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(71) Applicant *(for all designated States except US):* **QLT** USA, **INC.** [US/US]; 2579 Midpoint Drive, Fort Collins, CO 80525-441 7 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only):* **GARRETT, John Steven** [US/US]; 7113 Silver Moon Lane, Fort Collins, CO 80252 (US).

(74) Agents: STEFFEY, **Charles E.** et al; Schwegman, Lundberg & Woessner, PA, P.O. Box 2938, Minneapolis, Minnesota 55402 (US).

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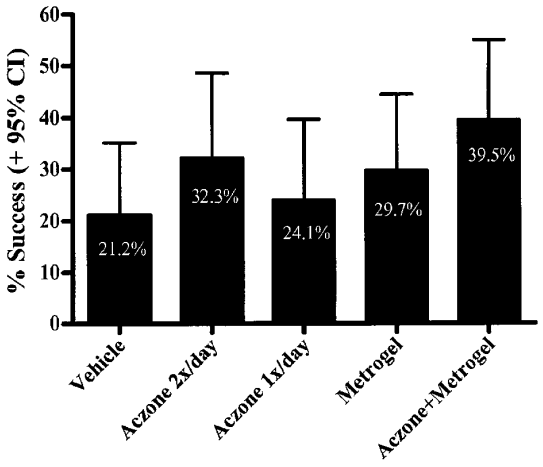
(54) Title: DAPSONE TO TREAT ROSASCEA



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(57) Abstract: The methods described herein provide treatment of rosacea using topical formulations of dapsone. The methods also provide treatment of rosacea with topical dapsone in combination with other active agents, including metronidazole. The methods avoid negative hematologic side effects, including hemolysis and hemolytic anemia, that are associated with oral administration of dapsone.

DAPSONE TO TREAT ROSACEA

Background of the Invention

Rosacea is a dermatological syndrome affecting approximately 14 million Americans. It is characterized by flushing of the skin, erythema, inflammatory papules and pustules, edema, telangiectasia, ocular symptoms and rhinophyma. To date, the etiology of rosacea is unknown and there is no clearly recognized cure (Bikowski and Goldman, 2004; Stone and Chodosh, 2004).

Four subtypes and one variation of rosacea have been defined. The subtypes are papulopustular rosacea, erythematotelangiectatic rosacea, phymatous rosacea, and ocular rosacea; the rosacea variation is granulomatous rosacea. Some patients may have features of more than one subtype simultaneously, and differences in severity occur within each subtype.

Management of rosacea is difficult because of the complexity of the syndrome and the sensitivity of rosacea-affected skin. Various therapies, including topical application of metronidazole, azelaic acid, sodium sulfacetamide/sulfur preparations, and antibiotics including erythromycin, clindamycin and tetracycline, are used in the management of rosacea with varying rates of success. Systemic therapy with oral tetracyclines, metronidazole and isotretinoin is also employed in the management of rosacea (Buechner, 2005). Dapsone antibiotic is effective for treating rosacea redness, facial flushing, papules and pustules when administered orally; however, the side effect profile makes the risMienefit ratio too high for most rosacea sufferers (Nase, 2005).

What is needed are safe, effective treatments for the management of rosacea symptoms.

Summary of the Invention

The invention is directed to the treatment of rosacea. The invention includes a method to treat rosacea by topically administering a pharmaceutical composition of dapsone and a pharmaceutically acceptable carrier to a patient. In preferred embodiments, the rosacea is papulopustular rosacea. In other embodiments, the rosacea is ocular rosacea. The invention is also directed to the

treatment of ocular disorders. The invention includes a method to treat an ocular disease or disorder by topically administering a pharmaceutical composition of dapsone and a pharmaceutically acceptable carrier.

In some embodiments, the dapsone of the topical composition is entirely dissolved in the carrier; or partially dissolved and partially microparticulate; or may be present as an emulsion, suspension or colloid. In an entirely dissolved state, dapsone exists completely in solution in the solvent, with no solid dapsone present. If the dapsone is partially dissolved and partially microparticulate, a portion of the dapsone is present in solution and a portion of the dapsone is present in a solid form. A dapsone emulsion includes two immiscible, unblendable substances wherein one substance (the dispersed phase) is dispersed in the other (continuous phase). The dapsone can be part of the dispersed phase or part of the continuous phase of the emulsion. A dapsone suspension is a heterogenous fluid containing solid particles of dapsone dispersed throughout a fluid. A dapsone colloid is a homogenous mixture of dispersed dapsone particles that are distributed evenly and stably throughout the continuous phase.

