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September 30, 2003

VIA FEDERAL EXPRESS, EMAIL & FACSIMILE

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, MD 20852

Re: Comments on ANDA Suitability Petition CP 2003P-0279

Request for a Change in Dosage Form from a Cream to a Topical Solution for Fluocinolone Acetonide, Hydroquinone and Tretinoin

The Petition Should be Denied - Investigations Must Be Conducted To Demonstrate The Safety And Effectiveness Of The Proposed Change In Dosage Form

Dear Sir/Madam:

I am writing on behalf of our client, Hill Dermaceuticals, Inc., to provide comments on the above referenced ANDA Suitability Petition requesting a change in dosage form from a cream to a topical solution for a topical combination product containing Fluocinolone Acetonide, Hydroquinone and Tretinoin, 0.01%, 4% and 0.05% w/w, respectively. The approved reference listed drug is Hill's TRI-LUMA® Cream, NDA 21-112. The proposed change in dosage form raises some significant clinical safety and effectiveness issues that have not been addressed by the Petitioner in the Suitability Petition. The Petition should be denied since investigations must

be conducted to demonstrate the safety and effectiveness of the proposed change in dosage form. The basis for Hill's position is set forth below.

Background. TRI-LUMA® Cream is approved for the indication of short-term treatment of moderate to severe melasma of the face, in the presence of measures for sun avoidance, including the use of sunscreens. As you know, melasma is a skin condition that is manifested by dark (hyper pigmented) spots on the facial skin, especially on the cheeks and forehead. This condition usually happens with hormone changes.

Labeling Precautions Raise Issues About the Safety of a Topical Solution. The current approved package insert and patient medication guide for TRI-LUMA® Cream contain the following information in the **PRECAUTIONS** sections:

> Application of TRI-LUMA® Cream should be kept away from the eyes, nose or angles of the mouth because the mucosa is much more sensitive than the skin to the irritant effect. If local irritation persists or becomes severe, application of the medication should be discontinued and the health care provider consulted. Allergic contact dermatitis, blistering, crusting, and severe burning or swelling of the skin and irritation of the mucous membranes of the eyes, nose and mouth require medical attention.

If the medication is applied excessively, marked redness, peeling or discomfort may occur.

The proposed change in dosage form from a cream to a topical solution raises safety issues that have not been addressed by the Petitioner. As the Agency well knows, the pharmaceutical characteristics of a topical solution dosage form include properties that affect the fluidity and viscosity of the product and the ease of spreadability in comparison to a cream. It will be much more difficult for a patient to control the application of a topical solution to the face to prevent it from coming into contact with the mucous membranes of the eyes, nose and mouth. As noted in the **PRECAUTIONS** section of the labeling, contact of the drugs with the mucous membranes of the eyes, nose and mouth can cause irritation and other adverse events. The Petitioner must conduct studies to demonstrate the safety of the topical solution dosage form.

The **PRECAUTIONS** section of the labeling also contains a statement that if the medication is applied excessively, marked redness, peeling or discomfort may occur. Given the pharmaceutical properties of a topical solution, it will be much more difficult for a patient to control the amount of medication in the topical solution dosage form that is applied to the face. This too can contribute to adverse effects. The Petitioner has not addressed this issue in the Petition, nor has the Petitioner addressed the frequency of dosing to effect therapeutic equivalence to the listed drug. Dosing frequency with a topical solution with known irritants will greatly affect adverse reactions.

In addition, excipients commonly used as a vehicle in topical solutions contain materials that can be irritating such as PEG, alcohol and citric acid. The Petitioner has not identified the excipients to be used in the proposed topical solution formulation. The Petitioner must conduct safety trials to fully characterize the safety profile of the topical solution dosage form.

Based upon the above, the Petition should be denied since investigations must be conducted to demonstrate the safety of the proposed change in dosage form.

The Change in Dosage Form to a Topical Solution Has the Potential to Impact the Pharm/Tox Profile of the Triple Combination

The Petitioner is proposing to change the dosage form to a topical solution; such a change has the potential to impact the percutaneous absorption of each of the individual components. The Petitioner must be required to conduct preclinical studies to demonstrate that the change in dosage form has no impact on carcinogenicity, mutagenicity and teratogenicity.

The Change in Dosage Form to a Topical Solution Has the Potential to Impact the Safe and Effective Dose of Each Ingredient of the Triple Combination

As previously noted, such a change in dosage form has the potential to impact the percutaneous absorption of each of the individual components. The Petitioner must demonstrate that the change in dosage form does not have an impact on the safe or effective concentration of each ingredient in the combination.

