For the use of a registered medical practitioner or a hospital or a laboratory only

Hydroquinone USP 4.00% w/w + Tretinoin USP 0.05% w/w + Fluocinolone Acetonide IP 0.01%w/w Topical Cream

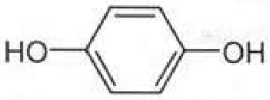
TRILUMA® Cream

COMPOSITION:

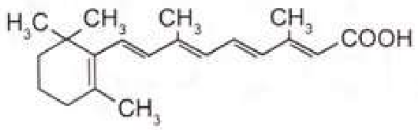
Hydroquinone USP	4.00% w/w
Tretinoin USP	0.05% w/w
Fluocinolone Acetonide IP	0.01% w/w
In a cream base	q.s.

DESCRIPTION

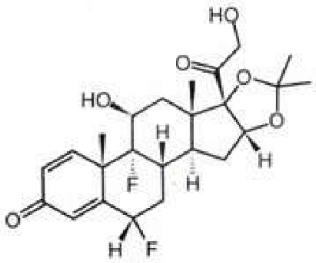
TRILUMA® Cream contains Hydroquinone USP 4.00%, Tretinoin USP 0.05% and Fluocinolone Acetonide IP 0.01% in a hydrophilic cream base for topical application. Hydroquinone is therapeutically classified as a depigmenting agent. It is prepared from the reduction of p-benzoquinone with sodium bisulfite. It occurs as fine white needles that darken on exposure to air. The chemical name for hydroquinone is: 1,4-benzediol. The molecular formula is $C_6H_6O_2$ and the 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 reticene to a carboxyl group. It occurs as yellow to lightorange crystals or crystalline powder. It is highly reactive to light and moisture. Tretinoin is therapeutically classified as a keratolytic. The chemical name for Tretinoin is: (all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclo-hexen-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:



Fluocinolone Acetonide is a synthetic fluorinated corticosteroid for topical dermatological use and is classified therapeutically as an antiinflammatory. It is a white crystalline powder that is odorless and stable in light. The chemical name for Fluocinolone Acetonide is: (6+,118,16+)6, 9-difluoro-11, 21-dihrdroxy-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:



CLINICAL PHARMACOLOGY

One of the components in **TRILUMA®** Cream, hydroquinone, is a depigmenting agent. It is a hydroxyphenolic chemical and inhibits conversion of DOPA to melanin by inhibiting tyrosinase enzyme. The other proposed mechanisms are:

- Inhibition of DNA, RNA synthesis
- Degradation of melanosomes
- Destruction of melanocytes

Tretinoin accelerates desquamation, and removes preformed melanin. The role of retinoids is likely to be due to its promotion of keratinocyte proliferation and acceleration of epidermal turnover. Tretinoin induces dispersion of pigment granules inside the keratinocytes and accelerates the turnover of epidermal cells, facilitating the elimination of the dispersed pigment.

Fluocinolone Acetonide, a corticosteroid, inhibits the tyrosinase activity, affects the secretory function of melanocytes and has anti metabolic effect on keratinocytes. Corticosteroids also inhibit the various mediators of inflammation and hence also inhibit the stimulatory impulses for melanocytes. However, the mechanism of action of the active ingredients in **TRILUMA®** 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 the triple combination cream containing hydroquinone 4%, tretinoin 0.05% and fluocinolone acetonide 0.01%. 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 Cmax 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 the triple combination 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 Cmax 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.

NON-CLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility When fluocinolone acetonide, hydroquinone, and tretinoin in fixed combinations equivalent to 10%, 50%, 100%, and 150% of the concentrations in the clinical formulation of the triple combination cream were applied topically to male and female CD-1 mice for up to 24 months at dosages approximating up to 50, 19,000, and 250 g/kg/day, respectively (corresponding to dosages of 150, 57,000, and 750 g/m2/day, respectively), no statistically significant changes in tumor incidence were observed.

