PRODUCT MONOGRAPH

SOLAGÉ®

(Mequinol 2% / Tretinoin 0.01%)

Topical Solution

Agent for the treatment of solar lentigines and related hyperpigmented lesions

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THERAPEUTIC CLASSIFICATION

Agent for the treatment of solar lentigines and
related hyperpigmented lesions

ACTION AND CLINICAL PHARMACOLOGY

Solar lentigines and related hyperpigmented lesions are localized, pigmented, macular lesions of the skin, usually on the areas of the body which have been chronically exposed to sunlight. These lesions are characterized by increased numbers of active melanocytes and increased melanin production.

The exact mechanism of action of mequinol as a depigmenting agent is unknown.

Mequinol is a substrate for the enzyme tyrosinase and acts as a competitive inhibitor of the formation of melanin precursors.

The exact mechanism of action of tretinoin also is unknown. It is believed that the therapeutic effect of topically-applied tretinoin is due to its ability to inhibit melanogenesis by inhibiting the induction of tyrosinase thus decreasing melanin content in the epidermis. Tretinoin is also believed to act as a regulator in controlling differentiation of various cell types.

The percutaneous absorption of tretinoin was approximately 4.4 % and systemic concentrations did not increase over endogenous levels, following the assessment of the percutaneous absorption of tretinoin and the systemic exposure to tretinoin and mequinol in healthy subjects (n=8) after two weeks of twice daily topical treatment with SOLAGÉ®. Approximately 0.8 mL of SOLAGÉ® was applied to a 400 cm^2 area of the back, corresponding to a dose of 37.3 µg/cm^2 for mequinol and 0.23 µg/cm^2 for tretinoin.

INDICATIONS AND CLINICAL USE

SOLAGÉ® (mequinol 2%, tretinoin 0.01%) Topical Solution is indicated for the treatment of solar lentigines and related hyperpigmented lesions resulting from chronic sun exposure.

SOLAGÉ® should be used as part of a comprehensive skin care and sun avoidance program that should include the use of effective sunscreens and protective clothing.

CONTRAINDICATIONS

SOLAGÉ® (mequinol 2%, tretinoin 0.01%) Topical Solution is contraindicated in individuals with a history of sensitivity reactions to any of its ingredients.

SOLAGÉ® should be administered with caution if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented photosensitivity.

WARNINGS

Use of SOLAGÉ® (mequinol 2%, tretinoin 0.01%) should be discontinued if hypersensitivity to any of the label ingredients is noted. SOLAGÉ® should be used with caution by patients with a history, or family history, of vitiligo.

SOLAGÉ® should be kept out of the eyes, mouth, paranasal creases, and mucous membranes. SOLAGÉ® may cause skin irritation, erythema, burning, stinging or tingling, peeling, and pruritus. If the degree of such local irritation warrants, patients should be directed to use less medication, decrease the frequency of application, discontinue use temporarily, or discontinue use altogether. The efficacy at reduced frequencies of application has not been established.

Tretinoin should not be used on inflamed or irritated skin.

USE IN WOMEN

Use In Pregnancy

There have been rare reports of birth defects among babies born to women exposed to topical tretinoin during pregnancy. However, there are no adequate and well-controlled prospective studies of the use of topical tretinoin in pregnant women. A retrospective study of mothers exposed to topical tretinoin during the first trimester of pregnancy found no increase in the incidence of birth defects. Topical retinoid teratology studies in rats and rabbits have been inconclusive. As with all retinoids, tretinoin administered orally at high doses is teratogenic. SOLAGÉ® should be used by women of childbearing years only after contraceptive counselling. SOLAGÉ® should not be used during pregnancy. (See TOXICOLOGY)

Lactating Women

It is not known to what extent mequinol and/or tretinoin is excreted in human milk. SOLAGÉ® should not be administered to a nursing woman.

USE IN PAEDIATRICS

The safety and effectiveness of this product have not been established in paediatric patients. It is intended for the treatment of solar lentigines and related hyperpigmented lesions, which is not usually observed in the paediatric population.

PRECAUTIONS

General

Exposure to sunlight and sun lamps should be avoided or minimized during the use of SOLAGÉ® (Mequinol 2% / Tretinoin 0.01%), because of heightened susceptibility to UV radiation as a result of the use of tretinoin. SOLAGÉ® should be used as part of a comprehensive skin care and sun avoidance program that should include the use of sunburn protectant products with a SPF of at least 15 and protective clothing over treated areas is recommended when exposure cannot be avoided. Patients with sunburn should be advised not to use SOLAGÉ® until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise caution when using SOLAGÉ®.

Weather extremes, such as wind or cold, may be more irritating to patients using SOLAGÉ®.

DRUG INTERACTIONS

Concomitant topical products with a strong skin drying effect, products with high concentrations of alcohol, astringents, spices or lime, medicated soaps or shampoos, permanent wave solutions, electrolysis, hair depilatories or waxes, or other preparations that might dry or irritate the skin should be used with caution in patients being treated with SOLAGÉ® because they may increase irritation with SOLAGÉ®.

Skin Irritation

The application of SOLAGÉ® may cause transitory stinging, burning or irritation. Tretinoin should not be used on inflamed or irritated skin. Application of larger amounts of medication than recommended will not lead to more rapid or better results, and marked redness, peeling, discomfort, or hypopigmentation of the skin may occur.

Carcinogenesis

Animal studies have shown increased tumorigenic risk with the use of retinoids when exposed to ultraviolet radiation. Although the significance of these studies to human use is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial ultraviolet irradiation sources. (See TOXICOLOGY)

USE IN GERIATRICS

Of the total number of patients in clinical studies of SOLAGÉ®, approximately 43% were 65 and older, while approximately 8% were 75 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

In clinical trials, adverse reactions were primarily mild in intensity, limited to the skin and occurred early in treatment. The most frequent adverse reactions in patients treated with SOLAGÉ® (mequinol 2%, tretinoin 0.01%) were erythema (by approximately 50% of patients), burning, stinging or tingling (approximately 25%), desquamation and pruritus (between 10 - 15%), and skin irritation (approximately 5%). Some patients experienced temporary hypopigmentation of treated lesions (5%) or of the skin surrounding treated lesions (7%). These resolved upon discontinuation of treatment to the lesion, and/or re-instruction on proper application to the lesion only. Approximately 6% of patients discontinued study participation with SOLAGÉ® due to adverse reactions. SOLAGÉ® was generally well tolerated.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

If SOLAGÉ® (mequinol 2%, tretinoin 0.01%) is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur. Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of vitamin A (hypervitaminosis A) including teratogenesis in women of childbearing years. If oral ingestion occurs, the patient should be monitored, and appropriate supportive measures should be administered as necessary. Women of childbearing years should have a pregnancy test. The maximal no-effect level for oral administration of SOLAGÉ® in rats was 5.0 mL/kg (30 mg/m^2).

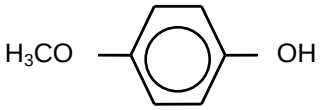
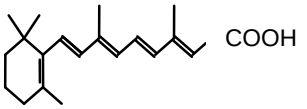
DOSAGE AND ADMINISTRATION

Apply SOLAGÉ® (mequinol 2%, tretinoin 0.01%) to the solar lentigines using the applicator tip while avoiding application to the surrounding skin. Use twice daily, at least eight hours apart, or as directed by a physician.