The Petitioner Has Not Addressed How to Establish the Bioequivalence of the Topical Solution Dosage Form to the Currently Approved Reference Listed Drug, TRI-LUMA® Cream

The Petitioner has failed to include any information in the Petition on how to establish the bioequivalence of the topical solution dosage form to the currently approved reference listed drug, TRI-LUMA® Cream. Given the proposed change in dosage form, a study must be conducted to characterize the percutaneous absorption of tretinoin, hydroquinone and fluocinolone acetonide into the systemic circulation. While percutaneous absorption was very minimal with TRI-LUMA® Cream, it is unknown with the change in dosage form.

Since the approved reference listed drug, TRI-LUMA® Cream is intended for its local effect, in order to establish the bioequivalence of a topical solution dosage form, a study with clinical endpoints must be performed. Since the proposed change in dosage form could impact the safety and effectiveness of the proposed product, the Petitioner should be required to demonstrate the superiority of the proposed triple combination topical solution against various dyads in terms of efficacy at the end of 8 weeks. The proposed topical solution dosage form must also be of equal effectiveness in terms of change in melasma severity when compared to treatment with the reference listed drug, TRI-LUMA® Cream, at the end of 8 weeks of treatment. The proposed dosage form must also be studied in terms of effectiveness for the treatment of melasma after 8 weeks of use, as well as safety with use for longer than 8 weeks.

The Petitioner Has Not Addressed Monitoring the Unintended Usage in Pregnancy and Provide Measures on How This Can be Reduced

Since one of the ingredients in combination is tretinoin, which is a known teratogen, the Agency has required applicants to monitor the unintended usage of the drug in pregnancy and provide measures on how unintended exposure to the drug during pregnancy can be reduced. The Petitioner has not addressed this matter and must be required to do so.

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In conclusion, the proposed change in dosage form from a cream to a topical solution raises some significant clinical safety and effectiveness issues that have not been addressed by the Petitioner in the Suitability Petition. The Petition should be denied since investigations must be conducted to demonstrate the safety and effectiveness of the proposed change in dosage form.

In addition, in any new drug application submitted for the proposed product, the Petitioner must be required to (1) characterize the percutaneous absorption of tretinoin, hydroquinone and fluocinolone acetonide into the systemic circulation; (2) demonstrate the safety of the proposed dosage form; (3) demonstrate the superiority of the proposed triple combination topical solution against various dyads in terms of efficacy at the end of 8 weeks; (4)

demonstrate equal effectiveness in terms of change in melasma severity when compared to treatment with the reference listed drug, TRI-LUMA® Cream at the end of 8 weeks of treatment; and (5) monitor the unintended usage of the drug in pregnancy and provide measures on how unintended exposure to the drug during pregnancy can be reduced.

If you have any questions or need any additional information, please contact me at (202) 238-7749.

Sincerely yours,

David L. Rosen, R.Ph., J.D.

Enclosure: TRI-LUMA® Cream Package Insert and Approval Letter

cc: Jonathan K. Wilkin, M.D.
Director, Division of Dermatological and Dental Drug Products

Mr. Jerry Roth
President
Hill Dermaceuticals, Inc.

TRI-LUMA™ Cream

(fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%)

For External Use Only   Not for Ophthalmic Use   Rx only

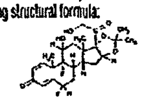
DESCRIPTION: TRI-LUMA™ Cream (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) contains fluocinolone acetonide, USP, hydroquinone, USP, and tretinoin, USP, in a hydrophilic cream base for topical application.

Fluocinolone acetonide is a synthetic fluorinated corticosteroid for topical dermatological use and is classified therapeutically as an anti-inflammatory. It is a white crystalline powder that is odorless and stable in light.

The chemical name for fluocinolone acetonide is: (6α,11β,16α)-6,9-difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-pregna-1,-4-diene-3,20-dione.

The molecular formula is $C_{24}H_{30}F_2O_6$ and molecular weight is 452.50.

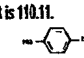
Fluocinolone acetonide has the following structural formula:



Hydroquinone is classified therapeutically as a depigmenting agent. It is prepared from the reduction of *p*-benzoquinone with sodium bisulfite. It occurs as fine white needles that darken on exposure to air.

The chemical name for hydroquinone is: 1,4-benzenediol.

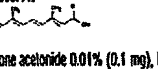
The molecular formula is $C_6H_6O_2$ and molecular weight is 110.11.

Hydroquinone has the following structural formula: 

Tretinoin is all-*trans*-retinoic acid formed from the oxidation of the aldehyde group of retinene to a carboxyl group. It occurs as yellow to light-orange crystals or crystalline powder with a characteristic odor of ensilage. It is highly reactive to light and moisture. Tretinoin is classified therapeutically as a keratolytic.

The chemical name for tretinoin is: (all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid.

The molecular formula is $C_{20}H_{28}O_2$ and molecular weight is 300.44.

