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(54) **Title:** TOPICAL FORMULATIONS CONTAINING LEUKOTRIENE RECEPTOR ANTAGONIST AND USES THEREOF

(57) **Abstract:** Topical formulations containing at least one leukotriene receptor antagonist, and methods of using topical formulations containing at least one leukotriene receptor antagonist to treat and/or prevent conditions including capsular contracture, scarring, pigmentation irregularities such as liver spots and melasma, and a variety of other dermatological conditions.

# TOPICAL FORMULATIONS CONTAINING LEUKOTRIENE RECEPTOR ANTAGONIST AND USES THEREOF

## RELATED APPLICATION DATA

**[0001]** This application claims the benefit of priority of U.S. Provisional Application No. 60/907,032, filed March 16, 2007, and U.S. Provisional Application No. 60/903,320, filed February 26, 2007. The contents of these applications are incorporated herein by reference in their entirety.

## FIELD OF THE INVENTION

**[0002]** The present invention is related to topical formulations containing leukotriene receptor antagonists and the use thereof to treat or prevent a number of dermatological conditions.

## BACKGROUND OF THE INVENTION

**[0003]** Scarring is a common side effect resulting from injuries and surgery, as well as certain skin conditions, such as acne. Capsular contracture is a known "side effect" commonly related with breast enhancement surgery. Capsular contracture is actually considered to be more of an exaggeration of a normal physiologic response than a side effect, and it is a thickened periprosthetic scar which engulfs the breast implant, thereby resulting in an unnaturally hard breast. Additionally, the shape of the breast can be distorted and physical pain can result from the capsular contracture.

**[0004]** People with certain skin types are predisposed to hyperpigmentation after a traumatic event to their skin. This is particularly true for surgical procedures, laser phototherapy, dermabrasion, and other cosmetic procedures that may traumatize the skin.

**[0005]** Liver spots are flat brown-black spots that usually occur in sun-exposed areas of the body. They are also called age spots. They are unrelated to the liver or liver function. Liver spots are changes in skin color associated with older skin. The increased pigmentation may be brought on by aging, exposure to sun or other forms of ultraviolet light, or other unknown causes. Liver spots are extremely common after the

age of 40. They occur most often on the backs of the hands, on the forearms, shoulder, face, and forehead, areas of highest sun exposure. They are harmless and painless, but they may affect the cosmetic appearance. Occasionally, liver spots may obscure the diagnosis of skin cancers.

**[0006]** Melasma is a form of facial discoloration that can affect anyone, but is most common in women, particularly women who are pregnant, and those who take oral contraceptives or hormone replacement therapy. Melasma is also known as chloasma or the "mask of pregnancy" when it occurs in pregnant women. Melasma generally causes dark, irregular patches on the cheeks, nose, lips, upper lip, and forehead, where the patches develop gradually over time. It is thought to be the result of stimulation of melanocytes by estrogen and progesterone, which causes them to produce more melanin pigment when the sun is exposed to sunlight.

**[0007]** Many dermatological conditions attributable to bacterial, fungal, and viral infections, trauma, autoimmune disorders, and diseases, as well as dermatological conditions of unknown etiology, are known to afflict the skin of patients, including acanthosis nigricans, all forms of acne (including, but not limited to, cystic acne, acne rosacea, acne globata, acne inversa, and acne vulgaris), allergic contact dermatitis, alopecia areata, androgenic alopecia, basal cell carcinoma, bullous pemphigoid, canker sores, cellulite, chondrodermatitis nodularis helicis, dandruff, dermatitis, dermatomyositis, discoid lupus erythematosus, disseminated superficial actinic porokeratosis, dry skin (xerosis), dystrophic epidermolysis bullosa (EB), ectodermal dysplasia, eczema/atopic dermatitis, erysipelas, erythema infectiosum, erythema multiforme, erythema nodosum, female pattern hair loss, folliculitis, granuloma annulare, Grover's disease, hidradenitis, hidradenitis suppurativa, hyperhidrosis, ichthyosis, keloids and hypertrophic scars, keratoacanthoma, keratosis pilaris, lentigo, lichen planus, lichen striatus, lupus erythematosus (LE), Lyme disease, male pattern hair loss, mastocytosis, necrobiosis lipoidica diabeticorum, nummular eczema, onycholysis, palmoplantar pustulosis, pemphigus, piedra, pityriasis rosea, pityriasis rubra pilaris, pityrosporum folliculitis, polymorphous light eruption, progressive pigmentary purpura, prurigo nodularis, pseudofolliculitis barbae, pseudoxanthoma elasticum (PXE), pyogenic granuloma, rhinophyma, rosacea, scleroderma, seborrheic

dermatitis, seborrheic keratoses, Sjögren's syndrome, stomatitis, telogen effluvium hair loss, urticaria (hives), vitiligo, and xeroderma pigmentosum (XP).