Improvement continues gradually through the course of therapy and use may be continued until a satisfactory improvement is seen. To prevent further progression of the condition, avoid or minimize sun exposure by wearing protective clothing and/or using a sunscreen (a minimum sun protection factor (SPF) of 15 is recommended).

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCES

Common Name	Mequinol	Tretinoin
Chemical Name	1 hydroxy-4-methoxy benzene	(all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1- yl)-2,4,6,8-nonatetraenoic acid
Structural Formula		
Molecular Formula	$C_7H_8O_2$	$C_{20}H_{28}O_2$
Molecular Weight	124.14 g/mol	300.44 g/mol
Description	Mequinol is a crystalline powder with a pKa of 10.25.	Tretinoin is a crystalline powder with a pKa of 4.7.

COMPOSITION (Solution)

Mequinol 2% (w/v)
Tretinoin 0.01% (w/v)
Ascorbic Acid
Ascorbyl Palmitate
Alcohol, Ethyl (77.8% v/v)
Butylated Hydroxytoluene
Citric Acid
Edetate Disodium
Polyethylene Glycol 400
Water

STABILITY AND STORAGE RECOMMENDATIONS

The bottle should be protected from light by continuing to store in the carton after opening. Store at controlled room temperature, 15-30 °C.

Note: FLAMMABLE. Keep away from heat and open flame.

AVAILABILITY OF DOSAGE FORM

SOLAGÉ® (mequinol 2%, tretinoin 0.01%) Topical Solution is a clear, yellowish liquid. The product is available in 30 mL plastic bottles with an applicator.

SOLAGÉ® Topical Solution is a prescription drug (Schedule F).

INFORMATION FOR THE PATIENT

Patients using SOLAGÉ® (mequinol 2%, tretinoin 0.01%) should receive the following information and instructions:

1. This medication is to be used twice daily at least 8 hours apart or as directed by the physician. It is a drug for external use only and is not a cosmetic preparation. Avoid contact with eyes, lips, creases of the nose or mucous membranes. If product gets in eyes, rinse thoroughly with water.
2. Avoid or minimize exposure to sunlight and sun lamps because SOLAGÉ® heightens the susceptibility of your skin to the adverse effects of the sun. Use of sunburn protectant products with a sun protection factor (SPF) of at least 15 and protective clothing over treated areas is recommended when exposure cannot be avoided. Following discontinuation of SOLAGÉ®, continued avoidance of the sun or use of a sunscreen is recommended.
3. Do not use SOLAGÉ® if you are sunburned, have eczema or other inflamed or irritated chronic skin condition(s).
4. Do not use SOLAGÉ® if you are inherently sensitive to sunlight or taking other drugs that increase sensitivity to sunlight.
5. SOLAGÉ® should be used with caution if you are also using other topical products with a strong skin drying effect, products with high concentrations of alcohol, astringents, spices or lime, medicated soaps or shampoos, permanent wave solutions, electrolysis , hair depilatories or waxes, or other preparations or processes that might dry or irritate your skin, unless otherwise instructed by your physician.
6. This medication may cause stinging, burning or irritation on application to affected areas of your skin.
7. If sensitivity or increased chemical irritation occurs, you should discontinue use and consult with your physician.
8. If the hyperpigmentation worsens with treatment, the patient should discontinue use and consult with their physician.
9. Apply SOLAGÉ® to the solar lentigines using the applicator tip, while avoiding application to the surrounding normally pigmented skin. Only enough SOLAGÉ® should be used to make the lesion appear moist; running or dripping should be avoided. Applications of larger amounts of medication or more frequently than recommended will not lead to more rapid or better results, and marked redness, peeling, or irritation may occur.
10. Women of childbearing years should use SOLAGÉ® only after consulting their physician about contraceptive counselling. If pregnant, use of SOLAGÉ® should be discontinued.
11. SOLAGÉ® should be kept away from heat or open flame, and the bottle should be protected from light by continuing to store in the carton after opening.
12. This medication must only be used by you. Do not allow anyone else to use it.
13. Keep this and all other medication out of the reach of children.

PHARMACOLOGY

Animal Model

The Yucatan miniature pig is an appropriate model for human dermal studies since the morphologic and functional similarities between pig skin and human skin are well recognized. The combination of mequinol /tretinoin (BMS 181158/BMS 181159) was evaluated for its potential depigmenting activity in two unique Yucatan miniature pig models which represent the two major types of skin hyperpigmentation: melanotic and melanocytic hyperpigmentation.

Dark-skinned Yucatan pigs were used as a model of melanotic hyperpigmentation. This model represents the hyperpigmentation seen in post-inflammatory hypermelanosis and in melasma, but without the hormonal influences occurring with melasma. Healthy Yucatan pigs with even, dark-brown skin were selected to test the depigmenting effect of several compounds. The skin of these animals exhibit normal numbers of melanocytes but the melanocytes contain larger amounts of melanin pigment.

Test formulations were applied twice daily, five days a week to the dorsal flank of the pigs skin for up to 12 weeks. The model was validated using three known human depigmenting agents, hydroquinone, hydroxyanisole and tert-butyl catechol.

The optimum concentrations of mequinol and tretinoin in the combination product were selected from studies in pigs designed to determine an effective concentration ratio with minimal skin irritation. In order to clearly demonstrate synergy, various concentrations of both components were evaluated. The mequinol concentrations ranged from 0.5% to 5% and the tretinoin concentrations ranged from 0.01% to 0.1%. Since 2% mequinol showed a minimal degree of hypopigmentation when it was applied as a single agent, this dose was selected for evaluating the synergistic effect with varying concentrations of tretinoin.

The 2% mequinol /0.01% tretinoin combination produced slight to moderate depigmentation between 6 to 12 weeks of b.i.d. dosing. Minimal irritation was observed. Seven weeks after discontinuing treatment, the pigmentation of the sites treated with 2% mequinol /0.01% tretinoin appeared to have returned to near normal colour. The depigmentation produced by 2% mequinol combined with tretinoin at 0.1% and 0.025% concentrations did not significantly differ from that observed with 2% mequinol combined with 0.01% tretinoin.

Electron microscopic examination of skin biopsies taken from Yucatan pigs after treatment demonstrates that the mequinol /tretinoin combination did not cause melanocyte cell death. This observation in conjunction with the repigmentation of the treated areas suggests that the mequinol /tretinoin combination interferes with the normal pigmentation process in a reversible manner. In addition, in these 12 week studies of the Yucatan pig there was no evidence of basal keratinocyte pseudopodia as was previously reported at exaggerated experimental concentrations of 20% mequinol in black guinea pigs.

A second model was used to evaluate the effect of mequinol /tretinoin on melanocytic hyperpigmentation. UV-induced hyperpigmentation in the light skinned Yucatan miniature pig may be representative of a melanocytic disorder. Such disorders are characterized by both an increased number of active melanocytes and increased melanin production. This condition may be representative of the changes typical of melanocytic hyperpigmentation disorders such as

solar lentigines. The UV-induced hyperpigmented areas on light skinned pigs were treated with the mequinol /tretinoin combination product to determine its ability to reverse the induced hyperpigmentation.

As single agents, 2% mequinol and 0.01% tretinoin showed very little depigmentation of the hyperpigmented spot or of the normal skin surrounding the spot after eight weeks of treatment. The combination of 2% mequinol /0.01% tretinoin produced the first signs of depigmentation of the UV-induced hyperpigmented skin after the second week of treatment. In contrast, the first definitive signs of depigmentation of the normal skin surrounding the UV-induced hyperpigmented spot were apparent after six weeks of treatment. The combination of 2% mequinol /0.01% tretinoin produced complete depigmentation of the UV-induced hyperpigmented spots and only mild depigmentation of the surrounding normal skin after eight weeks of treatment.