When fluocinolone acetonide, hydroquinone, and tretinoin in fixed combinations equivalent to 10%, 25%, 50%, and 100% of the concentrations in the clinical formulation of the triple combination cream were applied topically to male and female SD rats for up to 24 months at dosages approximating up to 10, 4000, and 50 ug/kg/day, respectively (corresponding to dosages of 60, 24,000, and 300 ug/m?/day, respectively), statistically significant increases in the incidences of islet cell adenomas and combined islet cell adenomas and carcinomas of the pancreas in both males and females were observed. The clinical relevance of these findings is unknown.

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 of the triple combination cream. 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.

INDICATIONS AND USAGE

TRILUMA 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.

LIMITATION FOR USE

- **TRILUMA** Cream, a combination drug product containing corticosteroid, retinoid, and bleaching agent, is not indicated for the maintenance treatment of melasma. After achieving control with **TRILUMA** Cream, some patients may be managed with other treatments instead of triple therapy with **TRILUMA** Cream. Because melasma usually recurs upon discontinuation of **TRILUMA** 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 **TRILUMA** 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 **TRILUMA** Cream in patients with 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 **TRILUMA** 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 childbearing potential had to use birth control measures in the clinical trials, the safety and efficacy of **TRILUMA** Cream in pregnant women and nursing mothers have not been established.

CONTRAINDICATIONS

TRILUMA Cream is contraindicated in individuals with a history of hypersensitivity to this product or any of its components.

WARNINGS AND PRECAUTIONS:

Hypersensitivity

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

Exogenous Ochronosis

TRILUMA Cream contains hydroquinone which may produce exogenous Ochronosis, a gradual black-blue 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 **TRILUMA** Cream has been reported in the literature.

Cutaneous Reactions

TRILUMA 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.

Effects on Endocrine System

TRILUMA 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 glycosuria can also be produced by systemic absorption of topical corticosteroid while on treatment. If HPA axis suppression is noted, the use of **TRILUMA** Cream should be discontinued. Recovery of HPA axis function generally occurs on discontinuation of topical corticosteroids. The ACTH or cosyntropin stimulation test may be helpful in evaluating patients for HPA axis suppression.

Drug Interactions

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

Pregnancy: Category C

TRILUMA Cream contains the teratogen, tretinoin, which may cause embryo-fetal death, altered fetal growth, congenital malformations, and potential neurologic deficits. There are no adequate and well-controlled studies in pregnant women. In general, use of drugs should be reduced to a minimum in pregnancy. If a patient has been inadvertently exposed to **TRILUMA** Cream in pregnancy, she should be counseled on the risk of teratogenesis due to this exposure. 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. **TRILUMA** 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 **TRILUMA** 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 **TRILUMA** Cream is administered to a nursing woman. Care should be taken to avoid contact between the infant being nursed and **TRILUMA** Cream.

Pediatric use:

Safety and effectiveness of **TRILUMA** Cream in pediatric patients have not been established.

Safety and effectiveness of **TRILUMA** cream in patients younger than 18 years have not been established.

Geriatric Use:

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.

CLINICAL STUDIES

Two adequate and well-controlled efficacy and safety trials were conducted in 641 subjects between the ages of 21 to 75 years, having Fitzpatrick Skin types I-IV and moderate to severe melasma of the face. The triple combination cream containing hydroquinone 4%, tretinoin 0.05% and fluocinolone acetonide 0.01% 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 the triple combination cream. Subjects 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. Subjects 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. Subjects 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 subjects 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 subjects enrolled in the two trials were white (approximately 66%) and female (approximately 98%). The triple combination cream was demonstrated to be significantly more effective than any of the other combinations of the active ingredients.