**[0008]** U.S. Patent No. 6,951,869 is directed to the use of leukotriene receptor antagonists in the treatment or prevention of scarring or capsular contracture. Although topical treatment is disclosed as one option, no specific topical formulations are provided.

**[0009]** U.S. Patent Application Publication No. US2003/0207932 discloses a topical composition for the prevention of post-traumatic hyperpigmentation, comprising a leukotriene receptor antagonist, melatonin, menthol, benzyl alcohol, polysorbate 80, and trisoleooxymethylmethylamino-1-ethane sulfonic acid.

**[0010]** U.S. Patent No. 6,440,994 is directed to a method of treating skin disorders selected from acne vulgaris, acne rosacea, acne conglobata and hidrandenitis suppurativa, by administering zafirlukast or montelukast.

**[0011]** *Transdermal and Topical Drug Delivery Systems* (1997), 579-592, discloses topical formulation development of leukotriene receptor antagonists for treatment of psoriasis.

**[0012]** *Opthalmic Research* (1991), 23(6), 330-334, discloses the topical administration of leukotriene receptor antagonists in immunogenic keratitis.

**[0013]** There is a need in the art for improved topical formulations containing leukotriene receptor antagonists for treatment or prevention of certain dermatological conditions.

## SUMMARY OF INVENTION

**[0014]** The present invention is directed towards a topical formulation containing at least one leukotriene receptor antagonist.

**[0015]** The present invention is also directed to a method of treating capsular contracture in a patient in need thereof, comprising administering to the patient a topical formulation containing at least one leukotriene receptor antagonist.

**[0016]** The invention is further directed towards a method of preventing capsular contracture in a patient in need thereof, comprising administering to the patient a topical

formulation containing at least one leukotriene receptor antagonist administered to the patient prior to the formation of a capsular contracture.

**[0017]** The invention is additionally directed towards a method of treating scar tissue in a patient in need thereof, comprising administering to the patient a topical formulation containing at least one leukotriene receptor antagonist.

**[0018]** Further, the invention is also directed to a method of preventing scarring in a patient in need thereof, comprising administering to the patient a topical formulation containing at least one leukotriene receptor antagonist administered to the patient prior to the formation of a scar.

**[0019]** Further, the invention is directed to a method of treating or preventing pigmentation irregularities in a patient in need thereof, comprising administering to the patient a topical formulation containing at least one leukotriene receptor antagonist. The pigmentation irregularities may be selected from liver spots and/or melasma.

**[0020]** The invention is also directed to a method of treating or preventing liver spots in a patient in need thereof, comprising administering to the patient a topical formulation containing at least one leukotriene receptor antagonist.

**[0021]** The invention is additionally directed to a method of treating or preventing melasma in a patient in need thereof, comprising administering to the patient a topical formulation containing at least one leukotriene receptor antagonist.

**[0022]** The invention is further directed to a method of treating or preventing a dermatological disorder selected from the group consisting of acanthosis nigricans, all forms of acne (including, but not limited to, cystic acne, acne rosacea, acne globata, acne inversa, and acne vulgaris), allergic contact dermatitis, alopecia areata, androgenic alopecia, basal cell carcinoma, bullous pemphigoid, canker sores, cellulite, chondrodermatitis nodularis helicis, dandruff, dermatitis, dermatomyositis, discoid lupus erythematosus, disseminated superficial actinic porokeratosis, dry skin (xerosis), dystrophic epidermolysis bullosa (EB), ectodermal dysplasia, eczema/atopic dermatitis, erysipelas, erythema infectiosum, erythema multiforme, erythema nodosum, female pattern hair loss, folliculitis, granuloma annulare, Grover's disease, hidradenitis, hidradenitis suppurativa, hyperhidrosis, ichthyosis, keloids and hypertrophic scars, keratoacanthoma, keratosis pilaris, lentigo, lichen planus, lichen striatus, lupus