In vitro Animal Skin

In vitro studies with whole mouse skin using the Franz diffusion cell chamber, demonstrated that the permeability of the skin to mequinol is relatively high (50-60% within 10 hours). The high skin permeation of mequinol alone is not unexpected and can be explained by its physico-chemical characteristics such as low molecular weight and its ability to solubilize both in aqueous and lipid domains of the skin.

A single *in vitro* application of tretinoin to mouse skin did not significantly increase the penetration of mequinol. However, skins taken from mice that were pretreated *in vivo* for one week with the mequinol /tretinoin combination appeared to be directionally more permeable to mequinol at 10 hours when compared to skin taken from mice pretreated with vehicle. However, the total amount of mequinol that penetrated during the entire 24 hour study period was not significantly different between the two groups.

In vitro Human Skin

An *in vitro* human skin study utilizing the Franz diffusion chamber and an hydroalcoholic solution containing a finite dose of mequinol /tretinoin demonstrated that mequinol rapidly permeated the skin; 40% at 24 hours and 60% at 72 hours. Seventy-two hours after application, less that 1% of the applied dose was retained in either the epidermis or dermis. Here, as in the mouse skin, a single *in vitro* application of tretinoin did not significantly alter the permeation of mequinol across the skin.

In vivo Animal Skin

The effect of the mequinol /tretinoin combination on melanocyte morphology of Yucatan pig was evaluated using light and electron microscopy. The results suggest that the combination has a direct effect on melanocyte function and morphology. The mequinol /tretinoin treatment decreased the apparent number of melanosomes formed in melanocytes and appeared to result in a lower rate of transfer of melanosomes to keratinocytes. Melanocytes were observed in all specimens including those that had complete depigmentation. Therefore, the treatment does not appear to be melanocidal and this feature may account for the reversibility of the depigmentation effect.

The mode of action responsible for the synergistic depigmentation induced by mequinol combined with tretinoin is not clear, but probably involves more than one pathway.

The most likely candidates include 1) the down regulation of tyrosinase activity, 2) the ability to interfere with the transfer of melanosomes to keratinocytes and 3) the inhibition of tyrosinase activity by mequinol.

An *in vivo* study was performed in rats to determine the tissue distribution of an intravenous dose of [^{3}H] tretinoin. The highest concentrations of radioactivity were observed in tissues from the group of rats sacrificed 30 minutes post dose. Plasma concentrations in this group averaged 8.3 µg-equivalent/mL and the tissue concentrations ranged from a high of 35 µg-equivalent/g in liver to a low of 0.71 µg-equivalent/g in bone. The results of this study show that radioactive [^{3}H] tretinoin and/or its metabolites are extensively distributed throughout the body of male Long-Evans rats.

In summary, the pharmacologic studies demonstrate that the combination of 2% mequinol /0.01% tretinoin acts synergistically to depigment the normal dark skin of the Yucatan pig and reverse the UV-induced hyperpigmentation of the normal light-skinned pig. The depigmentation was reversible and only minimal skin irritation following repeated administration was observed.

CLINICAL PHARMACOLOGY

Solar lentigines are characterized by increased numbers of active melanocytes and increased melanin production. Historically, there are two types of topical agents which are used in the treatment of solar lentigines and which presumably act on melanocytes. Tretinoin, a retinoid related to Vitamin A, is the most widely used agent in this class for the treatment of sun induced changes (photodamage) of the skin, including hyperpigmentation.

The ability of tretinoin to inhibit melanogenesis is believed to involve inhibition of tyrosinase induction. Tyrosinase is a key enzyme in the biosynthetic pathway leading to melanin production. Decreasing melanocyte melanin production would result in the lightening of the skin since fewer melanosomes would be available for transfer to keratinocytes. Tretinoin has also been reported to reduce the cohesiveness of corneocytes and promote desquamation.

Hydroquinone is the second most widely used topical agent for the treatment of solar lentigines. Hydroquinone may depigment solar lentigines by serving as a substrate analog in the melanin biosynthetic pathway. Hydroquinone is very similar to tyrosine, the substrate of tyrosinase. Mequinol, the mono-methyl ether of hydroquinone, can also serve as a substrate for tyrosinase. Oxidation of hydroquinone or mequinol by tyrosinase is believed to result in the production of a semiquinone free radical. This free radical can damage the melanocyte cell membrane and interfere with melanocyte function, possibly resulting in cell death.

To support radiation dosimetry calculations in preparation for a human percutaneous absorption study with [^{3}H]tretinoin, a tissue distribution study was conducted in male Long-Evans rats. The study showed that after IV administration, [^{3}H]tretinoin and/or its metabolites were extensively distributed throughout the body. The data also suggested that [^{3}H]tretinoin was extensively excreted by the biliary route.

A human pharmacokinetics study (DE132-008) was conducted to estimate the extent of percutaneous absorption of [^{3}H] tretinoin and the systemic exposure to 4-HA and tretinoin after topical application of 2% mequinol /0.01%[^{3}H] tretinoin to the back of healthy normal volunteers. The radiolabelled dose was applied after 14 days of twice daily non-radiolabeled applications.

Based on the recovery of drug-related radioactivity in urine and feces samples collected for 7 days following administration of the radiolabelled dose 2.0% mequinol /0.01% [^{3}H]tretinoin the percutaneous absorption of tretinoin averages 4.43%. This value is similar to the percutaneous absorption of tretinoin reported in the literature for other topical preparations where the percutaneous absorption ranged from 0.5% to about 7.0%. The mean overall recovery of radioactivity from urine, feces and the application site combined was 92.4%. No increase beyond endogenous levels of tretinoin (1 ng/mL of plasma) was seen in this study.

The systemic exposure to mequinol in humans was determined following the topical application of a formulation containing 2.0% mequinol . The mean CMAX value, TMAX value and AUC (0-12) are presented in the Table below.

Cmax, Tmax and AUC for Mequinol (4-hydroxy anisole) in Human Plasma

Statistic	Cmax (ng/mL)	Tmax (hr)	AUC (0-12) (ng·h/mL)
Mean	9.92	2.00*	33.43
SD	7.48	(1.00, 2.00)	14.3

*** Median (Minimum, Maximum)**

The maximum exposure to mequinol in mice was 16.6 times the exposure of humans in the pharmacokinetics study. The maximum exposure to mequinol in rats was 34.6 times the exposure of humans in the pharmacokinetics study.

Additionally, biopsies of clinically diagnosed solar lentigines were collected in two studies where mequinol /tretinoin was used to treat these lesions. In the phase II pilot study (DE132-002), biopsies were collected for light microscopy to assess the accuracy of the diagnosis of solar lentigo. In the first pivotal study (DE132-005), biopsies of clinically diagnosed solar lentigines were obtained at baseline, at the end of treatment and at the end of study (6 months after the end of treatment) for electron microscopy analysis. This analysis was designed to evaluate the effects of up to six months of treatment with mequinol /tretinoin on melanocyte structure and melanocytes cytology after up to six months of treatment.

The light microscopic evaluation of the skin biopsies in DE132-002 confirmed the clinical diagnosis of solar lentigines for 72% of the lesions at baseline and at the end of treatment. The increase in the end of treatment diagnosis of other benign lesions is the result of these lesions failing to meet the criteria for being classified as a solar lentigo. The pathologist reported this to be the result of surgical artefact caused by the biopsy procedures.