Tretinoin has the following structural formula: 

Each gram of TRI-LUMA Cream contains **Active:** fluocinolone acetonide 0.01% (0.1 mg), hydroquinone 4% (40 mg), and tretinoin 0.05% (0.5 mg). **Inactive:** butylated hydroxytoluene, cetyl alcohol, citric acid, glycerin, glyceryl stearate, magnesium aluminum silicate, methyl gluceth-10, methylparaben, PEG-100 stearate, propylparaben, purified water, *sodium metabisulfite*, stearic acid, and stearyl alcohol.

CLINICAL PHARMACOLOGY: One of the components in TRI-LUMA Cream, hydroquinone, is a depigmenting agent, and may interrupt one or more steps in the tyrosine-tyrosinase pathway of melanin synthesis. However, the mechanism of action of the active ingredients in TRI-LUMA Cream in the treatment of melasma is unknown.

Pharmacokinetics: Percutaneous absorption of unchanged tretinoin, hydroquinone and fluocinolone acetonide into the systemic circulation of two groups of healthy volunteers (Total n=59) was found to be minimal following 8 weeks of daily application of 1g (Group I, n=45) or 6g (Group II, n=14) of TRI-LUMA Cream.

For tretinoin quantifiable plasma concentrations were obtained in 57.78% (26 out of 45) of Group I and 57.14% (8 out of 14) of Group II subjects. The exposure to tretinoin as reflected by the C_{max} values ranged from 2.01 to 5.34 ng/mL (Group I) and 2.0 to 4.99 ng/mL (Group II). Thus, daily application of TRI-LUMA Cream resulted in a minimal increase of normal endogenous levels of tretinoin. The circulating tretinoin levels represent only a portion of total tretinoin-associated retinoids, which would include metabolites of tretinoin and that sequestered into peripheral tissues.

For hydroquinone quantifiable plasma concentrations were obtained in 18% (8 out of 44) Group I subjects. The exposure to hydroquinone as reflected by the C_{max} values ranged from 25.55 to 86.52 ng/mL. All Group II subjects (6g dose) had post-dose plasma hydroquinone concentrations below the quantitation limit. For fluocinolone acetonide, Groups I and II subjects had all post-dose plasma concentrations below quantitation limit.

Clinical Studies: Two adequate and well-controlled efficacy and safety studies were conducted in 641 patients between the ages of 21 to 75 years, having skin phototypes I-IV and moderate to severe melasma of the face. TRI-LUMA Cream was compared with 3 possible combinations of 2 of the 3 active ingredients [(1) hydroquinone 4% (HQ) + tretinoin 0.05% (RA); (2) fluocinolone acetonide 0.01% (FA) + tretinoin 0.05% (RA); (3) fluocinolone acetonide 0.01% (FA) + hydroquinone 4% (HQ)], contained in the same vehicle as *TRI-LUMA Cream*. Patients were instructed to apply their study medication each night, after washing their face with a mild soapless cleanser, for 8 weeks. Instructions were given to apply a thin layer of study medication to the hyperpigmented lesion, making sure to cover the entire lesion including the outside borders extending to the normal pigmented skin. Patients were provided a mild moisturizer *for use as needed. A sunscreen with SPF 30 was also provided with instructions for daily* use. Protective clothing and avoidance of sunlight exposure to the face was recommended.

Patients were evaluated for melasma severity at Baseline and at Weeks 1, 2, 4, and 8 of treatment. Primary efficacy was based on the proportion of patients who had an investigators' assessment of treatment success, defined as the clearing of melasma at the end of the eight-week treatment period. *The majority of patients enrolled in the* two studies were white (approximately 66%) and female (approximately 98%). TRI-LUMA Cream was demonstrated to be significantly more effective than any of the other combinations of the active ingredients.

PRIMARY EFFICACY ANALYSIS:

Investigators' Assessment of Treatment Success* At the End of 8 Weeks of Treatment

		TRI-LUMA	HQ+RA	FA+RA	FA+HQ
Study No. 1	Number of Patients	85	83	85	85
	No. of Successes	32	12	0	3
	Proportion of Successes	38%	15%	0	4%
	p-value		<0.001	<0.001	<0.001
Study No. 2	Number of Patients	76	75	76	76
	No. of Successes	10	3	3	1
	Proportion of Successes	13%	4%	4%	1%
	p-value		0.045	0.042	0.005

*Treatment success was defined as melasma severity score of zero (melasma lesions cleared of hyperpigmentation).

p-value is from Cochran-Mantel-Haenszel chi-square statistics controlling for pooled investigator and comparing TRI-LUMA Cream to the other treatment groups.

