, wherein the composition is formulated as a solid dosage form.
14. The pharmaceutical composition of claim 12, wherein the composition comprises liposomal beads or is formulated as a gel, ointment, cream, lotion, serum, spray or emulsion.
15. The pharmaceutical composition of claim 12, wherein the composition is formulated as a transdermal patch.
16. The pharmaceutical composition of claim 11, wherein the composition is formulated for extended release.
17. The pharmaceutical composition of claim 11, wherein the composition comprises 10-300 μ M of voriconazole, preferably 150 μ M of voriconazole.
18. The pharmaceutical composition of claim 11, further comprising a local anesthetic.
19. The pharmaceutical composition of claim 18, wherein the local anesthetic is lidocaine, benzocaine, or articaine.
20. The pharmaceutical composition of claim 18, wherein the composition is formulated for topical administration.
21. The pharmaceutical composition of claim 18, wherein the composition is formulated for extended release.
22. A method of alleviating pain or hyperalgesia in a patient in need thereof, the method comprising topically administering to the patient, a therapeutically effective amount of voriconazole and one or more pharmaceutically acceptable carriers.
23. The method of claim 22, wherein the pain or hyperalgesia is associated with a thermal injury or burns.
24. The method of claim 22, wherein the pain or hyperalgesia is associated with sunburns, inflammation, viral infection or mucosal injury.
25. The method of claim 24, wherein the viral infection is herpes zoster.

26. The method of claim 24, wherein the mucosal injury is burning mouth syndrome or vulvodynia.
27. The method of claim 22, further comprising administering a local anesthetic.
28. The method of claim 27, wherein the local anesthetic is lidocaine, benzocaine, or articaine.
29. The method of claim 27, wherein the voriconazole and local anesthetic are administered simultaneously as a single dosage unit.
30. The method of claim 27, wherein the voriconazole and the local anesthetic are administered as separate compositions simultaneously or sequentially.
31. The method of claim 29, wherein the single dosage unit is formulated for topical administration.
32. The method of claim 27, wherein the voriconazole and local anesthetic are formulated for topical administration.
33. A pharmaceutical composition comprising voriconazole and one or more pharmaceutically acceptable carriers, wherein the composition is formulated for topical administration, and wherein the composition is in a unit dosage form comprising 150 μ M of voriconazole.
34. A pharmaceutical composition comprising voriconazole and one or more pharmaceutically acceptable carriers, wherein the composition comprises liposomal beads or is formulated as a gel, ointment, cream, lotion, serum, spray or emulsion.
35. The pharmaceutical composition of claim 34, wherein the composition is administered topically.
36. The pharmaceutical composition of claim 34, wherein the composition is formulated for extended release.
37. The pharmaceutical composition of claim 34, wherein the composition comprises 10-300 μ M of voriconazole, preferably 150 μ M of voriconazole.
38. The pharmaceutical composition of claim 34, wherein the composition is in a unit dosage form comprising 0.3 mg/ml to 3.5 mg/ml of voriconazole.
39. The pharmaceutical composition of claim 34, further comprising a local anesthetic.

40. The pharmaceutical composition of claim 39, wherein the local anesthetic is lidocaine, benzocaine, or articaine.
41. The pharmaceutical composition of claim 39, wherein the composition is formulated for topical administration.
42. The pharmaceutical composition of claim 39, wherein the composition is formulated for extended release.