The changes in melanocyte and keratinocyte morphology seen in the end of DE132-005

treatment specimens of the mequinol /tretinoin and tretinoin treatment groups are significant and correlate with the decrease in pigmentation noted in the clinical evaluations. These changes normalized during the no-drug treatment follow-up and it was concluded that the drug induced changes seen at the end of treatment are reversible and do not result in the death of melanocytes. Reversibility was also observed in the histological analysis of biopsies taken from the Yucatan pig.

Halo hypopigmentation and hypopigmentation are two treatment related outcomes that can occur with the use of any effective, topical depigmentation agent. Melanocytes are distributed throughout both normal and hyperpigmented skin and would be expected to respond to treatment with depigmentation agents.

Halo hypopigmentation is defined as the presence of a ring or 'halo' surrounding a treated, hyperpigmented lesion. This ring or 'halo' is lighter than both the hyperpigmented lesion and the normal, surrounding, untreated skin and therefore has a 'white' or 'light' appearance. Halo hypopigmentation is believed to result from consistent application of the depigmentation agent beyond the edge of the hyperpigmented lesion.

Hypopigmentation is defined as the replacement of a treated hyperpigmented lesion with a lesion which is now 'white' or 'light' when compared to normal, untreated surrounding skin. Hypopigmentation is believed to result from continued application of the depigmentation agent beyond the point in time where the treated lesion has reached a level of pigmentation equal to the surrounding, normal, untreated skin.

There were more reports of halo hypopigmentation than hypopigmentation. Most of the reports of halo hypopigmentation resolved without the need for discontinuation of dosing of the hyperpigmented lesion. When halo hypopigmentation was observed, the subject was reinstructed by the investigator and/or study coordinator in the proper use of the study drug and dose application.

Most occurrences of hypopigmentation of treated lesions were mild and resolved.

CONTROLLED CLINICAL TRIALS

Two adequate and well-controlled trials evaluated changes in treated hyperpigmented lesions on the face, forearms/back of hands in 421 patients treated with SOLAGÉ® Topical Solution, 420 patients treated with tretinoin topical solution, 208 patients treated with mequinol topical solution and 106 patients treated with vehicle for up to 24 weeks. In these studies, patients were to avoid sun exposure and use protective clothing, and use of sunscreens was prohibited. Physicians assessed the extent of improvement or worsening of all the treated lesions from the baseline condition on a 7 point scale. The results of these evaluations are shown below.

	Face		Forearms / Back of Hands	
	SOLAGÉ®	Vehicle	SOLAGÉ®	Vehicle
Moderate Improvement or greater[1]	56%	15%	53%	14%
Slight Improvement	28%	35%	27%	31%
No Change[2]	16%	50%	21%	55%

[1] Includes the following grades: Moderate Improvement, Marked Improvement, Almost Clear, Completely Clear. Moderate Improvement or greater was considered clinically meaningful.

[2] Includes the following grades: No Change, Worse (less than 1% of patients treated with SOLAGÉ® were rated as worse)

After eight weeks of treatment with SOLAGÉ®, 23% and 21% of patients experienced moderate improvement or greater for the face and forearms/back of hands, respectively. After 24 weeks of treatment, 56% and 53% of patients experienced moderate improvement or greater, and 3% and 1% of patients were completely clear of all treated lesions for the face and forearms/back of hands, respectively.

After 24 weeks of treating the forearm/back of hands treatment site, the percentage of patients treated with tretinoin topical solution with moderate improvement or greater, slight improvement, or no change, were 37%, 37%, and 26%, respectively, and for mequinol topical solution were 25%, 40% and 36%, respectively. For the face treatment site, the percentage of patients treated with tretinoin topical solution with moderate improvement or greater, slight improvement, or no change, were 46%, 34%, and 21%, respectively, and for mequinol topical solution were 33%, 30% and 36%, respectively.

The duration of effect was investigated in two adequate and well-controlled clinical studies which had 24 week no-treatment, follow-up periods after treatment cessation. Results from these studies showed that the majority of patients maintained the level of clinical improvement of their treated lesions from the end of treatment through the 24 week follow-up period. Those patients who did not maintain the level of improvement showed signs of repigmentation, demonstrating reversibility of the depigmenting action of SOLAGÉ®.

In the clinical studies, some patients experienced temporary hypopigmentation of treated lesions (5%) or of the skin surrounding treated lesions (7%). Hypopigmentation of the skin surrounding treated lesions occurred because of improper application of the drug beyond the lesion border. These resolved upon discontinuation of treatment to the lesion, and/or upon re-instruction on proper application to the lesion only. This further demonstrates the reversibility of the depigmenting action of SOLAGÉ®.

Over 150 patients used SOLAGÉ® twice daily for 52 weeks in an open label clinical study. The safety profile for SOLAGÉ® in this long term study was similar to that seen in the 24 week studies.

Over 90 patients used SOLAGÉ® twice daily and a concomitant sunscreen (PreSun® 29) daily

for up to 24 weeks in an open label clinical study. The safety profile for SOLAGÉ® in this study was similar to that seen in studies which prohibited sunscreen use.

The clinical studies of SOLAGÉ® included individuals of Skin Type I - V. Safety and effectiveness of SOLAGÉ® in individuals with Skin Type VI (never burns from the sun, deeply pigmented skin) have not been established.

TOXICOLOGY

ANIMAL

Single-Dose Studies

In the **single-dose dermal toxicity study in rabbits**, a single dose of 2.0 mL/kg (40/0.2 mg/kg) of the SOLAGÉ® formulation under 24-hour occlusion produced transient skin irritation. No mortality was observed and in general all animals gained weight. Dermal irritation consisted of well-defined erythema and very slight edema. A lower degree of irritation was observed in the vehicle control rabbits.

In the **single-dose oral rat toxicity study** in rats, the minimum lethal dose (LD) of the SOLAGÉ® formulation was greater than 5.0 mL/kg (100/0.5 mg/kg). Clinical observations noted immediately following dosing were depressed locomotor activity and ataxia in all animals. These findings were considered to be related to the high alcohol content of the solution formulation (77.8%). Most animals appeared normal approximately 4 hours after dosing. One female animal was found dead on Day 13; however, mortality was apparently a result of trauma to the respiratory tract caused during dose administration, rather than an affect of the administration of SOLAGÉ®.