In the Investigators' assessment of melasma severity at Day 56 of treatment, the following table shows *improvement profile for all patients* treated with TRI-LUMA Cream based on severity of their melasma of treatment.

Investigators' Assessment of Change in Melasma Severity from Baseline to Day 56 of Treatment (combined results from studies 1 and 2)

	Baseline		Number (%) of Patients at Day 56[a]				
	Severity Rating	N	Cleared[b] N (%)	Mild[b] N (%)	Moderate[b] N (%)	Severe[b] N (%)	M
TRI-LUMA *Cream N=161*	Moderate	124	36 (29)	63 (51)	18 (15)	0 (0)	7
	Severe	37	6 (16)	19 (51)	9 (24)	2 (5)	1

[a] Assessment based on patients with severity scores at Day 56. Percentages are based on the total number in the treat population.

[b] Does not include patients who cleared before Day 56 or were missing from the Day 56 assessment.

Assessment Scale: Cleared (melasma lesions approximately equivalent to surrounding normal skin or with minimal resi pigmentation); Mild (slightly darker than the surrounding normal skin); Moderate (moderately darker than the surround skin); Severe (markedly darker than the surrounding normal skin).

Patients experienced improvement of their melasma with the use of TRI-LUMA Cream as early as However, among 7 patients who had clearing at the end of 4 weeks of treatment with TRI-LUMA Cream, did not maintain the remission after an additional 4 weeks of treatment.

After 8 weeks of treatment with the study drug, patients entered into an open-label extension period TRI-LUMA Cream was given on an as-needed basis for the treatment of melasma. The remission periods to shorten between progressive courses of treatment. Additionally, few patients maintained complete c melasma (approximately 1 to 2%).

INDICATIONS AND USAGE: TRI-LUMA Cream is indicated for the short-term treatment of moderate melasma of the face, in the presence of measures for sun avoidance, including the use of [illegible]s.

The following are important statements relating to the indication and usage of TRI-LUN

- TRI-LUMA Cream, a combination drug product containing corticosteroid, retinoid, and bleaching ager indicated for the maintenance treatment of melasma. After achieving control with TRI-LUMA Crea patients may be managed with other treatments instead of triple therapy with TRI-LUMA Cream. Becau ma usually recurs upon discontinuation of TRI-LUMA Cream, patients need to avoid sunlight exposure, screen with appropriate SPF, wear protective clothing, and change to non-hormonal forms of birth hormonal methods are used.
- In clinical trials used to support the use of TRI-LUMA Cream in the treatment of melasma, patients were ed to avoid sunlight exposure to the face, wear protective clothing *and use a sunscreen with SPF 30* They were to apply the study medication each night, after washing their face with a mild soapless clea
- The safety and efficacy of TRI-LUMA Cream in patients of skin types V and VI have not been studied. bleaching resulting in undesirable cosmetic effect in patients with darker skin cannot be excluded.
- *The safety and efficacy of TRI-LUMA Cream in the treatment of hyperpigmentation conditions other th* ma of the face have not been studied.
- Because pregnant and lactating women were excluded from, and women of child-bearing potential h birth control measures in the clinical trials, the safety and efficacy of TRI-LUMA Cream in pregnant w *nursing mothers have not been established (See PRECAUTIONS, Pregnancy).*

CONTRAINDICATIONS: TRI-LUMA Cream is contraindicated in individuals with a history of hypersensiti gy, or intolerance to this product or any of its components.

WARNINGS: TRI-LUMA Cream contains sodium metabisulfite, a sulfite that may cause allergic-type including anaphylactic symptoms and life-threatening asthmatic episodes in susceptible people.

TRI-LUMA Cream contains hydroquinone, which may produce exogenous ochronosis, a gradual blue-bl ening of the skin, whose occurrence should prompt discontinuation of therapy. The majority of patients ing this condition are Black, but it may also occur in Caucasians and Hispanics.

Cutaneous hypersensitivity to the active ingredients of TRI-LUMA Cream has been reported in the litera patch test study to determine sensitization potential in 221 healthy volunteers, three volunteers develop tivity reactions to TRI-LUMA Cream or its components.

PRECAUTIONS: ***General:*** TRI-LUMA Cream contains hydroquinone and tretinoin that may [illegible]d to irritation. Local irritation, such as skin reddening, peeling, mild burning sensation, dryness, and pruritu expected at the site of application. Transient skin reddening or mild burning sensation does not preclude t If a reaction suggests hypersensitivity or chemical irritation, the use of the medication should be discont TRI-LUMA Cream also contains the corticosteroid fluocinolone acetonide. Systemic absorption of topi costeroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potenti cocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrom glycemia, and glucosuria can also be produced by systemic absorption of topical corticosteroid while on t If HPA axis suppression is noted, the use of TRI-LUMA Cream should be discontinued. Recovery of HPA tion generally occurs upon discontinuation of topical corticosteroids.