PRIMARY EFFICACY ANALYSIS

Table 1: Investigators' Assessment of Treatment Success* at the End of 8 Weeks of Treatment

-	-	HQ + RA + FA	RA + HQ	FA + RA	FA + HQ
Trial 1	Subject, n	85	83	85	85
	Successes, n	32	12	0	3
	Proportion of Successes	38%	15%	0	3
	p value		<0.001	<0.001	<0.001
Trial 2	Subjects, n	76	75	76	76
	Successes, n	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 the triple combination 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 subjects treated with the triple combination cream based on severity of their melasma at the start of treatment

Table 2 : Investigators assessment of change in Melasma Severity from Baseline to day 58 of treatment (Combine results from trials 1 and 5)

	Baseline		Number (%) of subjects at Day 56a				
			Cleared[b]	Mild[b]	Moderate[b]	Severe[b]	Missing[b]
Triple combination HQ + RA + FA (n=161)	Severity Rating	n	n(%)	n(%)	n(%)	n(%)	n(%)
	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 subjects with severity scores at Day 56. Percentages are based on the total number in the treatment group population.

b. Does not include subjects 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).

Subjects experienced improvement of their melasma with the use of triple combination cream as early as 4 weeks. However, among 7 subjects who had clearing at the end of 4 weeks of treatment with the triple combination cream, 4 of them did not maintain the remission after an additional 4 weeks of treatment. After 8 weeks of treatment with the trial drug, subjects entered into an open-label extension period in which the triple combination 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 subjects maintained complete clearing of melasma (approximately 1 to 2%).

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the controlled clinical trials, adverse events were monitored in the 161 subjects who used the triple combination cream once daily during an 8-week treatment period. There were 102 (63%) subjects who experienced at least one treatment-related adverse event during these trials. 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 the triple combination cream from the controlled clinical trials are summarized (in decreasing order of frequency) as follows

Table 3 : Incidence and Frequency of Treatment-related Adverse Event with Triluma Cream In at Least 1% or More of Subject (N=161)

Adverse event	n (%)	Adverse event	n (%)
Erythema	66 (41%)	Pigmentary changes	3 (2%)
Desquamation	61 (38%)	irritation	3(2%)
Burning	29 (18%)	Papules	2 (1%)
Dryness	23 (14%)	Acne like rash	1 (1%)
Pruritus	18 (11%)	Rosacea	1 (1%)
Acne	8 (5%)	Dry mouth	1 (1%)
Paresthesia	5 (3%)	Rash	1 (1%)
Telangiestasia	5 (3%)	Vesicles	1 (1%)
Hyperesthesia	3 (2%)	-	-

In an open-label trial, subjects who had cumulative treatment of melasma with the triple combination 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 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.

Post -marketing experience:

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a casual relationship to drug exposure.The following adverse

reactions have been identified during post approval use of TRILUMA®:

- Eye disorder (frequency not known): blurred vision (see section 4.4)

- Skin disorder (Frequency not known): Skin pain

DOSAGE AND ADMINISTRATION

TRILUMA® 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. Therapy should be discontinued when control is achieved. 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.

Overdose

A limited number of overdose cases has been reported since the launch of TRILUMA® cream. The majority of the adverse events were skin disorders which are compatible with the known safety profile of TRILUMA®. No particular safety concern has been identified in the cumulative review of overdose cases.

PATIENT COUNSELING INFORMATION

- Avoid exposure to sunlight, sunlamp, or ultraviolet light. Patients who are consistently exposed to sunlight or skin irritants either through their work environment or habits should exercise particular caution. Use sunscreen and protective covering (such as the use of a hat) over the treated areas. 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 TRILUMA® Cream.

Because of the drying effect of this medication, a moisturizer may be applied to the face in the morning after washing.

- Application of TRILUMA® 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.

Mfg. Lic. No. 361

FOR EXTERNAL USE ONLY

HOW SUPPLIED

TRILUMA® Cream is supplied in 15g laminated tubes.

Storage: Keep away from direct sunlight.

Store below 25°C. Do not freeze.

Keep the tube tightly closed after use.

Keep out of reach of children.

GALDERMA

Marketed by:
Galderma India Private Limited
8th floor, D Wing, Unit 801 & 802,
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