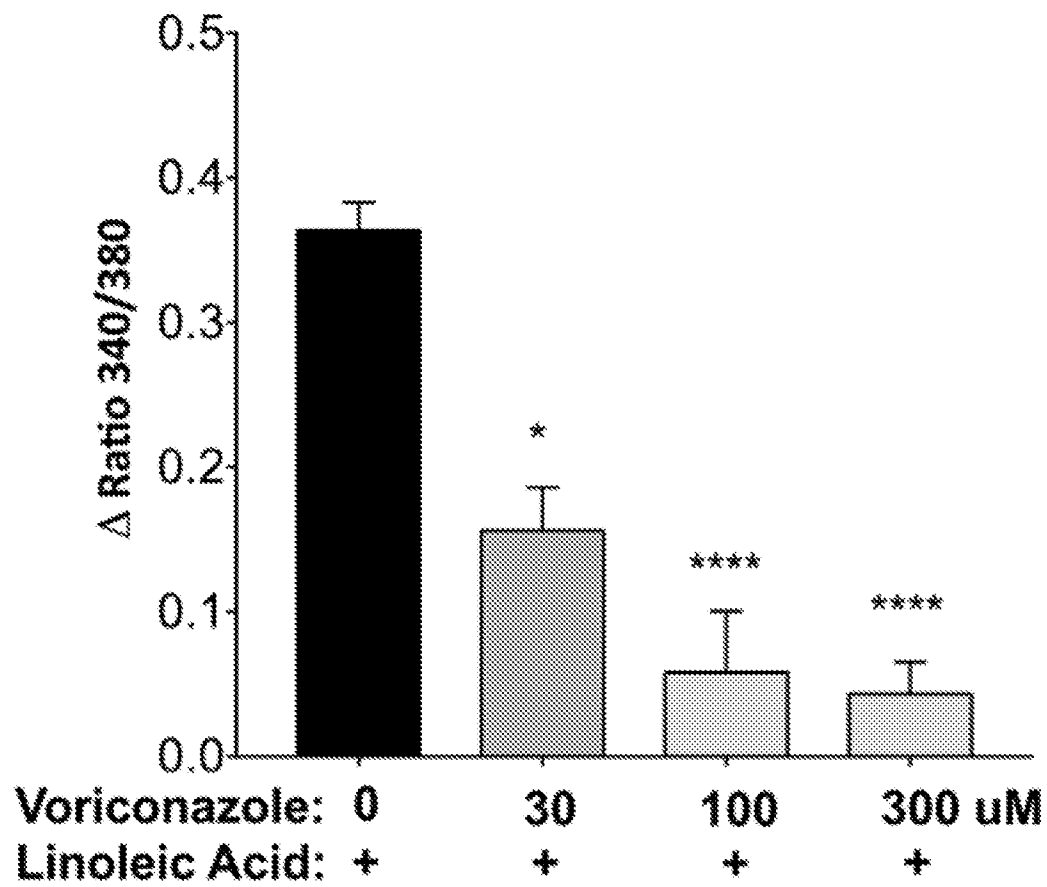


FIG. 1

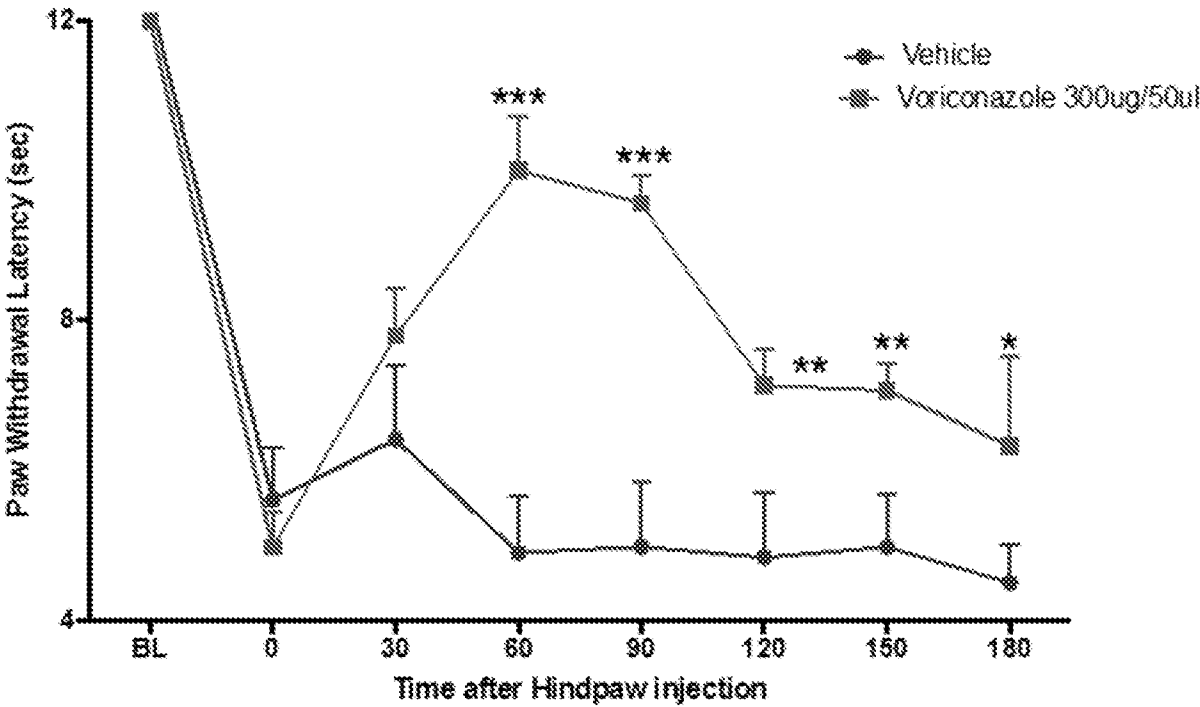