erythematosus (LE), Lyme disease, male pattern hair loss, mastocytosis, necrobiosis lipoidica diabeticorum, nummular eczema, onycholysis, palmoplantar pustulosis, pemphigus, piedra, pityriasis rosea, pityriasis rubra pilaris, pityrosporum folliculitis, polymorphous light eruption, progressive pigmentary purpura, prurigo nodularis, pseudofolliculitis barbae, pseudoxanthoma elasticum (PXE), pyogenic granuloma, rhinophyma, rosacea, scleroderma, seborrheic dermatitis, seborrheic keratoses, Sjögren's syndrome, stomatitis, telogen effluvium hair loss, urticaria (hives), vitiligo, and xeroderma pigmentosum (XP), comprising administering to a patient suspected of contracting or currently suffering from any of these disorders a topical formulation containing at least one leukotriene receptor antagonist.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

**[0023]** Leukotriene receptor antagonists useful in accordance with the present invention include, but are not limited to, acitazanolast, iralukast, montelukast, pranlukast, velukast, zafirlukast, and zileuton, or pharmaceutically acceptable salts thereof. Zafirlukast, montelukast, and pranlukast are the most preferred. Of these three compounds, zafirlukast and montelukast are more preferred, and zafirlukast is the most preferred. The term "pharmaceutically acceptable salts" includes salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

**[0024]** Topical dosage forms include any form suitable for topical, e.g., transdermal, application, and include but are not limited to, gels, solutions, suspensions, lotions, pastes, creams, ointments, aerosols, dusting powders, patches, and the like. These administration forms may be presented in unit dosage form and may be prepared by any of the methods well-known in the art of pharmacy. The active agent is typically present in an amount of from 1 to 99% by weight, based upon the total weight of the formulation, for example from 10 to 50% by weight.

**[0025]** The magnitude of a therapeutic dose varies with the nature of the severity of the condition to be treated and with the particular compound used. The dosage will also vary according to the age, weight and response of the individual patient. In general, the disclosed daily dose range for any use is within the range of from about 0.001 mg to

about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 10 mg per kg, and most preferably 0.1 to 1 mg per kg.

**[0026]** Preferably, the methods of preventing scar formation, including post-surgery scarring, post-acne scarring and capsular contracture following insertion of surgical implants, and pigmentation irregularities, such as liver spots and melasma, comprise administering the topical formulation of the invention to a patient prior to the formation of a scar or a capsular contracture or liver spots or melasma, or events related to pigmentation irregularities. The administration of the topical formulation to a patient may begin up to one year or more prior to a traumatic event, such as the potential scar or capsular contracture or hyperpigmentation causing event, such as surgery. Preferably, though, the administration of the topical formulation begins one month before the potential traumatic event. More preferably, the administration begins two weeks before the potential traumatic event. Most preferably, the administration begins between one week and one hour before the potential traumatic event.

**[0027]** However, administration of the topical formulation after a scar or capsular contracture-causing event, or after an event that causes pigmentation irregularities, or after the formation of a scar or capsular contracture, or after the formation of liver spots or melasma, will still alleviate or eliminate the condition. This is true even if the topical formulation is administered one year or more after the traumatic event or after the formation of the scar or the capsular contracture or the pigmentation irregularity or the liver spots or the melasma. Preferably, however, the administration of the topical formulation is begun within one month of the traumatic event or the formation of the scar or the capsular contracture or the pigmentation irregularity or the liver spots or the melasma. More preferably, the administration of the topical formulation is begun within two weeks of the scar or the capsular contracture or the pigmentation irregularity-causing event or the formation of the scar or the capsular contracture or the pigmentation irregularity or the liver spots or the melasma. Even more preferably, the administration of the topical formulation is begun within one week of the scar or capsular contracture or pigmentation irregularity-causing event, or the formation of the scar or the capsular contracture or the pigmentation irregularity or the liver spots or the melasma. Most preferably, the administration of the topical formulation is begun within

24 hours of the traumatic event or the formation of the scar or the capsular contracture or the pigmentation irregularity or the liver spots or the melasma.

**[0028]** Additionally, if the patient is receiving a breast implant, it is preferred that the administration of the topical formulation is begun prior to the insertion of the breast implant. The administration of the topical formulation to a patient may begin up to one year or more prior to the insertion of the breast implant. Preferably, though, the administration of the topical formulation begins one month before the insertion of the breast implant. More preferably, the administration begins two weeks before the insertion of the breast implant. Most preferably, the administration begins one week before the insertion of the breast implant.

