

Edema Not Necessary After Laser Hair Removal

BY DAMIAN McNAMARA
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ORLANDO — A strong edematous response immediately after laser hair removal is not necessary to achieve treatment efficacy, according to a prospective study.

"There is zero need to drive patients into an intense edematous response," Albert J. Nemeth, M.D., said at the annual meeting of the Florida Society of Dermatologic Surgeons.

Dr. Nemeth conducted a study to correlate immediate postlaser response with efficacy of permanent hair removal, which he said is an area with insufficient research.

He also proposed that a less visible immediate reaction might be better for patients. "Selection of more aggressive fluences based on a perceived inadequate immediate response might cause more adverse sequelae," said Dr. Nemeth, who is in private practice in Clearwater, Fla.

Dr. Nemeth assessed 200 patients treat-

ed with the MeDioStar 810-nm power-pulsed diode laser (Asclepion Laser Technologies, Jena, Germany).

The average participant age was 36 years, 86% were female, and mean follow-up was 5 months. The majority of patients had Fitzpatrick skin types of I, II, and III.

Immediate perifollicular response and surrounding erythema were rated on a scale of 1 (very mild) to 5 (intense). Patients with a low score still had effective permanent hair reduction.

The laser features a 12-mm actively chilled handpiece with a sapphire spot. "The actively chilled handpiece is vital for epidermal protection," said Dr. Nemeth, also of the department of dermatology and cutaneous surgery at the University of South Florida, Tampa.

Laser fluences were set between 10 J/cm² and 36 J/cm². The intermittent pulse pause of MeDioStar's power pulse technology does not heat surrounding tissue as much as do other lasers, Dr. Nemeth pointed out.

"I've never seen such efficacy with other lasers—I think the power pulse makes that much of a difference," he said. Dr. Nemeth disclosed no conflict of interest regarding the MeDioStar laser or its manufacturer.

Multiple treatment sessions were required. After the first treatment, there was a mean 26% reduction in hair. After the second treatment, there was a mean 47% reduction, and after a third session, 64%.

Adverse events were infrequent. These included occasional crusting, and "easily resolvable" postinflammatory hyperpigmentation in 5 out of a total of 978 treatment sessions.

"There is physician supervision without exception for every treatment session," Dr. Nemeth said. A highly trained nurse who also is a licensed electrologist performed all procedures in the study to minimize variations in treatment.

Solag [®]

Rx only
(mequinol 2%, tretinoin 0.01%) Topical Solution
Brief Summary

For Dermatologic use only. Not for ophthalmic, oral or intravaginal use.

INDICATIONS AND USAGE

(To understand fully the indication for this product, please read the entire INDICATIONS AND USAGE section of the labeling.)

Solag  (mequinol 2%, tretinoin 0.01%) Topical Solution is indicated for the treatment of solar lentigines. **Solag ** Solution should only be used under medical supervision as an adjunct to a comprehensive skin care and sun avoidance program where the patient should primarily either avoid the sun or use protective clothing. Neither the safety nor effectiveness of **Solag ** Solution for the prevention or treatment of melasma or postinflammatory hyperpigmentation has been established.

The efficacy of using **Solag ** Solution daily for greater than 24 weeks has not been established.

The local cutaneous safety of using Solag  Solution in non-Caucasians has not been adequately established (see Clinical Studies section).

CONTRAINDICATIONS

The combination of mequinol and tretinoin may cause fetal harm when administered to a pregnant woman. Due to the known effects of these active ingredients, **Solag ** Topical Solution should not be used in women of childbearing potential.

In a dermal teratology study in New Zealand White rabbits, there were no statistically significant differences among treatment groups in fetal malformation data; however, marked hydrocephaly with visible doming of the head was observed in one mid-dose litter (12 and 0.06 mg/kg or 132 and 0.66 mg/m² of mequinol and tretinoin, respectively) and two fetuses in one high dose litter (40 and 0.2 mg/kg or 440 and 2.2 mg/m² of mequinol and tretinoin, respectively) of **Solag ** Solution, and two high-dose tretinoin (0.2 mg/kg, 2.2 mg/m²) treated litters. These malformations were considered to be treatment related and due to the known effects of tretinoin. This was further supported by coincident appearance of other malformations associated with tretinoin, such as cleft palate and appendicular skeletal defects. No effects attributed to treatment were observed in rabbits in that study treated topically with mequinol alone (dose 40 mg/kg, 440 mg/m²). A no-observed-effect level (NOEL) for teratogenicity in rabbits was established at 2.4 and 0.02 mg/kg (44 and 0.22 mg/m² mequinol and tretinoin, respectively) for **Solag ** Solution which is approximately the maximum possible human daily dose, based on clinical application to 5% of total body surface area. Plasma tretinoin concentrations were not raised above endogenous levels, even at teratogenic doses. Plasma mequinol concentrations in rabbits at the NOEL at one hour after application were 124 mg/mL or approximately twelve times the mean peak plasma concentrations of that substance seen in human subjects in a clinical pharmacokinetic study.

