DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Francois Fournier, President and CEO
Galderma Laboratories
14501 North Freeway
Fort Worth, TX 76177

RE: NDA 21-112
Tri-Luma Cream (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%)
MACMIS #17768

WARNING LETTER

Dear Dr. Fournier:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed two professional visual aids (TRI-486 and TRI-487) for Tri-Luma® Cream (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) (Tri-Luma) submitted by Galderma Laboratories (Galderma) under cover of Form FDA 2253. Your visual aids recommend or suggest uses for Tri-Luma that have not been approved by FDA, and thus create new "intended uses" for the drug for which the product lacks adequate directions, broaden the indication for Tri-Luma, and omit and minimize important risk information for the drug. The visual aids also contain unsubstantiated claims that significantly overstate the efficacy of Tri-Luma. Thus, these promotional materials misbrand the drug in violation of the Federal Food, Drug and Cosmetic Act (Act), 21 U.S.C. 352(a) & (f)(1); 321(n), and FDA implementing regulations. *See* 21 CFR 201.100, 201.128; *cf*. 21 CFR 202.1(e)(5), (e)(6)(i) & (iv).

Furthermore, your visual aids were disseminated with an unapproved version of the product labeling (unapproved PI) instead of the required FDA-approved product labeling (approved PI), in violation of the Act, 21 U.S.C. 352(a) & (f)(1), and FDA implementing regulations. 21 CFR 201.100(c)(2) & 201.115; *see also* 21 CFR 201.100(c)(1) & (d). This unapproved PI includes several false and misleading claims about the product, including claims that suggest unapproved new uses and overstate the effectiveness of Tri-Luma, and it omits risk information and minimizes the risks of using Tri-Luma.

These violations are extremely concerning from a public health perspective because they suggest that Tri-Luma is useful in a much broader range of patients and conditions than has been demonstrated by substantial evidence or substantial clinical experience, and that it is safer and more effective than has been demonstrated by substantial evidence or substantial clinical experience.

Background

Tri-Luma was approved on January 18, 2002 for "the short-term treatment of moderate to severe melasma [hyperpigmentation] of the face, in the presence of measures for sun avoidance, including the use of sunscreens." The INDICATIONS AND USAGE section of the FDA-approved product label (PI) also includes the following important statements related to the use of the drug:

> 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*).

The CLINICAL STUDIES section states (in relevant part):

> 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%).

The WARNINGS section of the PI states:

> 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.

The PRECAUTIONS section states (in relevant part):

> ***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….
>
> ***Drug Interaction:*** 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….
>
> ***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 …. 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.
>
> ….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.

….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….

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.

Promotion of Unapproved Uses/Broadening of Indication

Your visual aids misleadingly suggest that Tri-Luma is approved in a broader range of conditions and patients than is reflected in the drug's FDA-approved PI. For example, the visual aid TRI-486 contains numerous claims related to the combined use of Tri-Luma Cream with glycolic acid peels, including the following claims and presentations:

- "Tri-Luma Cream May enhance results with glycolic acid peels"
- "In a pilot study, Tri-Luma® Cream in sequence with glycolic acid peels showed promising results and was well tolerated (N=20)"
- "At week 12, 65% of patients (~12 of 18) were IGA [Investigators Global Assessment] clear to almost clear compared with baseline (P< .001) (95% CI: 40.78%, 84.61%)"
- "Greater than or equal to 90% of patients showed improvement compared with baseline at weeks 6 and 12 by both investigator and patient assessments"
- Before and after images that depict results at week 12 in an individual with skin type V ("Patient #017") identified as being treated with Tri-Luma used sequentially with glycolic acid peels. In these images, the skin in the "Baseline" photo displays and is captioned as "Moderate/Severe" melasma. The "Week 12" photo, which represents the same patient after 12 weeks of combination therapy, displays the patient's skin as being improved to "Clear/Mild."