Information for Patients: Exposure to sunlight, sunlamp, or ultraviolet light should be avoided. Patients consistently exposed to sunlight or skin irritants either through their work environment or habits shoul particular caution. Sunscreen and protective covering (such as the use of a hat) over the treated areas s used. Sunscreen use is an essential aspect of melasma therapy, as even minimal sunlight sustains me activity.

Weather extremes, such as heat or cold, may be irritating to patients treated with TRI-LUMA Cream. Becau drying effect of this medication, a moisturizer may be applied to the face in the morning after washing.

Application of TRI-LUMA Cream should be kept away from the eyes, nose, or angles of the mouth, be mucosa is much more sensitive than the skin to the irritant effect. *If local irritation persists or become* application of the medication should be discontinued and the health care provider consulted. Allergic cor matitis, blistering, crusting, and severe burning or swelling of the skin and irritation of the mucous mem the eyes, nose, and mouth require medical attention.

If the medication is applied excessively, marked redness, peeling, or discomfort may occur.

This medication is to be used as directed by the health care provider and should not be used for any disor than that for which it is prescribed.

Laboratory Tests: The following tests may be helpful in evaluating patients for HPA axis suppression:

ACTH or cosyntropin stimulation test

Remove this portion before dispensing

PATIENT INFORMATION

For External Use Only.   Not for Ophthalmic Use.

TRI-LUMA™ Cream

(fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%)

Read this information carefully before you begin treatment. Read the information you get whenever you get more medicine. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about TRI-LUMA (try-LOOM-ah), ask your doctor. Only your doctor can determine if TRI-LUMA is right for you.

What is the most important information I should know about TRI-LUMA Cream?

Use of TRI-LUMA Cream in pregnant women may carry the chance of having birth defects in the baby. Tell your doctor if you are pregnant, may be pregnant, or plan to become pregnant. Your doctor will talk with you about the benefits and risks of using TRI-LUMA during pregnancy to help decide if the benefits for you are greater than the risks. You may decide to delay treatment until after your baby is born.

If you become pregnant while taking TRI-LUMA Cream, tell your doctor right away. You should discuss the chances that your baby may be harmed. Using TRI-LUMA Cream early in pregnancy may be more likely to produce birth defects than using it later in pregnancy.

What is TRI-LUMA Cream?

TRI-LUMA (try-LOOM-ah) Cream is a medicine with three active components. You put TRI-LUMA Cream on your face to treat a skin condition called melasma. Melasma consists of dark (hyperpigmented) spots on facial skin, especially on the cheeks and forehead. This condition usually happens with hormone changes.

TRI-LUMA Cream is for **SHORT-TERM (up to 8 weeks)** treatment of **moderate to severe** melasma of the face. It is **NOT FOR LONG-TERM (more than 8 weeks) or maintenance (continuous)** treatment of melasma. Milder forms of melasma may not need treatment with medicine. Melasma can also be managed by staying out of the sun or by stopping the use of birth control methods that involve hormones.

In studies, after 8 weeks of treatment with TRI-LUMA Cream, most patients had at least some improvement. Some had their dark spots clear up completely (38% in one study and 13% in another). In most patients treated with TRI-LUMA Cream, their melasma came back after treatment. If the underlying cause of melasma, such as the use of certain birth control pills or too much exposure to sunlight, are not removed, *melasma will come back when you stop treatment.* **TRI-LUMA Cream may improve your melasma, but it is NOT a cure.**

Who should not use TRI-LUMA Cream?

Do not use TRI-LUMA if you are allergic to the medicine or any of its ingredients. See the end of this leaflet *for a list of ingredients.*

What should I tell my doctor before taking TRI-LUMA?

If you are pregnant, think you are pregnant, plan to be pregnant or are nursing an infant, tell your do tor. *Your doctor will decide with you whether the benefits in using TRI-LUMA Cream will be greater tha* the risks. If possible, delay treatment with TRI-LUMA Cream until after the baby is born.

Tell your doctor about all the other medicines and skin products you use, including prescription and no prescription medicines, cosmetics, and supplements. They may make your skin more sensitive to su light.

How should I use TRI-LUMA Cream?

TRI-LUMA Cream should be used as instructed by your doctor.