**[0029]** Methods of treating and/or preventing various additional dermatological conditions, such as those attributable to bacterial, fungal, and viral infections, trauma, autoimmune disorders, and diseases, as well as those that have an unknown etiology, are also provided in accordance with the present invention. The methods comprise administering the topical formulation of the invention to a patient suffering from such a dermatological condition for a period of time sufficient to treat the condition. Dermatological conditions that may be treated using the topical formulations of the present invention include, but are not limited to, acanthosis nigricans, all forms of acne (including, but not limited to, cystic acne, acne rosacea, acne globata, acne inversa, and acne vulgaris), allergic contact dermatitis, alopecia areata, androgenic alopecia, basal cell carcinoma, bullous pemphigoid, canker sores, cellulite, chondrodermatitis nodularis helicis, dandruff, dermatitis, dermatomyositis, discoid lupus erythematosus, disseminated superficial actinic porokeratosis, dry skin (xerosis), dystrophic epidermolysis bullosa (EB), ectodermal dysplasia, eczema/atopic dermatitis, erysipelas, erythema infectiosum, erythema multiforme, erythema nodosum, female pattern hair loss, folliculitis, granuloma annulare, Grover's disease, hidradenitis, hidradenitis suppurativa, hyperhidrosis, ichthyosis, keloids and hypertrophic scars, keratoacanthoma, keratosis pilaris, lentigo, lichen planus, lichen striatus, lupus erythematosus (LE), Lyme disease, male pattern hair loss, mastocytosis, necrobiosis lipoidica diabeticorum, nummular eczema, onycholysis, palmoplantar pustulosis, pemphigus, piedra, pityriasis rosea, pityriasis rubra pilaris, pityrosporum folliculitis,

polymorphous light eruption, progressive pigmentary purpura, prurigo nodularis, pseudofolliculitis barbae, pseudoxanthoma elasticum (PXE), pyogenic granuloma, rhinophyma, rosacea, scleroderma, seborrheic dermatitis, seborrheic keratoses, Sjögren's syndrome, stomatitis, telogen effluvium hair loss, urticaria (hives), vitiligo, and xeroderma pigmentosum (XP).

**[0030]** The patient may be administered the topical formulation indefinitely. However, it is preferred that the administration of the topical formulation last no more than one year. It is more preferable that the administration of the topical formulation last no more than six months. It is most preferable that the administration of the topical formulation last no more than three months. Furthermore, the administration of the topical formulation does not need to be continuous. In other words, a patient may be removed from administration and later have the topical formulation administered again.

**[0031]** In some embodiments, the topical formulation of the invention comprises an ointment, which is a semisolid pharmaceutical preparation based on well known materials such as an oleaginous base, lanolin, emulsions, or water-soluble bases. Preparation of ointments is well known in the art such as described in Remington, vol. 2, pp. 1585-1591. Such preparations may contain petrolatum or zinc oxide together with the active agent. Oleaginous ointment bases suitable for use in the present invention include generally, but are not limited to, vegetable oils, animal fats, and semisolid hydrocarbons obtained from petroleum. Absorbent ointment bases of the present invention may contain little or no water and may include components such as, but not limited to, hydroxystearin sulfate, anhydrous lanolin and hydrophilic petrolatum. Emulsion ointment bases of the present invention are either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, and may include, but are not limited to, cetyl alcohol, glyceryl monostearate, lanolin, polyalkylsiloxanes, and stearic acid. Water-soluble ointment bases suitable for use in the present invention may be prepared from polyethylene glycols of varying molecular weight. In an additional aspect, ointments of the present invention may include additional components such as, but not limited to, additional active agents, excipients, solvents, emulsifiers, chelating agents, surfactants, emollients, permeation enhancers, preservatives, antioxidants, lubricants, pH adjusters, adjuvants, dyes, and perfumes. The specific choice and compositions of such additional

components may be made by those skilled in the art in accordance with the principles of the present invention.

**[0032]** In another aspect of the present invention, a cream may be prepared in accordance with the principles of the present invention. Creams are a type of ointment which are viscous liquids or semisolid emulsions, either oil-in-water or water-in-oil, as is well known in the art. Cream bases may be soluble in water, and contain an oil phase, an emulsifier, an aqueous phase, and the active agent. In one embodiment of the present invention, the oil phase may be comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. In another embodiment of the present invention, the aqueous phase may exceed the oil phase in volume, and may contain a humectant. In another embodiment of the present invention, the emulsifier in a cream formulation may be a nonionic, anionic, cationic or amphoteric surfactant. For an oil-in-water emulsion, the water phase of the cream may contain between about 20 and about 60% w/w of water, between about 1 and about 15% w/w of at least one emulsifier, up to about 50% w/w of an oil phase, and up to about 1% w/w of a preservative such as a paraben. The oil phase of the cream may contain up to about 40% w/w of a solvent, up to about 15% w/w of at least one emulsifier, up to about 40% w/w of an oil phase, and up to about 1% w/w of a preservative such as a paraben.