Repeat-Dose Studies

Mouse

A **two-month dermal rangefinding phototoxicity study with ultraviolet radiation in hairless mice** was performed. Three groups of five male and five female Skh:hr-1 albino mice were given the SOLAGÉ® formulation at dose volumes of 10, 30 and 100 µL/mouse/day (corresponding to daily dose levels of approximately 8/0.04, 24/0.12 or 80/0.4 mg/kg/day) for 5 days per week. One group of control mice was given the vehicle formulation at 100 µL/mouse/day. All test and the vehicle control animals were irradiated 5 days per week with UVB radiation at a low-dose level equivalent to 0.272 Minimal Erythemal Dose (MED). Separate, untreated, control groups of mice were either irradiated with 0.272 MED or 0.382 MED (high-dose UV group). No treatment-related mortalities or body weight effects were observed during this study. Slight dryness or flaking of the treated skin was observed in all groups receiving the test formulation, beginning in the first week of the study and persisting until termination. Wrinkling of the application sites was observed in all mid- and high-dose animals and, in two of five males and four of five females in the low-dose group. The fine wrinkling was accompanied by sagging and decreased elasticity of the skin, particularly in the males. Slight treatment-related yellow discoloration of the application site was also seen in the males. No dermal changes were observed in either the low- or high-UV untreated or vehicle-control group

animals. At necropsy, enlargement of lymph nodes was observed in several males and females from each of the test formulation groups and one untreated control animal. Historical studies in hairless mice have shown that lymph node enlargement can result from chronic low- or high-dose UV irradiation. Microscopic examination of the skin sites revealed SOLAGÉ®-related changes of mild to moderate acanthosis, with minimal to mild chronic inflammation, hyperkeratosis and parakeratosis. The microscopic effects noted in the low-dose (10 µL) females were approximately the same as the effects observed in the untreated high-dose UVB irradiated group, while in the males, the effects of the low-dose level were greater than those associated with high-dose UVB phototoxicity. In the vehicle control and in the low- and high-dose UV untreated group, minimal focal to diffuse acanthosis was observed in the skin. Dose levels of 10, 30 and 100 µL/animal/day were selected for the 12-month photocarcinogenicity study.

A **three-month dermal rangefinding study in mice** was performed. The SOLAGÉ® formulation was administered dermally for 3 months to five groups of six male and six female CD-1 mice at dose volumes of 10, 25, 50, 100 and 150 µL/mouse/day (corresponding to daily dose levels of approximately 8/0.04, 20/0.2, 40/0.2, 80/0.4 or 120/0.6 mg/kg/day). A group of control mice was given the vehicle formulation at 150 µL/mouse/day. In this study, concentrations of SOLAGÉ® in plasma samples of the mice that were treated with the SOLAGÉ® formulation demonstrated a dose-related systemic exposure to SOLAGÉ®. No mortalities and no treatment-related systemic signs of toxicity or hematologic changes were observed. Dermal irritation, primarily erythema, was observed intermittently throughout the study in all groups treated with the SOLAGÉ® formulations. In general, the incidence and severity of irritation increased in a dose-related manner. Very slight erythema (grade 1) was noted in some animals at 10 and 25 µL/mouse/day, and well-defined erythema was noted in several animals treated at 50, 100 and 150 µL/day with SOLAGÉ®. In the high-dose group, moderate to severe and severe erythema (grades 3 and 4) occurred sporadically during the study and severe erythema with eschar was also noted in two animals in this group. Very slight to slight edema (grades 1 and 2) was observed sporadically in several dose groups. Desquamation and pinpoint scabbing were observed in all treatment groups during the study. No dermal irritation effects were observed in the vehicle control group. Male mice given the high-dose formulation (150 µL/animal) had increased spleen weights. Treatment-related gross lesions were confined to the application sites of mice treated with SOLAGÉ®. Histopathologic examination of the application sites revealed treatment-related changes in the skins of all SOLAGÉ®-treated mice. The incidence and severity of diffuse acanthosis of the epidermis (minimal to marked) occurred in a dose-related manner. No other treatment-related microscopic findings were observed. Based on the irritation data, the high dose of 150 µL/mouse/day exceeded the Maximum Tolerated Dose (MTD). Doses selected for the 2-year dermal study were 10, 30 and 100 µL/mouse/day.

Rat

A **two-week repeat-dose dermal toxicity study in rats** was performed. SOLAGÉ® combination solution prototypes at concentrations of 20.0/0.1 (2%/.01%) and 40.0/0.1 (4%/.01%) mg/mL and at a dose volume of 2.0 mL/kg/day were topically administered to Sprague-Dawley rats (three/sex/group), once daily for a period of 14 days. A vehicle control group received treatment at the same dose volume and frequency as the treated animals. No remarkable treatment-related findings were observed. Body weight data of the treated groups did not differ significantly from control throughout the study. Cumulative dermal effects included

observations of slight to moderate dermal irritation and focal eschar formation in the SOLAGÉ®-treated groups, with slightly increased severity in the 4% mequinol /0.01% tretinoin animals. No evidence of dermal irritation was observed in the male animals of the vehicle control groups; however, female control animals exhibited very slight, transient dermal irritation during the first week of the study. Microscopic evaluation revealed dermal and epidermal inflammation, acanthosis, hydropic degeneration, and incipient fibrosis. Female rats appeared to be slightly more affected than male rats.

A **one-month interim report of a 6-month dermal toxicity study in rats** was performed. During a 6-month study, the SOLAGÉ® formulation was administered dermally to three groups of 16 male and 16 female rats at single daily SOLAGÉ® doses of 4/0.02, 12/0.06 and 40/0.20 mg/kg (corresponding to dose volumes of 0.2, 0.6 and 2.0 mL/kg/day). As a comparative control, 2% mequinol was administered to a group of rats at mequinol doses of 40 mg/kg daily and served as the control. All animals were collared daily for up to 6 hours to prevent possible ingestion of test material. After 1 month of dosing, six of 16 males and six of 16 females from each group were sacrificed for interim pathologic evaluation. At 1 month, rats treated with the high-dose combination had slight decreases in hemoglobin, hematocrit, and erythrocyte count. No treatment-related changes were noted in rats given the mequinol formulation or vehicle formulation. Treatment-related gross and microscopic lesions were limited to the application sites of rats treated with SOLAGÉ®. All rats treated with the SOLAGÉ® formulation showed time- and dose-related increases in the incidence and severity of focal or multifocal scab formation at the application sites. Histopathologic examination of the application sites in rats sacrificed at 1 month revealed dose-related increases in the incidence and/or severity of acanthosis (thickening of the epidermis), chronic-active inflammation of the superficial dermis, and scabs. The severity of the application-site lesions was minimal in the low- and intermediate-dose groups, and mild in the high-dose group. No histopathologic lesions were noted at the application sites of the vehicle control or mequinol -treated animals.

In a **six-month dermal toxicity study in rats**, the SOLAGÉ® formulation was administered dermally to three groups of 16 male and 16 female rats at SOLAGÉ® doses of 4/0.02, 12/0.06, and 40/0.2 mg/kg/day (corresponding to dose volumes of 0.2, 0.6 and 2 mL/kg/day). As a comparative control, a 2% mequinol was administered to a group of rats at mequinol doses of 40 mg/kg daily. An additional group of rats was given the vehicle formulation at 2 mL/kg daily and served as the control. Six of 16 males and six of 16 females from each group were sacrificed for interim pathologic evaluation after 1 month (see above), and the remaining animals were sacrificed after 6 months of dosing. After 6 months, high-dose rats showed only a very slight increase in neutrophil count. At that time, females given the mequinol formulation showed a slight decrease in serum potassium. Following 6 months of treatment, female rats given the high dose of the SOLAGÉ® formulation had slightly increased liver weights. Treatment-related gross lesions were limited to the application sites of rats treated with SOLAGÉ®. The rats showed time- and dose-related increases in the incidence and severity of scab formation and, to a less extent, erythema/edema (intermediate and high doses) at the application sites. Histopathologic examination of the application sites revealed dose-related increases in the incidence and/or severity of acanthosis, chronic-active inflammation of the superficial dermis, and scabs. Minimal superficial dermal haemorrhage or edema and minimal to moderate erosion/ulceration were also noted, particularly in males at the intermediate and high doses. Minimal scabbing, acanthosis, or chronic-active inflammation were observed microscopically at the application sites of several rats treated with the mequinol formulation, only at the end of the 6-month dosing period.

