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:

[Structure]

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:

[Structure]

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:

[Structure]

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 the 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 the clinical improvement profile for all patients treated with TRI-LUMA Cream based on severity of their melasma at the start of treatment.

Investigators' Assessment of Change in Melasma Severity from Baseline to Day 56 of Treatment (combined results from studies 1 and 2)							
			Number (%) of Patients at Day 56[a]				
	Baseline		**Cleared[b]**	**Mild[b]**	**Moderate[b]**	**Severe[b]**	**Missing[b]**
	Severity Rating	N	N (%)	N (%)	N (%)	N (%)	N (%)
TRI-LUMA Cream N=161	Moderate	124	36 (29)	63 (51)	18 (15)	0 (0)	7 (6%)
	Severe	37	6 (16)	19 (51)	9 (24)	2 (5)	1 (3%)

[a] Assessment based on patients with severity scores at Day 56. Percentages are based on the total number in the treatment group 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 residual hyperpigmentation); Mild (slightly darker than the surrounding normal skin); Moderate (moderately darker than the surrounding normal 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 4 weeks. However, among 7 patients who had clearing at the end of 4 weeks of treatment with TRI-LUMA Cream, 4 of them 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 in which TRI-LUMA Cream was given on an as-needed basis for the treatment of melasma. The remission periods appeared to shorten between progressive courses of treatment. Additionally, few patients maintained complete clearing of melasma (approximately 1 to 2%).

INDICATIONS AND USAGE
TRI-LUMA Cream is indicated 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.

The following are important statements relating to the indication and usage of TRI-LUMA Cream:
- TRI-LUMA Cream, a combination drug product containing corticosteroid, retinoid, and bleaching agent, is NOT indicated for the maintenance treatment of melasma. After achieving control with TRI-LUMA Cream, some patients may be managed with other treatments instead of triple therapy with TRI-LUMA Cream. Because melasma usually recurs upon discontinuation of TRI-LUMA Cream, patients need to avoid sunlight exposure, use sunscreen with appropriate SPF, wear protective clothing, and change to non-hormonal forms of birth control, if hormonal methods are used.

- In clinical trials used to support the use of TRI-LUMA Cream in the treatment of melasma, patients were instructed to avoid sunlight exposure to the face, wear protective clothing and use a sunscreen with SPF 30 each day. They were to apply the study medication each night, after washing their face with a mild soapless cleanser.

- The safety and efficacy of TRI-LUMA Cream in patients of skin types V and VI have not been studied. Excessive 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 than melasma of the face have not been studied.

- Because pregnant and lactating women were excluded from, and women of child-bearing potential had to use birth control measures in the clinical trials, the safety and efficacy of TRI-LUMA Cream in pregnant women and nursing mothers have not been established (See PRECAUTIONS, *Pregnancy*).

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

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

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. The majority of patients developing 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 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.

PRECAUTIONS
General: TRI-LUMA Cream contains hydroquinone and tretinoin that may cause mild to moderate irritation. Local irritation, such as skin reddening, peeling, mild burning sensation, dryness, and pruritus may be expected at the site of application. Transient skin reddening or mild burning sensation does not preclude treatment. If a

reaction suggests hypersensitivity or chemical irritation, the use of the medication should be discontinued.

TRI-LUMA Cream also contains the corticosteroid fluocinolone acetonide. Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced by systemic absorption of topical corticosteroid while on treatment. If HPA axis suppression is noted, the use of TRI-LUMA Cream should be discontinued. Recovery of HPA axis function generally occurs upon discontinuation of topical corticosteroids.

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

Weather extremes, such as heat or cold, may be irritating to patients treated with TRI-LUMA Cream. Because of the 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, 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.

This medication is to be used as directed by the health care provider and should not be used for any disorder other 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
A.M. plasma cortisol test
Urinary free cortisol 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.

Studies of hydroquinone in animals have demonstrated some evidence of carcinogenicity. The carcinogenic potential of hydroquinone in humans is unknown.

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 later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources.

Mutagenicity studies were not conducted with this combination of active ingredients. Published studies have demonstrated 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 *in vitro* studies 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 of fluocinolone acetonide is not available.

A dermal reproductive fertility study was conducted in SD rats using a 10-fold dilution of the clinical formulation. No effect 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

not 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 when males were treated topically with the full strength drug product.

Pregnancy: *Teratogenic Effects: Pregnancy Category C.* TRI-LUMA Cream contains the teratogen, tretinoin, which may cause embryo-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 dermal applications in these studies cannot be assured, and comparison with clinical dosing is not possible. There are no adequate 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.

Summary Statement on Teratogenic Risk

TRI-LUMA Cream contains the teratogen, tretinoin, which may cause embryo-fetal death, altered fetal growth, congenital malformations, and potential neurologic deficits. However, human data have not confirmed an increased risk of these developmental abnormalities when tretinoin is administered by the topical route.