**[0033]** In another embodiment of the present invention, a lotion may be prepared. A lotion is a composition which may be a liquid or semi-liquid preparation in which solid particles, including the active agent, are present in a water or alcohol base. Lotions suitable for use in the present invention may be a suspension of solids or may be an oil-in-water emulsion. In another embodiment of the present invention, lotions may also contain suspending agents which improve dispersions or other compounds which improve contact of the active agent with the skin, e.g., hydrophilic polymers such as methylcellulose, sodium carboxymethylcellulose, or similar compounds. Lotions of the present invention may include additional components such as, but not limited to, additional active agents, excipients, solvents, emulsifiers, chelating agents, surfactants, emollients, permeation enhancers, preservatives, antioxidants, lubricants, pH adjusters, adjuvants, dyes, and perfumes. The specific choice and compositions of such additional components may be made by those skilled in the art in accordance with the

principles of the present invention and may differ from the components which would be chosen for other topical formulations of the present invention.

**[0034]** In another embodiment of the present invention, the lotion may be an emulsion of a water and oil phase. The water phase of the lotion may contain between about 20% w/w to about 90% w/w of an excipient such as water, up to about 5% w/w of a surfactant, up to about 5% w/w of a buffering agent such as sodium chloride or the like, and up to about 1% w/w of a preservative such as a paraben. The oil phase of the lotion may contain up to about 40% w/w of at least one solvent such as glycerin and cetyl alcohol, up to about 10% w/w of an absorbent base such as petrolatum, up to about 5% w/w of an antioxidant such as isopropyl palmitate, up to about 5% w/w of an oil phase such as dimethicone, and up to about 1% w/w of a preservative such as a paraben.

**[0035]** In yet another embodiment of the present invention, a paste may be prepared in accordance with the present invention. Pastes of the present invention are compositions in which there are significant amounts of solids which form a semisolid formulation in which the active agent is suspended in a suitable base. In one embodiment of the present invention, pastes may be formed of bases to produce fatty pastes or made from a single-phase aqueous gel. Fatty pastes suitable for use in the present invention may be formed of a base such as petrolatum, hydrophilic petrolatum or the like. Pastes made from single-phase aqueous gels suitable for use in the present invention may incorporate cellulose based polymers such as carboxymethylcellulose or the like as a base. Pastes of the present invention may include additional components such as, but not limited to, additional active agents, excipients, solvents, emulsifiers, chelating agents, surfactants, emollients, permeation enhancers, preservatives, antioxidants, lubricants, pH adjusters, adjuvants, dyes, and perfumes.

**[0036]** In another embodiment of the present invention, a gel may be prepared. A gel prepared in accordance with the present invention may be a preparation of a colloid in which a disperse phase has combined with a continuous phase to produce a viscous product. The gelling agent may form submicroscopic crystalline particle groups that retain the solvent in the interstices. As will be appreciated by those working in art, gels are semisolid, suspension-type systems. Single-phase gels can contain organic

macromolecules distributed substantially uniformly throughout a carrier liquid, which may be aqueous or non-aqueous and may contain an alcohol or oil. A variety of specific gel vehicles are known to those of ordinary skill in the art. Examples of specific gel types, their manufacture and use may be found, for example, in U.S. Pat. Nos. 2,909,462; 4,340,706; 4,652,441; 5,516,808; 5,643,584; 5,840,338; 5,912,009; and 6,258,830, each of which are incorporated herein by reference in their entirety. In some embodiments, the gel formulation may be prepared by providing a gelling agent, usually in a powdered form, and adding an excipient such as water in the case of a hydrophilic gelling agent or mineral oil in the case of a hydrophobic gelling agent. The gel then swells and may be optionally neutralized. In a separate vessel, the active agent may be dissolved in an appropriate solvent. The dissolved active agent and the gel may then be mixed to form the final gel formulation. Other methods of producing a drug-containing gel will be recognized by those of ordinary skill in the art. The gel may include a variety of additional components such as, but not limited to, additional active agents, excipients, solvents, emulsifiers, chelating agents, surfactants, emollients, permeation enhancers, preservatives, antioxidants, lubricants, pH adjusters, adjuvants, dyes, and perfumes. Further, in order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing or stirring, or combinations thereof. It will be recognized, however, by those skilled in the art that other methods and means of incorporating the active agent and other components into the gel may be employed consistent with the teachings of the present invention.