These claims and presentations misleadingly suggest that Tri-Luma is safe and effective for use in combination with glycolic acid peels. However, Tri-Luma is not approved for use with other agents and treatment methods. The approved PI does not include any information on the safety and efficacy of Tri-Luma when used in combination with glycolic acid peels or any other dermal products. On the contrary, the Precautions Section (Drug Interactions) of the approved PI clearly states that Tri-Luma should **not** be used in conjunction with other keratolytic drugs (such as glycolic acid). Furthermore, the before and after images depict a subject with skin type V; however, the approved PI indicates that the safety and efficacy of the drug in skin types V and VI have not been studied and that excessive bleaching resulting in undesirable cosmetic effect in patients with darker skin cannot be excluded.

Promotion of this unapproved combination use is concerning from a safety perspective. The concomitant use of Tri-Luma with the keratolytic drug glycolic acid, a known irritant, could increase the skin's permeability such that other topical agents, including those found in Tri-Luma Cream, may be more readily absorbed into the bloodstream. Systemic absorption of topical corticosteroids (such as the fluocinolone acetonide ingredient in Tri-Luma Cream) can produce HPA axis suppression. Other potential consequences of this unapproved use include increasing the skin's sensitivity to UV light, thereby increasing the risk of sun damage and subsequent worsening of melasma, and increasing post-inflammatory hyperpigmentation in patients with darker skin types, who are at higher risk of other dyspigmentation disorders that may be exacerbated by excessive irritation. Therefore, these claims and presentations in the visual aid contradict Tri-Luma's approved PI, undermine the safe use of the drug, and cause the approved PI to lack adequate directions for the use recommended in the promotional materials.

In addition, the reference provided in the visual aid to support the use of Tri-Luma in sequence with glycolic acid peels (Rendon et. al.)[1] describes a non-randomized, open-label, pilot study in which 20 patients were treated for 12 weeks with six rounds of alternating therapy with glycolic acid peels and Tri-Luma Cream. This design is not appropriate for an assessment of efficacy and this single pilot study does not constitute substantial evidence or substantial clinical experience to support efficacy and safety claims for the combined use of glycolic acid peels and Tri-Luma for the treatment of melasma.

Visual aid TRI-486 also suggests that Tri-Luma is safe and effective for long term use. Specifically, the visual aid contains the following presentation:

> "52 weeks of proven safety results
> Safe
> - 92 subjects used Tri-Luma® Cream qhs continuously for 1 year with no significant increase in treatment-related adverse events
> - Fluocinolone acetonide is a low-potency class-6 steroid that may reduce retinoid-induced irritation and may improve lightening effects"[2]

[1] Rendon M, Cardona LM, Bussear EW, et al. Successful treatment of moderate to severe melasma with triple combination cream and glycolic acid peels. *Cutis*. 2008 Nov;82(5):372-8.
[2] Torok H, Taylor S, Baumann L, et al. A large 12-month extension study of an 8-week trial to evaluate the safety and efficacy of triple combination (TC) cream in melasma patients previously treated with TC cream or one of its dyads. J Drugs Dermatol. 2005;4:592-597.

This presentation misleadingly suggests that Tri-Luma can be safely used to treat melasma for up to a year and that it may lighten hyperpigmentation during such use. However, Tri-Luma is only approved for the **short term** treatment of moderate-to-severe melasma; as stated in the Indication & Usage section of its approved PI, Tri-Luma is "NOT indicated for the maintenance treatment of melasma." Furthermore, the approved PI indicates that adverse events were monitored in controlled-clinical trials during an 8 week treatment period and for 6 months in an open-label long-term safety study. The PI does not provide information regarding the safety profile of Tri-Luma Cream for 52 weeks of use.