Clinical considerations relevant to actual or potential inadvertent exposure during pregnancy:

In clinical trials involving TRI-LUMA Cream in the treatment of facial melasma, women of child-bearing potential initiated treatment only after having had a negative pregnancy test and used effective birth control measures during therapy. Thus, safety and efficacy of TRI-LUMA Cream in pregnancy has not been established. In general, use of drugs should be reduced to a minimum in pregnancy. If a patient has been inadvertently exposed to TRI-LUMA Cream in pregnancy, she should be counseled on the risk of teratogenesis due to this exposure. The risk of teratogenesis due to topical exposure to TRI-LUMA Cream may be considered low. However, exposure during the period of organogenesis in the first trimester is theoretically more likely to produce adverse outcome than in later pregnancy.

The prescriber should have the following clinical considerations in making prescribing decisions:

- The potential developmental effects of tretinoin are serious but the risk from topical administration is small.
- Exposure during the period for organogenesis in the first trimester is theoretically more likely to produce adverse outcome than in later pregnancy.
- The risk to the mother for not treating melasma should be determined by the physician with the patient. Mild forms of melasma may not necessarily require drug treatment. TRI-LUMA Cream is indicated for the treatment of moderate to severe melasma. Melasma may also be managed with other forms of therapy such as topical hydroquinone in the presence of sunlight avoidance, or stopping the use of hormonal birth control methods. If possible, delaying treatment with TRI-LUMA Cream until after delivery should be considered.
- There are no adequate 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.

Data Discussion

Tretinoin is considered to be highly teratogenic upon systemic administration. Animal reproductive studies are not available with topical hydroquinone. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

1. Human Data.

- In clinical trials involving TRI-LUMA Cream in the treatment of facial melasma, women of child-bearing potential initiated treatment only after having had a negative pregnancy test, and used effective birth control measures during therapy. However, 13 women became pregnant during treatment with TRI-LUMA Cream. Most of the pregnancy outcomes have not been known. Three women gave birth to apparently healthy babies. One pregnancy was terminated prematurely, and another ended in miscarriage.
- Epidemiologic studies have not confirmed an increase in birth defects associated with the use of topical tretinoin. However, there may be limitations to the sensitivity of epidemiologic studies in the detection of certain forms of fetal injury, such as subtle neurologic or intelligence deficits.

2. Animal Data.

- In a dermal application study using TRI-LUMA Cream in pregnant rabbits, there was an increase in the number of *in utero* deaths and a decrease in fetal weights in litters from dams treated topically with the drug product.
- In a dermal application study in pregnant rats treated with TRI-LUMA Cream during organogenesis there was evidence of teratogenicity of the type expected with tretinoin. These morphological alterations included cleft palate, protruding tongue, open eyes, umbilical hernia, and retinal folding or dysplasia.
- In a dermal application study on the gestational and postnatal effects of a 10-fold dilution of TRI-LUMA Cream in rats, an increase in the number of stillborn pups, lower pup body weights, and delay in preputial

separation were observed. An increase in overall activity was seen in some treated litters at postnatal day 22 and in all treated litters at five weeks, a pattern consistent with effects previously noted in animals exposed *in utero* with retinoic acids. No adequate study of the 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.

All pregnancies 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.

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 secreted 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 dosing 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%)
Hyperesthesia	3 (2%)
Pigmentary changes	3 (2%)
Irritation	3 (2%)
Papules	2 (1%)
Acne-like rash	1 (1%)
Rosacea	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 ½ 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** 28105-300-30.

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

Hill Laboratories, Inc.
Sanford, FL 32773 USA

(code)
Revised: xxxx 2002

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 TRILUMA 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 causes 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 doctor. Your doctor will decide with you whether the benefits in using TRI-LUMA Cream will be greater than 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 non-prescription medicines, cosmetics, and supplements. They may make your skin more sensitive to sunlight.

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 your 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 ½ inch or less) of TRI-LUMA Cream on your fingertip. Apply a thin coat onto the discolored spot(s). Include about ½ inch of normal skin surrounding the affected area. 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 at 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 it 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 much 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 small 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 about 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 cause sunburn. Dark skin patches may become darker when the skin is exposed to sunlight. You don't have to 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 sunlamps 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 cleaners 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.

Hill Laboratories, Inc.
Sanford, FL 32773 USA Revised: xxxx 2002

CONTAINER LABEL - 30 GRAM TUBE

FRONT PANEL

NDC 28105-300-30
Rx only

TRI-LUMA™ Cream
(fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%)

30 g

BACK PANEL

For External Use Only. Not for Ophthalmic Use.

Usual dosage: Apply a thin film to affected areas once daily at night. See package insert for complete prescribing information.

Each gram 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.

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

Lot No. and Exp. Date on crimp.

Hill Laboratories, Inc.
Sanford, FL 32773 USA (label date code)

CARTON LABEL FOR 30 GRAM TUBE

FRONT PANEL (Horizontal Placement of Text)

NDC 28105-300-30 **Rx only**

TRI-LUMA™Cream
(fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%)

30 g

SIDE PANEL (Right)

For External Use Only. Not for Ophthalmic Use.

Usual dosage: Apply a thin film to affected areas once daily at night. See package insert for complete prescribing information.

Hill Laboratories, Inc. Sanford, FL 32773 USA (carton date code)

SIDE PANEL (Left)

Each gram 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.

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

TOPFLAP

Lot No.:
Exp. date:

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/s/

Jonathan Wilkin
1/18/02 06:24:25 PM