(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 May 2009 (14.05.2009)

PCT

(10) International Publication Number
WO 2009/061298 A1

(51) International Patent Classification:
A61K 31/136 (2006.01) *A61K 47/32* (2006.01)
A61K 9/00 (2006.01) *A61P 17/00* (2006.01)
A61K 9/06 (2006.01) *A61P 17/10* (2006.01)

(21) International Application Number:
PCT/US2007/023468

(22) International Filing Date:
7 November 2007 (07.11.2007)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant *(for all designated States except US)*: **QLT USA, INC.** [US/US]; 2579 Midpoint Drive, Fort Collins, CO 80525-4417 (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).

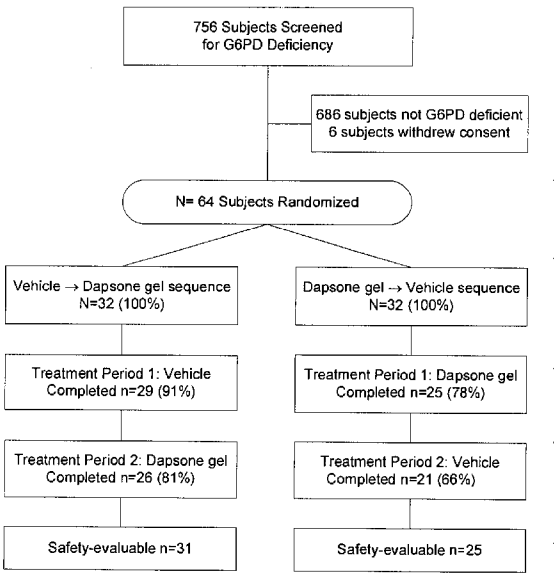
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(54) **Title:** TOPICAL TREATMENT WITH DAPSONE IN G6PD-DEFICIENT PATIENTS

Figure 1



(57) **Abstract:** The present invention provides a pharmaceutical carrier system comprising a dermatological composition that is a semi-solid aqueous gel, wherein dapsone is dissolved in the gel such that the dapsone has the capacity to cross the stratum corneum layer of the epidermis, and wherein the composition also contains dapsone in a microparticulate state that does not readily cross the stratum corneum of the epidermis. The present invention also discloses the treatment of dermatological conditions in G6PD-def icient patients with the composition, while avoiding adverse hematologic effects.

WO 2009/061298 A1

TOPICAL TREATMENT WITH DAPSONE IN G6PD-DEFICIENT PATIENTS

Background of the Invention

Dapsone is a sulfone with both anti-inflammatory and antimicrobial properties. The oral formulation of the drug is used to treat leprosy, dermatitis herpetiformis, and malaria, using typical doses of 100 mg to 300 mg daily, but historically, it was also used to treat severe acne in doses ranging from 50 mg/day to 300 mg/week (Wolf et al., 2002; Ross 1961; Prendiville et al., 1988). Currently, use of oral dapsone is generally limited to more severe forms of skin disease, as its use may be associated with hematologic side effects, including hemolysis and hemolytic anemia that are dose-dependent and occur more frequently with increasing dose (Zhu and Stiller 2001; Jollow et al., 1995).

The mechanism of dapsone-related hemolysis and hemolytic anemia involves oxidative damage to red blood cells and is associated with the dapsone hydroxylamine metabolite (Prendiville et al., 1988). Red blood cells are somewhat protected against oxidative injury and lysis by glutathione reduction, a metabolic pathway that involves the glucose-6-phosphate dehydrogenase (G6PD) enzyme. Consequently, individuals who are G6PD-deficient are more sensitive to developing hemolytic anemia after exposure to hemolytic stressors such as infection, administration of a variety of drugs, including dapsone, or ingestion of fava beans (Beutler 1994). G6PD deficiency is most prevalent in individuals of African, Southeast Asian, and Middle Eastern heritage, and because the G6PD enzyme is encoded on the X chromosome, the deficiency is more common in males. In the United States, a recent study of military personnel reported the prevalence of G6PD deficiency to be 2.5% in men and 1.6% in women (Chinevere et al., 2006). Amongst racial groups, the prevalence was highest in African American men (12.2%), Asian men (4.3%), and African American women (4.1%), and lowest in Caucasian men and women (0.3% and zero, respectively). An early study that compared the effects of oral dapsone treatment in G6PD-deficient and non-deficient men found that there was a direct, linear relationship between oral dapsone dose and extent of red blood cell

hemolysis in both the normal and deficient groups. The doses causing hemolysis in G6PD-deficient subjects were approximately half of the doses that caused hemolysis in subjects with normal G6PD levels (DeGowin et al., 1966).

What is needed is a method of treating dermatological conditions in patients including G6PD-deficient patients without the adverse hematologic effects associated with oral dapsone administration.

Summary of the Invention

The present invention provides methods to treat glucose-6-phosphate dehydrogenase-deficient patients with dapsone. In one embodiment, the treatment is directed to dermatological conditions and the treatment is provided by a topical dapsone composition. The composition may include dissolved dapsone and microparticulate dapsone. In certain embodiments, the dermatological condition to be treated is inflammatory acne, non-inflammatory acne or rosacea.