To help you use the medicine correctly, follow these steps:

- Gently wash your face with a mild cleanser. Don't use a wash cloth to apply the cleanser, just yo fingers. Rinse and pat your skin dry.
- Apply TRI-LUMA Cream at night, at least 30 minutes before bedtime.
- Put a small amount (pea sized or 1/2 inch or less) of TRI-LUMA Cream on your fingertip. Apply a th coat onto the discolored spot(s). Include about 1/2 inch of normal skin surrounding the affected are After you have used the medicine for a while, you may find that you need slightly less to do the job.
- Rub the medicine lightly and uniformly into your skin. The medicine should become invisible almost once. If you can still see it, you are using too much.
- Keep the medicine away from the corners of your nose, your mouth, eyes and open wounds. Spread away from those areas when applying it.
- **Do not** use more TRI-LUMA Cream or apply it more often than recommended by your doctor. Too mu TRI-LUMA Cream may irritate your skin, waste medicine, and won't give you faster or better results
- Do not cover the treated area with anything after applying TRI-LUMA Cream.
- If your skin gets too irritated, stop using TRI-LUMA Cream, *and let your doctor know.*
- To help avoid skin dryness, you may use a moisturizer in the morning after you wash your face.
- You may also use a moisturizer and cosmetics during the day.

Use a sunscreen of at least SPF 30 and a wide-brimmed hat over the treated areas. It requires only a sm *amount of sunlight to worsen melasma. Melasma can get worse even if you don't get sunburn.*

Only your doctor knows which other medicines may be helpful during treatment, and will tell you abc them if needed. Do not use other medicines unless your doctor approves them.

If you get sunburned, stop using TRI-LUMA Cream until your skin is healed.

After stopping TRI-LUMA treatment, continue to protect your skin from sunlight.

What should I avoid while using TRI-LUMA Cream?

Sunlight or ultraviolet light. Too much natural sunlight or artificial sunlight from a sunlamp can cau sunburn. Dark skin patches may become darker when the skin is exposed to sunlight. You don't have

have a sunburn to make your melasma worse.

TRI-LUMA can make your skin more likely to get sunburn or develop other unwanted effects from the sun. Protect your skin from natural sunlight as much as possible to help prevent further darkening of existing dark patches and formation of new ones. Staying out of the sun is especially important for women who take birth control pills or hormone replacement therapy, and for people who have had dark patches in the past.

Use an effective sunscreen **any time you are outside**, even on hazy days. The sunscreen should have SPF (sun protection factor) of 30 or more. Use sunscreen year-round on areas of the skin that are regularly exposed to sunlight, such as your face and hands. If possible, protect the treated area from sunlight exposure.

If you spend a lot of time outside, be especially careful of sunlight. Ask your doctor what SPF level will give you the needed high level of protection. If you will be outside, wear protective clothing, including a hat.

Do not use suntamps while you use TRI-LUMA Cream.

Heat, wind and cold. Heat and cold tend to dry or irritate normal skin. Skin treated with TRI-LUMA Cream may be more likely to react to heat and cold. Your doctor can recommend ways to manage your melasma under these conditions.

Other skin products and medicines. Avoid products that may dry or irritate your skin. These may include soaps and cleansers that are rough or cause drying; certain astringents, such as alcohol-containing products; soaps and toiletries containing alcohol, spices, or lime; or certain medicated soaps, shampoos, and hair permanent products. Do not use any other medicines with TRI-LUMA Cream unless you have consulted your doctor. The medicines and product you have used in the past may cause redness or peeling when used with TRI-LUMA.

What are the possible side effects of TRI-LUMA Cream?

A very few patients may get severe allergic reactions from TRI-LUMA. This includes people allergic to sulfites. **They may have trouble breathing or severe asthma attacks, which can be life-threatening.**

While you use TRI-LUMA Cream, your skin may develop mild to moderate redness, peeling, burning, dryness, or itching.

TRI-LUMA Cream contains a corticosteroid medicine as one of its active components. The following side effects have been reported with application of corticosteroid medicines to the skin: itching, irritation, dryness, infection of the hair follicles, acne, change in skin color, inflammation around the mouth, allergic skin reaction, skin infection, skin thinning, stretch marks, and sweat problems.

Stop using **TRI-LUMA Cream and contact your doctor if you have**

severe or continued irritation, blistering, oozing, scaling, or crusting

severe burning or swelling of your skin

irritation of your eyes, nose, and mouth

Some patients using TRI-LUMA Cream develop dark spots on their skin (hyperpigmentation), tingling, increased skin sensitivity, rash, acne, skin redness caused by a condition called rosacea, skin bumps, blisters, or tiny red lines or blood vessels showing through the skin (telangiectasia).

If you are concerned about how your skin is reacting to the medicine, call your doctor.

General information about prescription medicines

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use TRI-LUMA for a condition for which it was not prescribed. Do not give TRI-LUMA to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about TRI-LUMA. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about TRI-LUMA that is written for health professionals.