FIG. 2

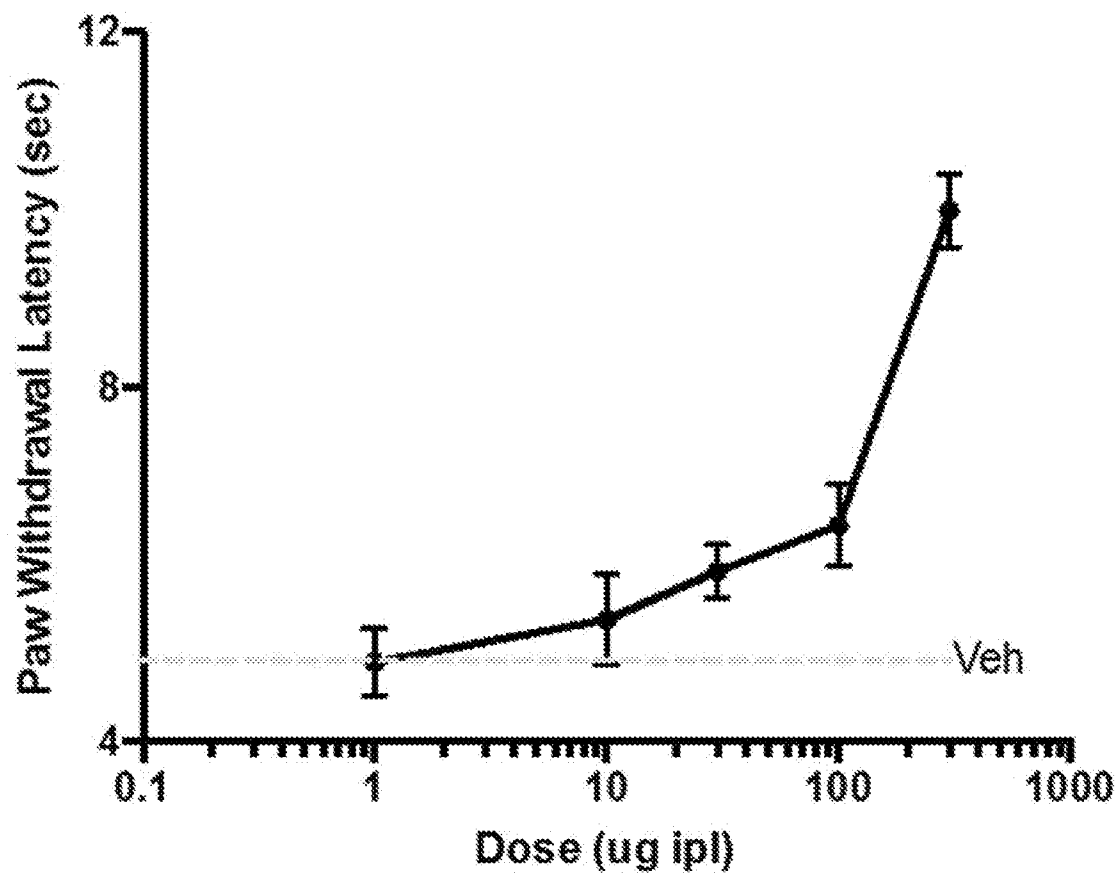


FIG. 3