Reproductive Studies

Rat

A **dermal study of fertility and early embryonic development in rats** was performed. The 2% mequinol /0.01% tretinoin solution was administered topically to 25 rats/sex/group at doses of 20/0/0.1, 40/0.2 or 80/0.4 mg/kg/day (corresponding to 1.0, 2.0 or 4.0 mL/kg/day of the formulation). Following 4 weeks of dosing in males and 2 weeks of dosing in females, the rats were placed in cohabitation for a maximum of 3 weeks. Daily dosing continued until Day 7 of gestation for females, which were sacrificed and caesarean-sectioned on Day 15 of gestation. Daily dosing continued for males until the day prior to scheduled sacrifice. All animals wore Elizabethan collars during the 6-hour daily exposure. No treatment-related mortalities or systemic clinical signs were observed. Body weights were significantly reduced in the high-dose males. There were no effects on female body weights or on male and female food consumption. Dose-related dermal irritation was observed in all treated male and female dose groups and consisted of very slight to severe erythema and edema (grades 1 to 4). Other irritation effects on the skin application sites included eschar, fissuring (males only), desquamation and exfoliation. Vocalization apparently related to the skin irritation effects occurred at the time of dosing in the mid- and high-dose animals. No dermal effects were observed in the vehicle control animals. In males, mating and fertility parameters, sperm evaluations and gonadal weights were unaffected by treatment at any dose level. Histopathological evaluation of the testes revealed no treatment-related changes. In females, estrous cycling, mating, fertility and intrauterine parameters were unaffected by treatment. The parental systemic no-observed-adverse-effect level (NOAEL) was considered to be 40/0.2 mg/kg/day and the NOAEL for reproductive performance was considered to be greater than 80/0.4 mg/kg/day. Based on the results of this study, SOLAGÉ® solution is not a reproductive toxicant in rats.

A **dermal study of embryo-foetal development in rats** was performed. The 2% mequinol / 0.01% tretinoin solution was administered dermally to groups of 25 pregnant rats from Days 6 through 15 of gestation at daily doses of 20/0.1, 40/0.2 or 80/0.4 mg/kg/day (corresponding to daily dose volumes of 1.0, 2.0 or 4.0 mL/kg/day). A separate control group was administered the vehicle solution at 4.0 mL/kg/day. All animals wore collars during the 6-hour daily exposure. All dams survived to the scheduled laparohysterectomy. No test article-related systemic clinical signs were observed in any test group. Dose-related irritation consisting of very slight to slight erythema (grades 1-2) and desquamation was observed on the skin application sites in the low-, mid-, and high-dose groups. The incidence of irritation was greatly increased in the high-dose group. Also, in the high-dose group, there was a significant decrease in mean body weight gain and food consumption values during the treatment period. There were no dermal or systemic vehicle-related effects in the control animals. Intrauterine parameters and foetal survival and growth were unaffected by treatment at any dose level. There were no signs of treatment-related changes in the foetuses. The systemic maternal no-observed-adverse-effect level (NOAEL) was considered to be 40/0.2 mg/kg/day and the NOAEL for developmental toxicity and teratogenicity was considered to be greater than 80/0.4 mg/kg/day. Based on the results of this study, 2% mequinol /0.01% tretinoin solution was not teratogenic in rats.

A **dermal study of pre- and postnatal development in rats** was performed. SOLAGÉ® solution was administered dermally to three groups of presumed-pregnant rats (25/group) from

Day 6 of gestation through Day 20 of lactation at daily doses of 12/0.06, 40/0.2 or 120/0.6 mg/kg/day (corresponding to daily dose volumes of 0.6, 2.0 or 6.0 mL/kg/day). Separate control group animals were administered the vehicle solution at 6.0 mL/kg/day. All animals wore collars during the 6-hour daily exposure. Due to extreme irritation, all dams and their offspring in the 120/0.6 mg/kg higher dose group were euthanized for humane reasons and necropsied during the initial week of the lactation period. Dose-related irritation consisting of very slight to severe erythema (grades 1-4) and very slight to moderate edema (grades 1-3) including fissuring (particularly in the high-dose group), desquamation, eschar and exfoliation was observed on the skin application sites. Vocalization in response to application of the test article solution was noted frequently in the 40/0.2 and 120/0.6 mg/kg groups. No signs of systemic maternal toxicity were observed in the 12/0.06 and 40/0.2 mg/kg groups during gestation and lactation. There were no dermal or systemic vehicle-related effects in the control animals. Drug-related changes in the F1 generation litters occurred only at the maternally toxic 120/0.6 mg/kg dose. These changes included increased pup mortality, decreased pup body weights, and an increased incidence of clinical signs consisting of small pups, hypoactivity, coolness to touch, and pale appearance of the pups and also gross lesions at necropsy (renal papilla not fully developed and/or ureter, and distended bladder). The systemic maternal, neonatal and developmental no-observed-adverse-effect level (NOAEL) was 40/0.2 mg/kg. Based on the results of this study, 2% mequinol /0.01% tretinoin solution caused changes in the F1 generation offspring only at a dose (120/0.6 mg/kg) that also caused severe maternal toxicity.

Rabbit

Two dermal teratology studies in rabbits were performed. In the initial study, the SOLAGÉ® was administered dermally to three groups of 20 female rabbits at doses of 4/0.02, 12/0.06 and 40/0.2 mg/kg/day (corresponding to dose volumes of 0.2, 0.6 and 2.0 mL/kg/day). These doses represent approximately 3-, 9-, and 30-times the maximum human dose level. Additional test groups received 2% mequinol formulation at 40 mg/kg/day or 0.01% tretinoin formulation at 0.2 mg/kg/day. A group of control rabbits was given the vehicle formulation at 2.0 mL/kg/day. Rabbits were dosed daily from gestation day 6 through 18. The concentrations of mequinol in plasma samples obtained on day 18 from animals treated with SOLAGÉ® indicated a dose-related exposure to mequinol. Rabbits treated with mequinol alone had lower concentrations of mequinol in plasma than rabbits treated with the combination, suggesting that tretinoin may increase the permeability of the skin to mequinol. No detectable levels of tretinoin were observed in the plasma samples. In females receiving mequinol, dermal changes consisted of only slight erythema. In females receiving the low-mid- and high-dose levels of SOLAGÉ®, the degree of dermal irritation appeared to be dose-dependent and consisted of slight to moderate erythema, slight to severe desquamation, and eschar formation with subsequent eschar exfoliation. Similar dermal changes were observed in females receiving tretinoin; however, the incidence and severity of eschar formation in this group were less than that observed in animals receiving the mid- and high-dose levels of SOLAGÉ®. These findings indicate that the irritation was primarily attributable to tretinoin. Following cessation of dosing, the dermal irritation diminished in all groups. No indications of systemic maternal toxicity in any of the treated female groups were observed. There were no statistical differences in foetal malformation data; however, marked hydrocephaly with visible doming of the head was observed in one mid-dose and two high-dose SOLAGÉ® foetuses, and two tretinoin foetuses. These anomalies were considered to be typical of retinoid-induced foetal malformations in this species. Accompanying malformations in these hydrocephalic foetuses consisted of high arched or cleft palate (2 of 5 foetuses) and appendicular skeletal defect (3 of 5 foetuses). No treatment-

related foetal malformations were observed in the low-dose mequinol /tretinoin or control groups. A no-observed-effect level for teratogenicity was established for this study at 4/0.02 mg/kg/day for SOLAGÉ®. Based upon the procedures used in this study, significant ingestion of the test material formulation was suspected.