In a repeated study in pregnant rabbits administered the same dose levels as the study described above, additional precautionary measures were taken to prevent ingestion, although there is no evidence to confirm that ingestion occurred in the initial study. Precautionary measures additionally limited transdermal absorption to a six hour exposure period, or approximately one-fourth of the human clinical daily continuous exposure time. This study did not show any significant teratogenic effects at doses up to approximately 13 times the human dose on a mg/m² basis. However, a concurrent tretinoin dose group (0.2 mg/kg/day) did include two litters with limb malformations.

In a published study in albino rats (J. Am. Coll. Toxicology 4(5):31-63, 1985), topical application of 5% of mequinol in a cream vehicle during gestation was embryotoxic and embryolethal. Embryonic loss prior to implantation was noted in that study where animals were treated throughout gestation. Coincidentally, mean preimplantation embryonic loss was increased in the first rabbit study in all mequinol treated groups, relative to control, and in the high dose mequinol/tretinoin and tretinoin only treated groups in the second study. In those studies, dosing began at gestation day 6, when implantation is purported to occur. Increased preimplantation loss was also noted at the high combination dose in a study of early embryonic effects in rats, as was decreased body weight in male pups; these findings are consistent with the published study.

Solag  Solution was not teratogenic in Sprague-Dawley rats when given in topical doses of 80 and 0.4 mg/kg mequinol and tretinoin, respectively (480 and 2.4 mg/m² or 11 times the maximum human daily dose). The maximum human dose is defined as the amount of solution applied daily to 5% of the total body surface area.

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty cases of temporally-associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin. Although no definite pattern of teratogenicity and no casual association has been established from these cases, 6 of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

No adequate or well-controlled trials have been conducted with **Solag ** Solution in pregnant women.

Solag  Topical Solution is contraindicated in individuals with a history of sensitivity reactions to any of its ingredients. It should be discontinued if hypersensitivity to any of its ingredients is noted.

WARNINGS

Solag  Solution is a dermal irritant and the results of continued irritation of the skin for greater than 52 weeks in chronic, long-term use are not known. Tretinoin has been reported to cause severe irritation on eczematous skin and should be used only with utmost caution in patients with this condition. Safety and effectiveness of **Solag ** Solution in individuals with moderately or heavily pigmented skin have not been established.

Solag  Solution should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) to treated areas should be avoided or minimized during the use of **Solag ** Solution. Patients must be advised to use protective clothing and comply with a comprehensive sun avoidance program when using **Solag ** Solution. Data are not available to establish how or whether **Solag ** Solution is degraded (either by sunlight or by normal interior lighting) following application to the skin. Patients with sunburn should be advised not to use **Solag ** Solution until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using **Solag ** Solution and ensure that the precautions outlined in the Patient Medication Guide are observed.

Solag  Solution should be kept out of the eyes, mouth, paranasal creases, and mucous membranes. **Solag ** Solution 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.

Solag  Solution should be used with caution by patients with a history, or family history, of vitiligo. One patient in the trials, whose brother had vitiligo, experienced hypopigmentation in areas that had not been treated with study medication. Some of these areas continued to worsen for at least one month post treatment with **Solag ** Solution. Six weeks later the severity of the hypopigmentation had decreased from moderate to mild and 106 days post treatment, the patient had resolution of some but not all lesions. 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.

PRECAUTIONS

General

For external use only.

Solag  Solution should only be used as an adjunct to a comprehensive skin care and sun avoidance program. (See INDICATIONS AND USAGE section.)

If a drug sensitivity, chemical irritation, or a systemic adverse reaction develops, use of **Solag ** Solution should be discontinued.

Weather extremes, such as wind or cold, may be more irritating to patients using **Solag ** Solution.

Information for patients

Patients require detailed instruction to obtain maximal benefits and to understand all the precautions necessary to use this product with greatest safety. The Patient Medication Guide is attached to this Package Insert.

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 **Solag ** Solution because they may increase irritation when used with **Solag ** Solution.

Solag  Solution should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Although a dermal carcinogenicity study in CD-1 mice indicated that **Solag ** Solution applied topically at daily doses up to 80 and 0.4 mg/kg (240 and 1.2 mg/m²) of mequinol and tretinoin, respectively, representing approximately 5 times the maximum possible systemic human exposure was not carcinogenic, in a photocarcinogenicity study utilizing Crl:Skh-1(hr/hr BR) hairless albino mice, median time to onset of tumors decreased. Also, the number of tumors increased in all dose groups administered 1.4, 4.3 or 14 µl of **Solag ** Solution/cm² of skin (24 and 0.12, 72 and 0.36, or 240 and 1.2 mg/m² of mequinol and tretinoin, respectively); 0.6, 1.9, or 6.5 times the daily human dose on a mg/m² basis) following chronic topical dosing with intermittent exposure to ultraviolet radiation for up to 40 weeks. Similar animal studies have shown an increased tumorigenic risk with the use of retinoids when followed by ultraviolet radiation. Although the significance of these studies to human use is not clear, patients using this product should be advised to avoid or minimize exposure to either sunlight or artificial ultraviolet irradiation sources.