Ingredients: TRI-LUMA Cream contains fluocinolone acetonide, hydroquinone, and tretinoin as active ingredients, as well as the following in the cream base: butylated hydroxytoluene, cetyl alcohol, citric acid, glycerin, glyceryl stearate, magnesium aluminum silicate, methyl gluceth-10, methylparaben, PEG-100 stearate, propylparaben, purified water, sodium metabisulfite, stearic acid and stearyl alcohol.

Marketed by:
Galderma Laboratories, L.P.
Fort Worth, TX 76177 USA
Manufactured by:
Hill Laboratories, Inc.
Sanford, FL 32773 USA
20011-0102 Revised January 2002

Unacceptable control test

Drug Interactions: Patients should avoid medicated or abrasive soaps and cleansers, soaps and cosmetics with drying effects, products with high concentration of alcohol and astringent, and other irritants or keratolytic drugs while on TRI-LUMA Cream treatment. Patients are cautioned on concomitant use of medications that are known to be photosensitizing.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies to determine the carcinogenic potential of TRI-LUMA Cream have not been conducted.

Hydroquinone is mutagenic in some in vitro test systems. Studies in hairless albino mice suggest that concurrent exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. This effect has been confirmed in a lifetime study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.1% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources.

Fertility studies were not conducted with this combination of active ingredients. Published studies have indicated that hydroquinone is a mutagen and a clastogen. Treatment with hydroquinone has resulted in positive findings for genetic toxicity in the Ames assay in bacterial strains sensitive to oxidizing mutagens, in vitro tests in mammalian cells, and in the in vivo mouse micronucleus assay. Tretinoin has been shown to be negative for mutagenesis in the Ames assay. Additional information regarding the genetic toxicity potential of tretinoin and hydroquinone is not available.

A rat reproductive fertility study was conducted in SD rats using a 10-fold dilution of the clinical formulation. No test was seen on the traditional parameters used to assess fertility, although prolongation of estrus was observed in some females, and there was a trend towards an increase in pre- and post-implantation loss that was statistically significant. No adequate study of fertility and early embryonic toxicity of the full-strength drug product has been performed. In a six-month study in minipigs, small testes and severe hypospermia were found in animals treated topically with the full strength drug product.

Pregnancy Effects, Pregnancy Category C: TRI-LUMA Cream contains the teratogen, tretinoin, which has been shown to cause fetal death, altered fetal growth, congenital malformations, and potential neurologic deficits. It is difficult to interpret the animal studies on teratogenicity with TRI-LUMA Cream, because the availability of the active ingredients in these studies cannot be assured, and comparison with clinical dosing is not possible. There are inadequate and well-controlled studies in pregnant women. TRI-LUMA Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Corticosteroids, when systemically administered, appear in human milk. It is not known whether topical application of TRI-LUMA Cream could result in sufficient systemic absorption to produce detectable quantities of fluocinolone acetonide, hydroquinone, or tretinoin in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRI-LUMA Cream is administered to a nursing woman. Care should be taken to avoid contact between the infant being nursed and TRI-LUMA Cream.

Pediatric Use: Safety and effectiveness of TRI-LUMA Cream in pediatric patients have not been established.

Geriatric Use: Clinical studies of TRI-LUMA Cream did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosage range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS: In the controlled clinical trials, adverse events were monitored in the 161 patients who used TRI-LUMA Cream once daily during an 8-week treatment period. There were 102 (63%) patients who experienced at least one treatment-related adverse event during these studies. The most frequently reported events were erythema, desquamation, burning, dryness, and pruritus at the site of application. The majority of these events were mild to moderate in severity. Adverse events reported by at least 1% of patients and judged by the investigators to be reasonably related to treatment with TRI-LUMA Cream from the controlled clinical studies are summarized in decreasing order of frequency as follows:

Incidence and Frequency of Treatment-related Adverse Events with TRI-LUMA Cream in at least 1% or more of Patients (N=161)

Adverse Event	Number (%) of Patients
Erythema	66 (41%)
Desquamation	61 (38%)
Burning	29 (18%)
Dryness	23 (14%)
Pruritus	18 (11%)
Acne	8 (5%)
Paresthesia	5 (3%)
Telangiectasia	5 (3%)
Hypoesthesia	3 (2%)
Pigmentary changes	3 (2%)
Irritation	3 (2%)
Papules	2 (1%)
Acne-like rash	1 (1%)
Nausea	1 (1%)
Dry mouth	1 (1%)
Rash	1 (1%)
Vesicles	1 (1%)

In an open-label long-term safety study, patients who have had cumulative treatment of melasma with TRI-LUMA Cream for 6 months showed a similar pattern of adverse events as in the 8-week studies.

The following local adverse reactions have been reported infrequently with topical corticosteroids. They may occur more frequently with the use of occlusive dressings, especially with higher potency corticosteroids. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and miliaria.