Recognizing the possibility that ingestion of the SOLAGÉ® occurred in the initial dermal teratology study in rabbits and based on similar reported studies in the literature with tretinoin in which extra precautionary design measures were taken to prevent ingestion, the rabbit teratology study was repeated. As in the previous study, SOLAGÉ® was administered dermally to three groups of 20 female rabbits at doses of 4/0.02, 12/0.06 and 40/0.2 mg/kg/day (corresponding to dose volumes of 0.2, 0.6 and 2.0 mL/kg/day). Additional test groups received either 0.01% tretinoin solution at 0.2 mg/kg/day or the vehicle solution at 2.0 mL/kg/day and another group served as an untreated control. To prevent potential ingestion of the dermally applied test materials, as precautionary measures, all rabbits were restrained in stocks during the 6-hour daily exposure. After exposure, the skin application sites were washed, and the rabbits were then collared and returned to clean caging. Similar to the previous study, signs of dermal irritation were observed in all treated doses. In rabbits receiving the low-, mid- and high-dose levels of SOLAGÉ®, the degree of dermal irritation was dose-dependent and consisted of very slight to severe erythema, very slight to moderate edema, slight to moderate desquamation, very slight to well-defined fissuring, atonia and hyper-reactivity (sensitive to touch). As in the previous study, similar dermal changes were observed in rabbits receiving tretinoin; and the incidence and severity of irritation in this group were generally slightly less than in animals receiving the mid- and high-dose levels of SOLAGÉ®. The vehicle solution alone produced a low incidence of erythema and desquamation. These findings indicate that the irritation was primarily attributable to tretinoin. Following cessation of dosing, the dermal irritation diminished in all groups. None of the deaths, moribund sacrifices, abortions or premature deliveries that occurred were considered related to treatment. There were no indications of systemic maternal or foetal toxicity in any of the treated groups. In contrast to the previous study, there were no treatment-related differences in foetal malformation data.

In summary, dermal dose levels up to 40 mg/kg/day of mequinol and 0.2 mg/kg/day of tretinoin produced dose-related dermal irritation without producing any drug-related changes in the foetuses in this study, which was at the same dose levels and of the same design as the previous study except for the extra precautionary measures that were taken to prevent ingestion. A NOAEL for teratogenicity was established for this dermal study at 40/0.02 mg/kg/day for SOLAGÉ®. On the basis of these data, SOLAGÉ® administered dermally to rabbits with precautions to prevent ingestion, was not teratogenic.

It has been recognized that the possible ingestion of the test article is a confounding factor in interpreting the results of topical tretinoin animal studies. While topical tretinoin has occasionally shown some evidence of teratogenicity in animal studies which were not strictly controlled for ingestion, studies that employed extra precautionary measures to avoid ingestion have not shown teratogenic effects.

Mutagenicity Studies

An **Ames/Salmonella microbial mutation assay** was performed on mequinol at Salmonella concentrations of 312.5 to 5000 µg/plate. No cytotoxicity was observed at any concentration either with or without metabolic activation. The histidine^{+}revertant frequencies were not

elevated significantly in the mequinol-treated cultures as compared to the negative control levels. The results indicate that, under the conditions of this study, mequinol was not mutagenic in the Ames/Salmonella assay up to and including cytotoxic doses.

A **micronucleus evaluation of bone marrow from a 6-month dermal rangefinding study in rats** (Table 13) on SOLAGÉ® was performed at doses equivalent to 4/0.02, 12/0.06 or 40/0.2 mg/kg or mequinol doses of 40 mg/kg. The incidences of micronucleated polychromatic erythrocytes (MN-PCEs) were not elevated in the bone-marrow of the SOLAGÉ® or mequinol - treated rats. The results indicate that the SOLAGÉ® formulations exhibit no *in vivo* potential to cause chromosomal or mitotic spindle damaging effects to rat bone-marrow cells following dermal administration for 6 months.

Additional exploratory genotoxicity assays, an Ames and an *in vitro* cytogenetics assay, were attempted on the neat drug formulation but were not feasible to evaluate due to cytotoxic effects at low dose volumes of the ethanolic-base formulation.

Carcinogenicity

A **12-month photocarcinogenicity study with ultraviolet radiation in hairless mice** was performed. The 2% mequinol /0.01% tretinoin formulation was administered dermally to albino hairless mice for 40 weeks. Three groups of 36 male and 36 female Crl:SkH1(hr/hr) BR mice were given the formulation, containing 2% mequinol and 0.01% tretinoin at dose volumes of 10, 30 or 100 µL/mouse/day, 5 days per week. One group of control mice was given the vehicle formulation at 100 µL/mouse/day. All test and vehicle control animals were irradiated daily with UVB radiation at 0.272 Minimal Erythema Dose (MED). Separate, untreated control groups of mice were irradiated with either 0.272 or 0.382 MED (high-dose UV group). During the 40-week dosing period and the 12-week post-dosing period, the animals were assessed for mortality, body weight, clinical and dermal abnormalities, and skin masses. In the high-dose group, there were reduced mean survival times. Test article administration caused dose-dependent increases in the numbers of mice with abnormal breathing, gait or posture, distended abdomens and enlarged lymph nodes; these effects were considered secondary to skin irritation and/or skin tumorigenesis. Drug- and dose-related dermal findings consisted of increases (in severity and incidence) of dryness, erythema, edema, and eschar. The median onsets of these effects in the drug-treated groups were generally accelerated and durations increased as compared to the vehicle and UV controls. The vehicle formulation was considered not to have modified photocarcinogenesis. Skin tumour onset rate analyses revealed a significant enhancement in all test article-treated groups of UV-induced tumorigenesis in comparison to the vehicle or low-dose UV controls. In male and female mice, trend analyses of the SOLAGÉ®-treated groups compared to combined vehicle and low-dose UV controls revealed significantly earlier times to tumour onset for all dose groups. There was no dose response in tumour onset rate observed between the SOLAGÉ®-treated male or female groups. Dermal administration of the SOLAGÉ® formulation at all dose levels enhanced photocarcinogenesis in both male and female mice. Tretinoin has also been previously reported to induce photocarcinogenesis in the hairless mouse exposed to ultraviolet radiation, and the enhanced photocarcinogenicity observed in this study was considered to be related to tretinoin.

A **dermal carcinogenesis study in CD-1 mice** was performed. The 2% mequinol /0.01% tretinoin solution was applied dermally to groups of 50 mice/sex at dose volumes of 10, 30 or 100 µL/mouse/day (corresponding to daily dose levels of approximately 8.0/0.04, 24.0/0.12 or

80/0.4 mg/kg of SOLAGÉ®) for 24 months. These doses represent approximately 4-, 12- and 40-times the intended clinical dose. Two additional groups of mice served as controls (untreated and vehicle), with the vehicle control mice receiving the solution vehicle at the same volume as the high-dose group. SOLAGÉ® solution produced dose-related decreases in survival in the mid- (males) and high-dose groups, which in general had the highest degree of dermal irritation. During the study, dose-related dermal irritation consisting of very slight to severe erythema, very slight to moderate edema, desquamation, and pinpoint scabbing (primarily in the mid- and high-dose groups) was observed. Leathery skin, exfoliation, thickening, sores, ulceration and atonia were also observed primarily on the mid- and high-dose application sites. A very low incidence of dermal irritation was also observed sporadically in the vehicle control group. There were no SOLAGÉ®-related systemic clinical signs, changes in body weights or haematological evaluations, or increases in tissue masses at gross examination. Dose-related histopathological findings were confined to the application site and included acanthosis, hyperkeratosis and chronic dermal inflammation. Other findings included exudate associated with inflammation and epidermal necrosis. Histopathologically, no treatment-related neoplasms occurred systemically or at the application sites. Based on the results of this study, 2% mequinol /0.01% tretinoin solution was not carcinogenic.