In addition, both visual aid TRI-486 and visual aid TRI-487 misleadingly suggest that Tri-Luma can be used in a much broader range of patients and conditions than the drug has been approved to treat. For example, visual aid TRI-486 includes the prominent claim "THE ONLY FDA-APPROVED TRIPLE-COMBINATION TOPICAL FOR MELASMA" (emphasis original), while visual aid TRI-487 states: "AMONG TOPICAL MEDICATIONS…nothing works better for ladies with dark spots" (emphasis original). These claims misleadingly suggest that Tri-Luma is approved for the treatment of any "dark spots," and any type of melasma, regardless of severity or location, when this is not the case. The term "dark spots" is completely inadequate to convey Tri-Luma's approved indication and suggests that Tri-Luma is useful for any dark spot on any part of the body, including ephiledes (freckles), lentigenes, moles, and actinically induced seborrheic keratosis.

The presentations in the visual aids also omit material facts about the limitations to Tri-Luma's indicated use in melasma, including the fact that Tri-Luma is not indicated for the maintenance treatment of melasma, that the safety and effectiveness of Tri-Luma has not been demonstrated in patients with skin types V and VI (in fact, one patient displayed in visual aid TRI-486 is identified as having skin type V), and that Tri-Luma is not approved for the treatment of hyperpigmentation conditions other than melasma of the face. We note that you include the statement "Safety and effectiveness have not been established in …individuals with darker skin" in a paragraph on the bottom of the reverse side of visual aid TRI-486 from the display of the patient with skin type V; however, this statement does not mitigate the misleading impression conveyed by the visual aid that Tri-Luma is effective in treating patients with skin type V. As a result of the visual aids' failure to adequately communicate material information about the limitations to the drug's approved indication, the pieces suggest that the drug can be used in a much broader range of patients than indicated. This is particularly concerning given that the drug poses special risks to these patient populations (e.g. excessive bleaching resulting in undesirable cosmetic effect and greater incidence of exogenous ochronosis in patients with darker skin (e.g., skin types V and VI)).

Omission/Minimization of Risk

Promotional materials are misleading if they omit material facts about the consequences that may result from the use of the drug as recommended or suggested by the materials. The visual aids make prominent claims of effectiveness for Tri-Luma Cream but omit material facts about the risks associated with Tri-Luma. Moreover, these materials downplay what little risk information is presented about the product.

For example, the visual aids include the statement: "HPA axis (adrenal function) suppression may result from exposure to the topical corticosteroid, fluocinolone acetonide." However,

they omit material information about the consequences of HPA axis suppression and information about discontinuation of treatment in the event of such an adverse reaction. As stated in the Precautions section of Tri-Luma's PI, "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." The omission of this information regarding the consequences of HPA axis suppression and the need to discontinue treatment is particularly concerning in light of the visual aid's promotion of the use of Tri-Luma Cream in conjunction with glycolic acid, as this unapproved combination could increase the systemic absorption of the steroid component of this drug.

Furthermore, the visual aids include the statement that: "Tri-Luma® Cream contains sulfites. People allergic to sulfites should not use Tri-Luma® Cream." However, they omit material information about this Warning from the approved PI. Specifically, the approved PI states that "sodium metabisulfite….may cause allergic type reactions **including anaphylactic symptoms and life-threatening asthmatic episodes** in susceptible people" (emphasis added).

The visual aids also omit material information relating to potential consequences that may result from the use of the drug in pregnant or nursing women. The visual aids fail to reveal **any** of the important Precautions information from the approved PI (see Background section above) regarding the potential teratogenic effects of the drug or regarding the caution for nursing mothers. This omission is particularly concerning given that hyperpigmentation is a condition frequently caused by pregnancy and many women with melasma will thus be pregnant or nursing mothers. We note that the visual aids state that "Safety and efficacy have not been established in pregnant or nursing women." However, this statement in no way suffices to disclose the risks associated with the use of the drug in pregnant and nursing women (including potential effects associated with the known teratogen, tretinoin, such as embryo-fetal death, altered fetal growth, congenital malformations, and potential neurologic deficits); the piece entirely omits this important risk information.