In certain embodiments, the pharmaceutical composition is a lotion, gel, ointment, cream, emulsion, suspension, spray, or cleanser. In a preferred embodiment, the pharmaceutical composition is a semisolid aqueous gel. The semisolid aqueous gel includes a thickening agent, water, a solvent, preservative, microparticulate dapsone, dissolved dapsone, and caustic materi al. hi a preferred embodiment, the caustic material is a base agent. In a preferred embodiment, the composition exhibits an optimal balance between dissolved dapsone that is available to cross through the stratum corneum of the epidermis and be absorbed into the lower two-thirds of the pilosebaceous unit; and microparticulate dapsone that is retained in or above the stratum corneum to serve as a reservoir or to provide dapsone to the supracorneum zone, crossing the stratum corneum of the epidermis only minimally as a solid. The solid microparticulate dapsone reservoir is slowly dissolved in body fluids before it is delivered through the stratum corneum. In preferred embodiments, the dapsone makes up about 0.5% to 10% of the pharmaceutical composition. The microparticulate dapsone can be a crystalline precipitate or an amorphous precipitate. Antioxidants, fragrance, colorants, sunscreens, or combinations thereof may also be present in the topical composition. In preferred

embodiments, the dapsone composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

The methods described herein include the treatment of papulopustular rosacea by applying the dapsone composition once or twice daily. In preferred methods the dapsone composition is applied twice daily. The methods additionally include the use of the dapsone pharmaceutical composition alone or in combination with other pharmaceutical compositions for rosacea, including topical and systemic treatments. The treatments are administered simultaneously or sequentially and include oral metronidazole, isotretinoin, tetracyclines including doxycycline, and topical metronidazole, azelaic acid, sodium sulfacetamide/sulfur preparations, and antibiotics including erythromycin, clindamycin and tetracycline. In some embodiments, the dapsone and other pharmaceutical are present in the same composition. In other embodiments, the dapsone and other pharmaceutical are present in separate compositions. In preferred embodiments, the dapsone pharmaceutical composition is applied topically in the AM and a separate metronidazole composition is applied topically in the PM, or vice versa.

In some embodiments, the patient has mild to severe papulopustular rosacea. In some embodiments, the patient has mild to moderate papulopustular rosacea. In other embodiments, the patient has moderate to severe papulopustular rosacea. In preferred embodiments, the rosacea is moderate to severe papulopustular rosacea. In some embodiments, the patient has at least ten papulopustular lesions before treatment, or preferably at least twenty papulopustular lesions before treatment. In a preferred embodiment, the number of papulopustular rosacea lesions is reduced by administering the dapsone composition topically. In some embodiments, the methods described herein result in blood plasma levels of dapsone of less than about 100 ng/mL.

In some embodiments, the patient has an Investigator's Global Assessment score of 3 or higher before treatment. In some embodiments, treatment results in a mean reduction of at least 13 papulopustular lesions. In some embodiments, treatment results in a mean reduction of at least 43 % of the papulopustular lesions.

Brief Description of the Figures

Figure 1 shows the mean change from baseline in inflammatory lesion counts in the intent to treat (ITT) population having ≥ 10 inflammatory lesions (papules and/or pustules) above the mandibular line.

Figure 2 shows the mean percent change from baseline in inflammatory lesion counts in the ITT population having ≥ 10 lesions (ITT).

Figure 3 shows mean change from baseline in inflammatory lesion counts for subjects with <20 lesions.

Figure 4 shows mean percent change from baseline in inflammatory lesion counts for subjects with <20 lesions.

Figure 5 shows the mean change from baseline in lesion counts for the subgroup of subjects with ≥ 20 lesions.

Figure 6 shows mean percent change from baseline in inflammatory lesion counts for subjects with ≥ 20 lesions.

Figure 7 shows the Investigator's Global Assessment (IGA) success rate over the course of the study in the intent to treat (ITT) population having ≥ 10 inflammatory lesions.

Figure 8 summarizes the Investigator's Global Assessment (IGA) success rate at week 12 in the intent to treat (ITT) population having ≥ 10 inflammatory lesions.

Figure 9 shows the Investigator's Global Assessment (IGA) success rate over the course of the study in subjects with <20 inflammatory lesions.

Figure 10 shows the Investigator's Global Assessment (IGA) success rate over the course of the study in subjects with ≥ 20 lesions.

Figure 11 summarizes the Investigator's Global Assessment (IGA) success rate at week 12 for the subgroup of subjects with ≥ 20 lesions.

Detailed Description of the Invention

Definitions

As used herein, "adverse event" means any adverse change in health or "side-effect" that occurs in a patient who is participating in a study while the patient is receiving treatment (dermatological composition or vehicle) or within a pre-specified period of time after their treatment has been completed.

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