Second medical uses of the dapsone composition and methods of manufacture using the dapsone composition for treating dermatological conditions in a glucose-6-phosphate dehydrogenase-deficient patient are also contemplated by the present invention.

The present invention provides a pharmaceutical carrier system comprising a dermatological composition that is a semi-solid aqueous gel, wherein dapsone is dissolved in the gel such that the dapsone has the capacity to cross the stratum corneum layer of the epidermis and become available systemically, and wherein the composition also contains dapsone in a microparticulate state that does not readily cross the stratum corneum of the epidermis. The ratio of microparticulate to dissolved dapsone is adjustable, but is preferably five or less. Second medical uses of the dermatological composition and methods of manufacture of a medicament for treating dermatological conditions in a glucose-6-phosphate dehydrogenase-deficient patient using the dermatological composition are also contemplated by the present invention.

In some embodiments, the dermatological composition for use in methods of treating glucose-6-phosphate dehydrogenase-deficient patients includes a thickening agent; water; a high-boiling, nonionic organic solvent; a

preservative; dapsone in a microparticulate and dissolved state; and a base solution. In one preferred embodiment, the composition includes about 0.5% to 4.0% carbomer; about 53.8% to 84.2% water; about 10% to 30% ethoxydiglycol; about 0.2% methylparaben; about 5% to 10% dapsone in a microparticulate and dissolved state; and about 0.1% to 2% sodium hydroxide solution. In some embodiments, the composition includes about 1% carbomer; about 81.8% water; about 10% ethoxydiglycol; about 0.2% methylparaben; about 5% dapsone in a microparticulate and dissolved state; and about 2% sodium hydroxide solution. In another preferred embodiment, the dermatological composition includes about 0.85% carbomer; about 66.95% water; about 25% diethylene glycol monoethyl ether; about 0.2% methylparaben; about 5% dapsone; and about 0.2% sodium hydroxide. Second medical uses of the dermatological composition and methods of manufacture of a medicament for treating dermatological conditions in a glucose-6-phosphate dehydrogenase-deficient patient using the dermatological composition are also contemplated by the present invention.

In certain embodiments, the invention provides a method to treat a dermatological condition in a glucose-6-phosphate dehydrogenase-deficient patient comprising applying topically a dermatological gel composition that includes a semisolid aqueous gel; dapsone dissolved in the gel, wherein the dapsone has the capacity to cross the stratum corneum layer of the epidermis and become available systemically; and a microparticulate dapsone dispersed in the gel, wherein the microparticulate dapsone does not cross the stratum corneum of the epidermis in its microparticulate state. The dermatological condition can include inflammatory acne, non-inflammatory acne and/or rosacea.

In embodiments where acne is treated, the acne can be non-inflammatory acne, inflammatory acne, or both. In some embodiments, the dermatological dapsone composition is a semisolid aqueous gel. In other embodiments, the dermatological dapsone composition is a cream or a lotion. In still other embodiments, the dapsone composition is a suspension, ointment, or spray. In each of these embodiments, the dapsone may exist as a microparticulate form, a dissolved form, or both.

In a preferred embodiment, the invention provides a method to treat a dermatological condition in a glucose-6-phosphate dehydrogenase-deficient patient by applying a dermatological composition to the condition, wherein the

dermatological composition includes dapsone, wherein the method results in blood plasma levels of dapsone and N-acetyl dapsone below the levels associated with hemolysis. Second medical uses of the dermatological composition and methods of manufacture of a medicament for treating dermatological conditions in a glucose-6-phosphate dehydrogenase-deficient patient using the dermatological composition are also contemplated by the present invention.

In another preferred embodiment, the invention provides a method to treat a dermatological condition in a glucose-6-phosphate dehydrogenase-deficient patient by applying a dermatological composition to the condition, wherein the dermatological composition includes dapsone, and wherein the method results in blood plasma levels of dapsone and N-acetyl dapsone between about 0.5μg/mL and 1.0 μg/mL. Second medical uses of the dermatological composition and methods of manufacture of a medicament for treating dermatological conditions in a glucose-6-phosphate dehydrogenase-deficient patient using the dermatological composition are also contemplated by the present invention.

In another preferred embodiment, the invention provides a method to treat a dermatological condition in a glucose-6-phosphate dehydrogenase-deficient patient by applying a dermatological composition to the condition, wherein the dermatological composition includes dapsone, and wherein the method results in blood plasma levels of dapsone and N-acetyl dapsone of about 1 μg/mL or less. Second medical uses of the dermatological composition and methods of manufacture of a medicament for treating dermatological conditions in a glucose-6-phosphate dehydrogenase-deficient patient using the dermatological composition are also contemplated by the present invention.

In another preferred embodiment, the invention provides a method to treat a dermatological condition in a glucose-6-phosphate dehydrogenase-deficient patient by applying a dermatological composition to the condition, wherein the dermatological composition includes dapsone, and wherein the method results in blood plasma levels of dapsone between 0 and about 37 ng/mL and blood plasma levels of N-acetyl dapsone between 0 and about 50 ng/mL. Second medical uses of the dermatological composition and methods of manufacture of a medicament for treating dermatological conditions in a

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.