Overstatement of Efficacy

The visual aids contain numerous claims and presentations that overstate the efficacy of Tri-Luma Cream. For example, visual aid TRI-487 depicts a ladybug walking through a dollop of Tri-Luma Cream. Before the ladybug reaches the Tri-Luma Cream, it has approximately 7 black spots on its back. After walking through the cream, the ladybug has only 1 black spot. This visual portrayal of a complete disappearance of 6 out of 7 black spots equates to an efficacy rate of 85% for the drug. This image is accompanied by the claim "nothing works better for ladies with dark spots." This presentation misleadingly overstates the efficacy of Tri-Luma by implying that patients can achieve results like those depicted in the graphic (i.e., the complete disappearance of the large majority of melasma spots) upon treatment with Tri-Luma Cream. We are not aware of substantial evidence or substantial clinical experience to support the implication created by this presentation. The Clinical Studies section of the approved PI reports that the proportion of patients who had an investigators' assessment of treatment success with Tri-Luma Cream, defined as melasma severity score of zero (i.e.,

melasma lesions cleared of hyperpigmentation) at the end of the eight-week treatment period, was 38% and 13% in the two clinical trials supporting approval of this product. Additionally, as described in the approved PI, few patients who were entered into an open-label extension period maintained complete clearing of melasma (approximately 1 to 2%). These data, which reflect a low rate of treatment success among users of the product, are not supportive of the implication that the drug will completely clear most melasma spots. If you have data to support this claim, please submit the data to FDA.

Furthermore, visual aid TRI-486 includes the following presentation:

"Fast

- 66% of patients achieved an assessment of moderate to marked improvement, almost clear, or clear at week 4"

The visual aid references the Grimes et. al.[3] article to support this claim. This article describes an open-label, uncontrolled clinical study in which patients with skin types I through VI were treated for 8 weeks with Tri-Luma Cream. Results from a single open-label clinical trial with no control group do not constitute substantial evidence or substantial clinical experience to support this, or any other, efficacy claim.

Finally, visual aid TRI-486 includes before and after photographs of "Patient #461" along with the claim "ENLIGHTENING experience." These photographs start with a depiction of the patient with "Moderate/Severe" melasma at baseline and then depict the patient with "Clear/Mild" skin in the "Week 8" photo. The totality of this presentation overstates the efficacy of Tri-Luma by suggesting that the results depicted in the photographs are typical, i.e., patients with moderate to severe melasma will improve to clear/mild after 8 weeks of treatment with Tri-Luma Cream. While this may be accurate for the patients who achieved "success" in the pivotal trials (38% of patients in study 1 and 13% in study 2), the majority of the patients in these studies **did not** achieve such results. Furthermore, as stated in the Indication and Usage section of the PI, "melasma usually recurs upon discontinuation of TRI-LUMA Cream."

Use of Unapproved Product Labeling

In order to be exempt from the Act's adequate direction for use requirement and avoid misbranding the drug under 21 U.S.C. 352(f)(1), the product labeling distributed by the manufacturer for prescription drug products must be the labeling authorized by the product's approved new drug application (NDA) and this labeling must contain adequate information for the drug's safe use. 21 CFR 201.100(c) & (d); 201.115. The version of the Tri-Luma product labeling that Galderma has been distributing is **not** the FDA-approved labeling authorized under Tri-Luma's NDA, but rather is an unapproved PI. Through consultation with the CDER Office of Compliance, we have been informed that this unapproved PI is not only being distributed with promotional materials but also with the drug product itself. Specifically, during an inspection of Tri-Luma's manufacturing facility in September, 2008, the FDA noted that this unapproved PI is being shipped with the drug. The FDA is **extremely** concerned about your dissemination of an unapproved PI for Tri-Luma Cream. There are numerous alarming differences between the FDA-approved PI (dated January 18, 2002) and the unapproved PI that is being disseminated by Galderma, as summarized

[3] Grimes P, Kelly AP, Torok H, Willis I. Community-based trial of a triple-combination agent for the treatment of facial melasma. Cutis. 2006;77:177-184.

below:

- The unapproved PI suggests that Tri-Luma Cream is indicated for long term, repeated, or maintenance treatment of melasma. Specifically, the unapproved PI states in the Indications and Usage section that Tri-Luma is indicated for "intermittent" treatment "with cumulative treatment time of 180 days" and that "patients can be re-treated with TRI-LUMA® until melasma is resolved." However, according to the approved PI, Tri-Luma is indicated for short-term use (up to 8 weeks) only, and is "NOT indicated for the maintenance treatment of melasma." The approved PI also indicates that remission periods appear to shorten between progressive courses of treatment.