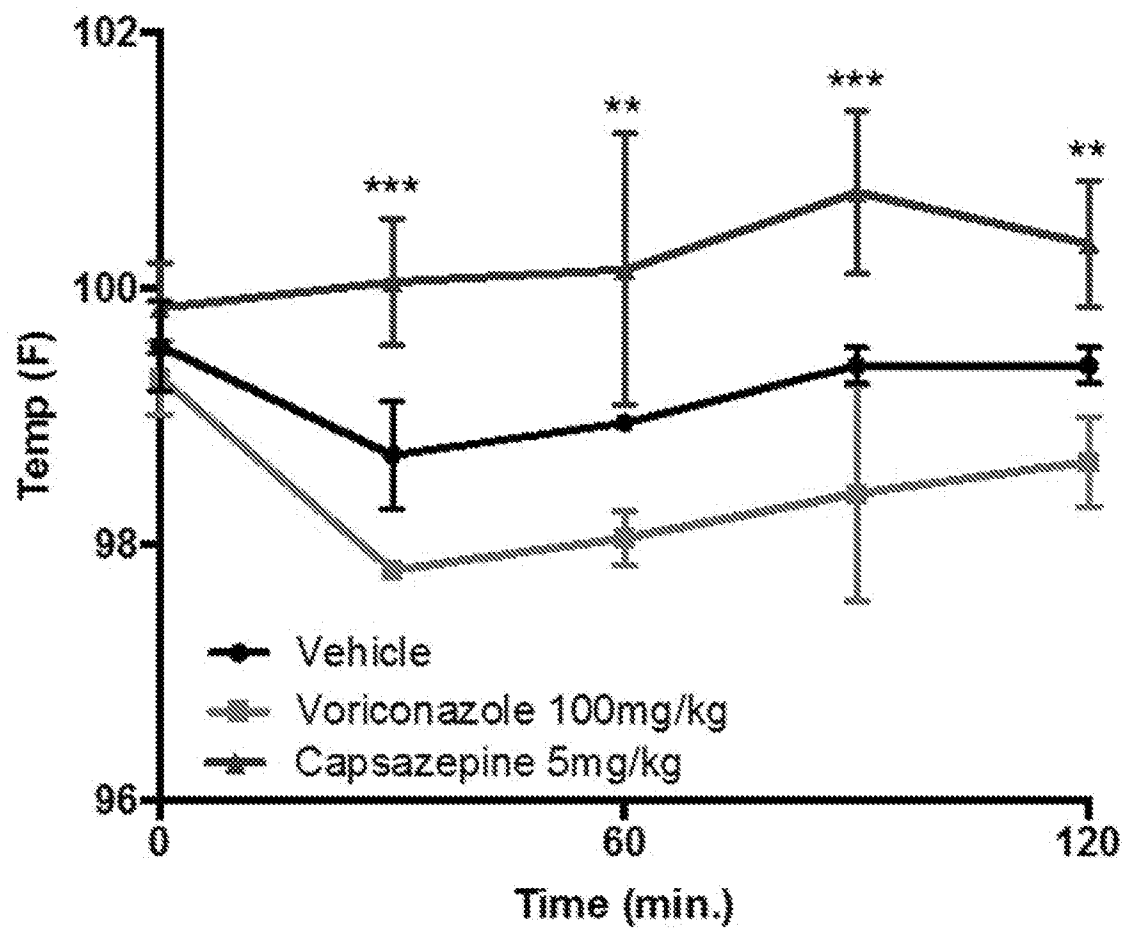
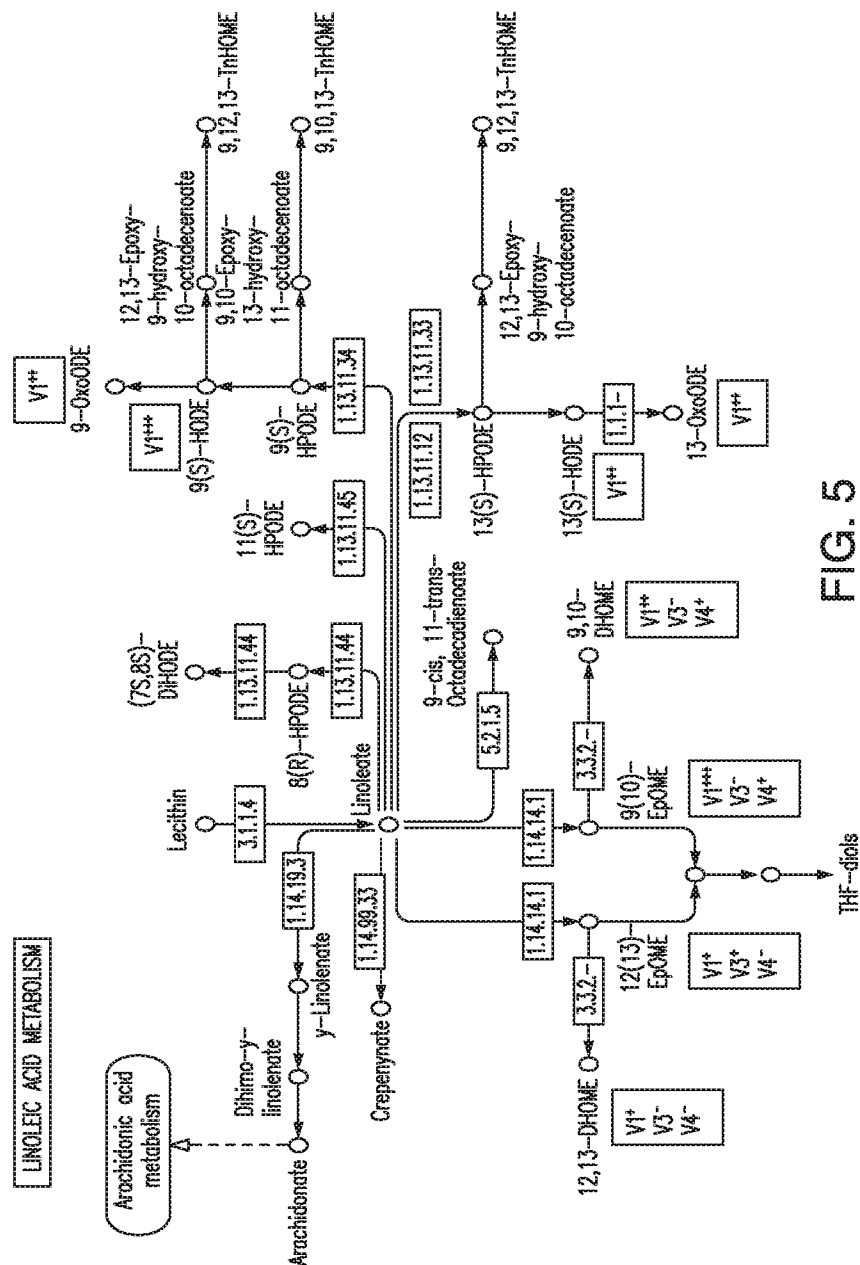