**[0037]** In one embodiment of the present invention, aqueous gels may comprise water or water/ethanol and about 1-5 wt % of a gelling agent. In another aspect of the present invention, non-aqueous gels may be comprised of silicone fluid, such as colloidal silicon dioxide, or mineral oil. The suitability of a particular gel depends upon the compatibility of its constituents with both the active agent and a permeation enhancer, if used, and any other components in the formulation.

**[0038]** In accordance with the present invention, the gelling agent may be a compound of high molecular weight which acts as a thickening agent to produce a semisolid or suspension-type formulation. Gelling agents may be hydrophobic or hydrophilic and are

generally polymers. Gels which incorporate hydrophilic polymers are referred to as hydrogels, as is understood by those skilled in the art. Examples of suitable gelling agents for use in the present invention may include synthetic polymers such as, but not limited to, polyacrylic acids or poly(1-carboxyethylene), carboxypolymethylenes prepared from acrylic acid cross-linked with allyl ethers of (polyalkyl) sucrose or pentaerythritol (e.g. CARBOPOL 940/941/980/981/1342/1382 and carbamer polymers such as carbomer 934P/974P), sodium acrylate polymers (e.g. AQUAKEEP J-550/J-400), other polycarboxylic acids, alkyl acrylate polymers (e.g. PEMULEN), and mixtures or copolymers thereof. In another embodiment of the present invention, suitable gelling agents may include vinyl polymers such as but not limited to carboxyvinyl polymers, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl methyl ether, polyvinyl ether, polyvinyl sulfonates, and mixtures or copolymers thereof. In a further embodiment of the present invention, suitable gelling agents may include polymers such as but not limited to polyethylene compounds (e.g. polyethylene glycol, etc.), polysaccharides (e.g. polysucrose, polyglucose, polylactose, etc.) and salts thereof, acrylic acid esters, alkoxybutyninpolymers (e.g. polyoxyethylene-polyoxypropylene copolymers such as the PLURONIC line of BASF, Parsippany, N.J.), polyethylene oxide polymers, polyethers, gelatin succinate, colloidal magnesium aluminum silicate (which may be useful as a gel stabilizer in conjunction with another gelling agent), petroleum jelly and mixtures of copolymers thereof.

**[0039]** Suitable gelling agents also include cellulose polymers such as hydroxypropyl cellulose (e.g. KLUCEL), hydroxypropylmethyl cellulose (e.g. KLUCEL HF, METHOCEL), hydroxypropylethyl cellulose, hydroxypropylbutyl cellulose, hydroxypropylpentyl cellulose, hydroxyethyl cellulose (NATROSOL), ethylcellulose, carboxymethyl cellulose, hydroxypropylmethyl cellulose phthalate, and cellulose acetate. Suitable gelling agents may also be natural gelling agents include, dextran, gaur-gum, tragacanth, xanthan gum, sodium alginate, sodium pectinate, sodium alginate, acacia gum, Irish moss, karaya gum, guaiac gum, locust bean gum, etc., while natural high molecular weight compounds include, among others, various proteins such as casein, gelatin, collagen, albumin (e.g. human serum albumin), globulin, fibrin, etc. and various carbohydrates such as cellulose, dextrin, pectin, starches, agar, mannan,

and the like. These substances may be also be chemically modified, e.g. esterified or etherified forms, hydrolyzed forms (e.g. sodium alginate, sodium pectinate, etc.) or salts thereof.

**[0040]** The amount of gelling agent employed in a gel of the present invention may vary depending on the specific result to be achieved. However, in one aspect, the amount of gelling agent may be from about 0.05 to about 10 wt % of the gel formulation. In a more preferred aspect, the amount of gelling agent may be 0.1 to 5 wt % of the gel formulation prior to introduction of the active agent and any accompanying components.