TRI-LUMA Cream contains hydroquinone, which may produce exogenous ochronosis, a gradual blue-black darkening of the skin, whose occurrence should prompt discontinuation of therapy.

Cutaneous hypersensitivity to the active ingredients of TRI-LUMA Cream has been reported in the literature. In a patch test study to determine sensitization potential in 221 healthy volunteers, three volunteers developed sensitivity reactions to TRI-LUMA Cream or its components.

DOSAGE AND ADMINISTRATION: TRI-LUMA Cream should be applied once daily at night. It should be applied at least 30 minutes before bedtime.

Gently wash the face and neck with a mild cleanser. Rinse and pat the skin dry. Apply a thin film of the cream to the hyperpigmented areas of melasma including about 1/2 inch of normal appearing skin surrounding each lesion. Rub lightly and uniformly into the skin. Do not use occlusive dressing.

During the day use a sunscreen of SPF 30, and wear protective clothing. Avoid sunlight exposure. Patients may use moisturizers and/or cosmetics during the day.

HOW SUPPLIED: TRI-LUMA Cream is supplied in 30 g aluminum tubes.

NDC 0299-5950-30.

Storage: Keep tightly closed. Store at controlled room temperature 68° to 77°F (20°-25°C). Protect from freezing.

Marketed by:
Galderma Laboratories, L.P.
Fort Worth, TX 76177 USA
Manufactured by:
Hill Laboratories, Inc.
Sanford, FL 32773 USA
20011-0102 Revised: January 2002

ears at five weeks, a pattern consistent with effects previously noted in animals exposed *in utero* with retinoic acids. No adequate study of this late gestational and postnatal effects of the full-strength TRI-LUMA Cream has been performed.

It is difficult to interpret these animal studies on teratogenicity with TRI-LUMA Cream, because the availability of the dermal applications in these studies could not be assured, and comparison with clinical dosing is not possible.

At regnancies have a risk of birth defect, loss, or other adverse event regardless of drug exposure. Typically, estimates of increased fetal risk from drug exposure rely heavily on animal data. However, animal studies do not always predict effects in humans. Even if human data are available, such data may not be sufficient to determine whether there is an increased risk to the fetus. Drug effects on behavior, cognitive function, and fertility in the offspring are particularly difficult to assess.

Sep 30 03 02:43p Hill Dermaceuticals Inc 407 649 9213 p.7

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-112

Hill Dermaceuticals, Inc.
Attention: Rosario G. Ramirez, M.D.
Director, Medical/Regulatory
2650 South Mellonville Ave.
Sanford, Florida 32773

Dear Dr. Ramirez:

Please refer to your new drug application (NDA) dated March 19, 1999, received March 22, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRI-LUMA (fluocinolone acetonide, 0.01% / hydroquinone, 4% / tretinoin, 0.05%) Cream.

We acknowledge receipt of your submissions dated August 16, 21(two), 22, September 4, 18, 19, 26, October 25, November 1 and 22, December 10, 18, 20, 2001; January 10 and 15, 2002; and facsimile transmissions dated September 17 and 20, and November 16 and 22, 2001; and January 18(two), 2002. Your submission of July 20, 2001, constituted a complete response to our January 21, 2000, action letter.

This new drug application provides for the use of TRI-LUMA ((fluocinolone acetonide, 0.01% / hydroquinone, 4% / tretinoin, 0.05%) Cream for the short-term treatment of moderate to severe melasma of the face, in the presence of measures for sun avoidance, including the use of sunscreens.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-112." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your facsimile transmissions dated January 18, 2002. These commitments are listed below:

1. The Applicant commits to the collection of pregnancy outcome data arising from the use of TRI-LUMA Cream in pregnancy, monitor the unintended usage in pregnancy, and provide measures how this can be reduced. The Applicant will submit a protocol for review.

   Protocol Submission: Within 3 months of the date of this letter

2. The Applicant commits to performing dermal carcinogenicity testing of the combination drug product.

   Protocol Submission: Within 4 months of the date of this letter
   Study Start: Within 6 months of the date of the approval of the protocol
   Final Report Submission: Within 12 months after the study completion

In addition, the Applicant will provide to the Agency the complete study reports for Studies 29 and 30 as soon as each study is completed, and provide Safety Updates in these submissions.

The Agency reminds the Applicant of their commitment to provide a final report on the 12 months storage stability of tretinoin in human plasma on or before August 2002.

We also acknowledge your agreement on January 18, 2002, to implement changes within six months to revise the container and carton label to show (1) white space between the ingredients listing and the "Storage" condition line; and (2) the established name will be at least ½ the size of the tradename.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is

waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on

this application as the necessary studies are impossible or highly impractical to conduct because the number of patients is too small.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Victoria Lutwak, Project Manager, at 301-828-2073.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jonathan Wilkin
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