Special Toxicity Studies

A **primary skin irritation study in New Zealand White rabbits** was performed. Prototype ethanolic formulations containing 2% or 4% mequinol in combination with 0.01% tretinoin, 2% mequinol or vehicle solution were each administered to a group of six rabbits at a single dermal dose of 0.5 mL per skin site under 24-hour patch occlusion. In general, the 4%mequinol /0.01% tretinoin formulation was slightly more irritating than other test or vehicle formulations. The test formulations produced mild to moderate skin irritation potential; however, none of the test materials would be classified as a primary skin irritant.

A **primary skin irritation study in New Zealand White rabbits** was performed. Prototype 2% mequinol /0.01% tretinoin cream formulations produced moderate skin irritation potential while the respective vehicle creams had mild irritation potential. None would be classified as a primary skin irritant.

A **dermal phototoxicity study in guinea pigs** was performed. The 2% mequinol /0.01% tretinoin formulation was found to be non-phototoxic to hairless guinea pigs following a 1-hour UVA exposure.

A **dermal sensitization study in guinea pigs** was performed. During the study, dermal irritation considered to be local primary skin irritation effects related to the length of occlusion was observed. The irritation was attributed to the retinoid component of the formulation, tretinoin. Based on the results of this study, the 2% mequinol /0.01% tretinoin formulation was considered non-sensitizing.

SOLAGÉ® (2% mequinol /0.01% tretinoin) Topical Solution is a combination drug for the treatment of solar lentigines and related hyperpigmented lesions. The combination produced moderate skin irritation effects confined to the treatment site in mice, rats and rabbits. SOLAGÉ® solution has a low degree of acute toxicity in single-dose oral or dermal studies in rats or rabbits, respectively. In repeat-dose dermal studies up to 3 months in mice and 6 months in rats, dose-related dermal irritation effects were observed without any significant

systemic effects. SOLAGÉ® was not found to be a reproductive or developmental toxicant in rats in a series of dermal fertility, teratogenicity or pre- and postnatal development studies.

In the latter study, developmental effects occurred only at a high dose which also produced severe skin irritation and was maternally toxic. In these reproductive studies, the dermal irritation effects that were observed decreased following cessation of treatment. In one dermal teratology study in rabbits treated with mequinol /tretinoin combination, a low incidence of teratogenic effects (marked hydrocephaly) in the mid- and high-dose groups, and the high-dose tretinoin group was observed. Although these findings did not achieve statistical significance, they are consistent with effects that are known to be related to the retinoid drug component. However, based upon the procedures used in this dermal study, it was suspected that the animals ingested the test article. A second dermal teratology study conducted in rabbits was performed at the same doses and with the same experimental design as the previous study, except that extra precautionary procedures were employed to prevent ingestion. Under the conditions of this repeat study, the dermal administration of mequinol /tretinoin was not teratogenic. The lack of teratogenicity in this dermal study is in agreement with the assessment that the risk of topical tretinoin as a human developmental toxicant has been estimated to be minimal. Mequinol was non-genotoxic in an Ames test and the SOLAGÉ® drug formulation was non-genotoxic in an *in vivo* dermal micronucleus assay in rats. Both mequinol and tretinoin have been previously reported as non-genotoxic drugs. The SOLAGÉ® formulation was not carcinogenic in a 2-year dermal study in mice at dose levels of 8/0.04, 24/0.12 or 80/0.4 mg/kg, approximately 4-, 12- and 40-times the clinical dose. However, in a 12-month dermal photocarcinogenicity study in albino hairless mice, the SOLAGÉ® solution was found to enhance photocarcinogenesis. Tretinoin and other retinoids have been reported to enhance photocarcinogenesis. Special studies for toxicity demonstrated that the SOLAGÉ® formulation was non-phototoxic and non-sensitizing in guinea pigs. Although an eye irritation study was not performed on the SOLAGÉ® solution for humane reasons, it would be considered a potential ocular irritant based on the high alcohol content in the formulation.

Although there were no findings that would preclude the topical use of SOLAGÉ® for the treatment of solar lentigines and related hyperpigmented lesions, the finding of enhanced photocarcinogenicity in hairless mice is of some concern and is consistent with the tretinoin component of the combination. Therefore, it is recommended that patients should minimize exposure to the sun during treatment with SOLAGÉ® Topical Solution.

HUMAN

SOLAGÉ® Topical Solution, as established from 1155 subjects exposed to the product, was well-tolerated. Although many subjects reported adverse events, most events were mild or moderate in severity and only a few resulted in discontinuation of study participation. As expected, no serious adverse events were attributed to SOLAGÉ®.

The types of adverse events reported for mequinol /tretinoin, as well as the early onset, were typical of those reported for marketed topical tretinoin products. Erythema, the cardinal sign of tretinoin treatment, was observed in roughly half of the subjects treated with mequinol /tretinoin or tretinoin. Burning/stinging/tingling, the second most frequently reported event, occurred in approximately one third of the subjects exposed to mequinol /tretinoin or tretinoin. Desquamation and pruritus also were frequently reported. The rate of these adverse events for

mequinol /tretinoin-treated subjects was slightly lower than the rate for subjects treated with tretinoin.

The adverse event of burning/stinging/tingling was reported more frequently on the face than on the forearms/backs of hands. Since the face is more sensitive to tactile stimuli than the forearms, it is logical that burning/stinging/tingling would be reported more frequently on this anatomical site than on the forearms. The other adverse events described above were more frequently reported on the forearms/backs of hands than on the face. This difference may arise because more lesions were treated on the forearms/backs of hand than the face, and thus, there was a greater potential for adverse events.

Hypopigmentation adverse events are not unexpected with topical agents used for the treatment of hyperpigmented lesions. Such events have been reported with topical corticosteroids, tretinoin, azelaic acid, mequinol , and hydroquinone. The marketed topical mequinol product in France and topical tretinoin products in the U.S. all report this potential.

In these studies, two types of hypopigmentation were observed, halo hypopigmentation and lesional hypopigmentation. Halo hypopigmentation was presumed to be the result of over zealous application of the product beyond the border of the lesion, while lesional hypopigmentation developed as a result of treating a lesion for longer than necessary. Overall, most instances of hypopigmentation were mild in severity, and none were severe. Almost all the reported hypopigmentation events had resolved by the end of the studies. Of the several that did not, half have resolved, or have shown improvement since the end of the studies.

The reversibility of both the depigmentation of the treated lesions and the hypopigmentation reported as adverse events clinically confirms both the preclinical observation and the electron microscopy findings of Study DE132-005 that the cytologic and ultrastructural changes caused by mequinol /tretinoin were reversible and the product was clearly not melanocidal.

Among those subjects treated with mequinol /tretinoin, carcinoma of the skin (non-melanoma skin cancer) was rare and occurred at approximately the same rate (or less) than that expected for a U.S. population of this age range. No skin cancer was reported on a treated area.

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