**[0041]** In some embodiments of the present invention, an emulsifier may be used, preferably when a solvent is used. Emulsifiers suitable for use in the present invention include, but are not limited to, polyols and esters thereof such as glycols, propylene glycol, polyethylene glycol, glycolhexylene glycol, ethylene glycol, glycerol, butanediol, polyethylene glycol monolaurate, and propylene glycol ester of alginic acid. Emulsification may be accomplished by conventional dispersion techniques. For example, intermittent shaking, mixing by means of a propeller mixer, turbine mixer or the like, colloid mill operation, mechanical homogenization, ultrasonication, or other known methods may be utilized. Emulsifiers may form stable oil-in-water emulsion, and such emulsifiers are exemplified by anionic surfactants (e.g. sodium oleate, sodium stearate, sodium laurylsulfate, etc.), nonionic surfactants (e.g. polyoxyethylene sorbitan fatty acid esters (Tween 80 and Tween 60, Atlas Powder, U.S.A.), polyoxyethylene castor oil derivatives (HCO-60 and HCO-50, Nikko Chemicals, Japan], etc.), polyvinyl pyrrolidone, polyvinyl alcohol, carboxymethylcellulose, lecithin, gelatin, and combinations thereof. The concentration of the emulsifier may be selected from the range of about 0.01% to about 20%. It will be noted that many of these emulsifiers also act as gelling agents.

**[0042]** Solvents or solubilizing agents may also be used in the topical composition. Suitable solvents for use in the present invention include, but are not limited to lower alcohols, ethanol, isopropanol, benzyl alcohol, propanol, methanol, other $C_4$-$C_{10}$ mono-alcohols and mixtures thereof. In another aspect the solvents suitable for use in the present invention may include albumin, gelatin, citric acid, ethylenediamine sodium tetraacetate, dextrin, dimethylsulfoxide, dimethylacetamide, dimethylformamide, 2-

pyrrolidone, N-(2-hydroxyethyl) pyrrolidone, N-methylpyrrolidone, 1-dodecylazacycloheptan-2-one and other n-substituted-alkyl-azacycloalkyl-2-ones (azones), sodium hydrosulfite and mixtures thereof. In some embodiments, the topical formulation of the invention comprises a polar aprotic solvent, preferably selected from any one or more of the following: dimethylsulfoxide, dimethylacetamide, dimethylformamide or N-methylpyrrolidone. Dimethylsulfoxide is most preferred. The amount of the solvent in the topical formulation is preferably about 25-90% by weight, more preferably about 50-80% by weight, based on the total weight of the excipients in the formulation (i.e., not including the active agent(s)).

**[0043]** In some embodiments, the topical formulation of the invention comprises one or more carbamides. The one or more carbamides may include urea, carbamide peroxide, urea-D glucuronic acid, allantinon (5-ureidohydantoin), urea phosphate, urea sulfate, ureidoglycolic acid (glyoxylurea), ureidopropionic acid (N-Carbamyl-Balanine), ureidosuccinic acid (N-Carbamyl-aspartic acid), N-Carbamyl-arginine, N-carbamylglycine (hydantoic acid), N-carbamyl-phenylalanine or glycolylurea (hydantoin). Urea is the most preferred. The one or more carbamides may be present in amounts of about 5-50% by weight, more preferably about 10-40% by weight.

**[0044]** In some embodiments, the topical formulation of the invention comprises water in amounts of about 1-25% by weight, more preferably about 2-10% by weight.

**[0045]** Unless explicitly stated differently, all weight percentages herein are based on the total weight of the excipients in the formulation (i.e., not including the active agent(s)).

**[0046]** The invention will be exemplified below.

## EXAMPLE

**[0047]** Formulation 1: Excipients - 70% dimethylsulfoxide, 25% urea, 5% sterile water.

**[0048]** While the present invention has been described in connection with various preferred embodiments, it will be understood by those skilled in the art that variations and modifications of the preferred embodiments described above may be made without departing from the scope of the invention. Other embodiments will be apparent to those

skilled in the art from a consideration of the specification or from a practice of the invention disclosed herein. It is intended that the specification and the described examples are considered exemplary only.

**WHAT IS CLAIMED IS:**

1. A method of treating or preventing scarring in a patient in need thereof, comprising administering to the patient a topical formulation containing at least one leukotriene receptor antagonist.

2. The method of claim 1, wherein the leukotriene receptor antagonist is selected from the group consisting of acitazanolast, iralukast, montelukast, pranlukast, velukast, zafirlukast, zileuton, and pharmaceutically-acceptable salts thereof.