- The unapproved PI suggests that Tri-Luma Cream is safe for long term (52 week) use. Specifically, the unapproved PI presents data from uncontrolled, long term (52 week) safety studies that have not been reviewed or substantiated by the FDA. In addition, the unapproved PI claims that the long-term safety study was performed to demonstrate the local and systemic safety of Tri-Luma; however, no measures of "systemic" effects are reported in this unapproved PI. According to the approved PI, adverse events were monitored in controlled-clinical trials during an 8 week treatment period and for 6 months in an open-label long-term safety. Furthermore, long-term use may result in significant worsening of adverse events, particularly those associated with long-term use of fluorinated steroids, such as skin atrophy, steroid induced rosacea, telangiectasia and systemic absorption leading to adrenal suppression.

- The unapproved PI seriously minimizes the risks of Tri-Luma by omitting some of the documented side effects of Tri-Luma and by downplaying the severity and frequency of risks reflected in the approved PI. For example, the unapproved PI includes language in the WARNINGS section that downplays the prevalence of sulfite sensitivity in the general population and that does not appear in the approved PI. It also reports a higher number of healthy babies born from women who inadvertently used Tri-Luma during pregnancy than the approved PI, and omits the risks of dryness and pruritis at the site of application contained in parts of the approved PI's ADVERSE REACTIONS section. In addition, the unapproved PI contains assurances of safety about long-term use, stating that there was no significant increase in severity or incidence of the adverse events from long term use of Tri-Luma compared with events reported during the 8-week controlled clinical studies, and that the rate of erythema, desquamation, and burning at the site of application was actually "markedly lower" upon long-term use compared to the short-term study. As noted above, the drug is only approved for short-term use, and long-term use may result in significant worsening of adverse events.

- The unapproved label overstates the efficacy of Tri-Luma Cream by including unsubstantiated clinical study results that make Tri-Luma appear more efficacious than has been demonstrated by substantial evidence. For example, the unapproved PI reports a higher percentage of patients achieving treatment success at 8 weeks and after longer courses of therapy than the approved PI and, unlike the approved PI, it fails to mention that remission periods shorten upon repeated use of Tri-Luma.

By overstating the safety of Tri-Luma and minimizing the risks associated with the use of the product, you are suggesting that Tri-Luma is safer than demonstrated. Furthermore, you suggest that Tri-Luma is useful in a broader range of conditions and is more effective than has been demonstrated by substantial evidence. Thus, Galderma's dissemination of this unapproved PI raises significant public health concerns.

Conclusion and Requested Action

For the reasons discussed above, your promotional pieces and the unapproved labeling disseminated with these pieces misbrand Tri-Luma in violation of the Federal Food, Drug and Cosmetic Act (the Act), 21 U.S.C. 352(a), (f)(1), and 321(n), and FDA implementing regulations. 21 CFR 201.100, 201.115 & 201.128; *cf*. 21 CFR 202.1(e)(5), (e)(6)(i) & (iv).

DDMAC requests that Galderma immediately cease the dissemination of violative promotional materials for Tri-Luma Cream such as those described above. Furthermore, Galderma should immediately cease the dissemination of the unapproved product labeling. Please submit a written response to this letter on or before August 31, 2009, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for Tri-Luma Cream as of the date of this letter, identifying which of these materials contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Because the violations described above are serious and repeated, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audiences that received the violative materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, or facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS 17768 in addition to the NDA number. We remind you that only written communications are considered official. If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Tri-Luma Cream comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

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

/s/

THOMAS W ABRAMS
08/18/2009