Mequinol was non-mutagenic in the Ames/Salmonella assay using strains TA98, TA100, TA1535, and TA1537, all of which are insensitive to mutagenic effects of structurally-related quinones. **Solag ** Solution was non-genotoxic in an *in vivo* dermal micronucleus assay in rats, but exposure of bone marrow to drug was not demonstrated.

A dermal reproduction study with **Solag ** Solution in Sprague-Dawley rats at a daily dose of 80 and 0.4 mg/kg (480 and 2.4 mg/m²) of mequinol and tretinoin, respectively, approximately 11 times the corresponding maximum possible human exposure, assuming 100% bioavailability following topical application to 5% of the total body surface area, showed no impairment of fertility.

Pregnancy: Teratogenic effects: Pregnancy Category X.

Although the magnitude of the potential for teratogenicity may not be well-defined, **Solag ** Solution is labeled as an "X" because the potential risk of the use of this drug to treat this particular indication (solar lentigines) in a pregnant woman clearly outweighs any possible benefit (see CONTRAINDICATIONS section).

Nursing Mothers: It is not known to what extent mequinol and/or tretinoin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **Solag ** Solution is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of this product have not been established in pediatric patients. **Solag ** Solution should not be used on children.

Geriatric Use: Of the total number of patients in clinical studies of **Solag ** Solution, 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.

ADVERSE REACTIONS

In clinical trials, adverse reactions were primarily mild to moderate in intensity, occurring in 66% and 30% of patients, respectively. The majority of these events were limited to the skin and 64% had an onset of a skin related adverse reaction early in treatment (by week 8). The most frequent adverse reactions in patients treated with **Solag ** Solution were erythema (49% of patients), burning, stinging, or tingling (26%), desquamation (14%), pruritus (12%), and skin irritation (5%).

Some patients experienced temporary hypopigmentation of treated lesions (5%) or of the skin surrounding treated lesions (7%). Ninety-four of 106 patients (89%) had resolution of hypopigmentation upon discontinuation of treatment to the lesion, and/or re-instruction on proper application to the lesion only. Another 8% (9/106) of patients with hypopigmentation events had resolution within 120 days after the end of treatment. Three of the 106 patients (2.8%) had persistence of hypopigmentation beyond 120 days.

Approximately 6% of patients discontinued study participation with **Solag ** Solution due to adverse reactions. These discontinuations were due primarily to skin redness (erythema) or related cutaneous adverse reactions. **Solag ** Solution was generally well tolerated.

Adverse Events Occurring in >1% of the Population — All Studies								
Body System	Solag� Solution (mequinol 2%, tretinoin 0.01%)		Tretinoin, 0.01%		Mequinol, 2%		Vehicle	
	N	%	N	%	N	%	N	%
Skin and Appendages								
Erythema	549	44.6	261	55.3	13	5.1	8	4.6
Burning/Stinging/Tingling	270	21.9	173	36.7	26	10.2	20	11.4
Desquamation	155	12.6	93	19.7	7	2.8	2	1.1
Pruritus	135	11.0	66	14.0	12	4.7	3	1.7
Irritation Skin	90	7.3	25	5.3	1	0.4	1	0.6
Halo Hypopigmentation	76	6.2	16	3.4	2	0.8	2	1.1
Hypopigmentation	50	4.1	8	1.7	2	0.8	0	0.0
Skin Dry	38	3.1	18	3.8	3	1.2	1	0.6
Rash	31	2.5	21	4.4	0	0.0	1	0.6
Crusting	30	2.4	18	3.8	0	0.0	1	0.6
Rash Vesicular Bullae	18	2.1	8	1.7	0	0.0	0	0.0
Dermatitis	25	2.0	0	0.0	0	0.0	0	0.0

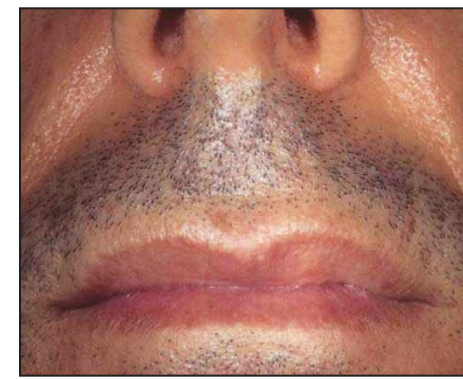
OVERDOSAGE

If **Solag ** Solution is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, discomfort, or hypopigmentation 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). If oral ingestion occurs, the patient should be monitored, and appropriate supportive measures should be administered as necessary. The maximal no-effect level for oral administration of **Solag ** Solution in rats was 5.0 mL/kg (30 mg/m²). Clinical signs observed were attributed to the high alcohol content (77%) of the drug formulation.

Barrier Therapeutics

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This patient is shown at baseline prior to treatment on his upper lip.



The patient is shown after receiving 810-nm MeDioStar laser hair removal.

PHOTOS COURTESY DR. ALBERT J. NEMETH

Guide to Quality Health Care

The Agency for Healthcare Research and Quality has released the booklet "Guide to Health Care Quality: How to Know It When You See It" to help consumers identify high-quality health care. To download a copy, visit www.ahrq.gov/consumer/guidetoq. To obtain a free single copy, call 800-358-9295.