3. The method of claim 2, wherein the leukotriene receptor antagonist is zafirlukast.

4. The method of claim 1, wherein the scarring is selected from the group consisting of post-surgery scarring, post-acne scarring and capsular contracture.

5. The method of claim 1, wherein administration of the leukotriene receptor antagonist is begun prior to a traumatic event to the patient, and continues after the traumatic event.

6. The method of claim 5, wherein the traumatic event is surgery.

7. The method of claim 1, wherein the dosage form is selected from the group consisting of gels, solutions, suspensions, lotions, pastes, creams, ointments, aerosols, dusting powders, and patches.

8. A method of treating or preventing a pigmentation irregularity in a patient in need thereof, comprising administering to the patient a topical formulation containing at least one leukotriene receptor antagonist.

9. The method of claim 8, wherein the pigmentation irregularity is selected

from the group consisting of liver spots and melasma.

10. The method of claim 8, wherein the leukotriene receptor antagonist is selected from the group consisting of acitazanolast, iralukast, montelukast, pranlukast, velukast, zafirlukast, zileuton, and pharmaceutically-acceptable salts thereof.

11. The method of claim 10, wherein the leukotriene receptor antagonist is zafirlukast.

12. The method of claim 8, wherein administration of the leukotriene receptor antagonist is begun prior to a traumatic event to the patient, and continues after the traumatic event.

13. The method of claim 12, wherein the traumatic event is surgery.

14. The method of claim 8, wherein the dosage form is selected from the group consisting of gels, solutions, suspensions, lotions, pastes, creams, ointments, aerosols, dusting powders, and patches.

15. A method of treating or preventing a dermatological condition in a patient in need thereof, comprising administering to the patient a topical formulation containing at least one leukotriene receptor antagonist,

wherein the dermatological condition is selected from the group consisting of acanthosis nigricans, all forms of acne (including, but not limited to, cystic acne, acne rosacea, acne globata, acne inversa, and acne vulgaris), allergic contact dermatitis, alopecia areata, androgenic alopecia, basal cell carcinoma, bullous pemphigoid, canker sores, cellulite, chondrodermatitis nodularis helicis, dandruff, dermatitis, dermatomyositis, discoid lupus erythematosus, disseminated superficial actinic porokeratosis, dry skin (xerosis), dystrophic epidermolysis bullosa (EB), ectodermal dysplasia, eczema/atopic dermatitis, erysipelas, erythema infectiosum, erythema multiforme, erythema nodosum, female pattern hair loss, folliculitis, granuloma

annulare, Grover's disease, hidradenitis, hidradenitis suppurativa, hyperhidrosis, ichthyosis, keloids and hypertrophic scars, keratoacanthoma, keratosis pilaris, lentigo, lichen planus, lichen striatus, lupus erythematosus (LE), Lyme disease, male pattern hair loss, mastocytosis, necrobiosis lipoidica diabeticorum, nummular eczema, onycholysis, palmoplantar pustulosis, pemphigus, piedra, pityriasis rosea, pityriasis rubra pilaris, pityrosporum folliculitis, polymorphous light eruption, progressive pigmentary purpura, prurigo nodularis, pseudofolliculitis barbae, pseudoxanthoma elasticum (PXE), pyogenic granuloma, rhinophyma, rosacea, scleroderma, seborrheic dermatitis, seborrheic keratoses, Sjögren's syndrome, stomatitis, telogen effluvium hair loss, urticaria (hives), vitiligo, and xeroderma pigmentosum (XP).

16. The method of claim 15, wherein the leukotriene receptor antagonist is selected from the group consisting of acitazanolast, iralukast, montelukast, pranlukast, velukast, zafirlukast, zileuton, and pharmaceutically-acceptable salts thereof.

17. The method of claim 16, wherein the leukotriene receptor antagonist is zafirlukast.

18. The method of claim 15, wherein the dosage form is selected from the group consisting of gels, solutions, suspensions, lotions, pastes, creams, ointments, aerosols, dusting powders, and patches.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US07/16015

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **A61K 31/4188**( 2006.01);**A61K 31/4184**( 2006.01);**A61K 31/437**( 2006.01)

USPC: 514/252.06;514/387;544/236
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)
U.S. : 514/252.06;514/387;544/236

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 6,974,815 B2 (DHAR et al) 13 December 2005 (13.12.2005), column 25, lines 36-50, column 26, lines 18-35, column 27, lines 54-60. | 1-18 |

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

* Special categories of cited documents:

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

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

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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

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