FIG. 4



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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/16618

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 31/167, 31/506, 31/4196 (2018.01)
CPC - A61K 9/06, 9/0014, 31/167, 31/506, 31/4196

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2015/0209442 A1 (THE BOARD OF REGENTS OF THE UNIVERSITY OF TEXAS SYSTEM) 30 July 2015; paragraphs [0021]-[0023], [0042]-[0043], [0047]-[0049], [0057]-[0060], [0063]	1-32, 34-42
Y	US 2005/0182074 A1 (HUMPHREY, MJ) 18 August 2005; paragraphs [0003], [0005], [0015]-[0016], [0089], [0091]	1-32, 34-42
Y	US 2012/0321574 A1 (BURNETT, KM et al.) 20 December 2012; claim 1	2-3, 13-14, 34-42
Y	US 2008/0008771 A1 (GARDNER, PR) 10 January 2008; claims 4, 6-7, 17-18	6, 17, 37
Y	US 2014/0154338 A1 (MURRELL, Z et al.) 05 June 2014; paragraphs [0006], [0008]-[0009], [0014]-[0015], [0020], [0023]-[0024], [0030]	7-10, 18-21, 27-32, 39-42
Y	US 2005/0043251 A1 (LANE, EM) 24 February 2005; paragraphs [0005], [0010]; claims 1-2	25
Y	US 2005/0222169 A1 (AHMAD, N et al.) 06 October 2005; paragraphs [0017], [0020]-[0021]	26
Y	WO 94/167101 A1 (JANSSEN PHARMACEUTICA N.V.) 04 August 1994; page 1, lines 18-23; page 1A, lines 1-4; page 7, lines 8-13	29-31
A	US 2016/0199351 A1 (ARNO THERAPEUTICS, INC., et al.) 14 July 2016; paragraphs [0009], [0042], [0053], [0070]-[0071], [0076]	33

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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

Date of the actual completion of the international search
17 March 2018 (17.03.2018)

Date of mailing of the international search report
05 APR 2018

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