

COMMENTARY

Using Cheek Implants to Improve Midface Aging

With experience, each implant takes 10-15 minutes from incision to suture

BY JOSPEH NIAMTU, III, D.M.D.

Over the past century, one of the main problems with cosmetic surgery has been that patients were made to look tighter but not younger. Cosmetic-oriented dermatologists were among the most influential forces leading to the contemporary view that volume restoration is integral to facial rejuvenation. Not only did they develop tumescent anesthesia, but they also pioneered many of the techniques of fat transfer and injectable fillers. Collectively, this has led to a more refined sense of how to make patients look younger.

The midface is one of the most overlooked areas in cosmetic surgery. It is common for patients to have comprehensive facial rejuvenation, including brow lifts and blepharoplasty procedures, as well as facelifts and submental rejuvenation. Unfortunately, many practitioners will completely neglect the midfacial region.

FACIAL AGING

Young people look young largely because they lack actinic damage and the resulting elastosis, and because they have adequate and well positioned fat. As a society, we are so used to fat being evil that we sometimes forget how important it is in the healthy person, especially with respect to aesthetics. Almost all youthful facial tissues have some fat, including the temples, cheeks, chin, lips, and the face in general. The youthful face is oval and has well defined malar fat pads that sit high face. As we age, the malar fat pads descend because of gravity and tissue laxity. What once



FIGURE 1



FIGURE 2

were the cheeks have become the jowls, and the face takes on a square appearance. Besides the loss of youthful form, the lack of malar and submalar volume produces a gaunt appearance and impacts the surrounding structures such as the lower eyelids, nasolabial folds, and cheeks. Older people look hollow, and younger patients look full. It is amazing that, in some patients, simply augmenting the midface will make huge changes as a sole rejuvenative procedure. When coupled with other cosmetic procedures, the results can be exponential.

The midface is one of the most overlooked areas in cosmetic surgery ...

My practice is limited to cosmetic facial surgery, and I perform at least two facelifts a week. I would estimate that more than 50 percent of these patients have concomitant facial implants with their surgery. The percentage would be higher but many patients opt out due to under appreciation or lack of understanding of the beneficial effects of midface implants. Educating doctors to educate their patients is the challenge. If you study your patients closely, you will see that most patients older than 40 years have lost the submalar fullness they had a decade previously. Midface deficiency is one of those things that you fail to notice if you do not look for it (or know how to look for it), but once you figure it out, most adult patients who come through your office are midface deficient.

A plethora of techniques is available to augment the midface, including, but not limited to, injectable fillers, fat transfer, lifting procedures, and facial implants. Each technique has advantages and drawbacks, but if one closely examines the options, midface implants shine above all others.

Fillers and fat are resorbed and must be reinjected, and lifting procedures are subject to further ptosis. Midface implants sit on the bony skeleton and stay in place for ever. In the event of significant future aging, they can easily be changed for a different size or configuration.

Contemporary midface implants are made of surgical grade silicone rubber and are anatomically designed, meaning that they come in a vast array of sizes and configurations to precisely augment specific facial deficiencies. They are easy to place and are reversible, meaning that they can be easily removed or replaced if the patient is unhappy with the result. For the cosmetic surgeon who has not placed facial implants, the procedure may sound daunting, but in reality it is a simple procedure to learn, a safe surgery to perform, and the learning curve is acceptable. Taking a basic facial implant course and observing a few surgeries is usually adequate for

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the average doc to get started.

The basis of treating patients with facial implants is first to understand the process of midfacial aging (which most cosmetic dermatologists already have expertise in) and to understand which implant to use in which situation. The latter can be a confusing process as there are scores of implants on the market. I personally place several hundred facial implants a year and have streamlined the process in my practice to three midface implants that satisfy 99 percent of the augmentation situations.

submalar region. Most patients look younger (and better) when they smile for the fact that they are filling the submalar region. If you hold their cheek up with your finger and tell them to relax, the cheek falls back to the jowl and illustrates to the patient what a submalar implant would do. Figure 1A shows a submalar implant in approximate position. The bulk of the implant fills the submalar region with a tapering tail over the zygomatic area. Note that there is very little fill over the actual cheekbone (malar) area. Ninety percent of the midfacial implants I place are of the submalar configuration.

In addition to submalar hypoplasia, some patients also exhibit actual malar



FIGURE 3

IMPLANT SELECTION

My cosmetic surgery practice is about 97 percent female, and by and large the most common area of midface hypoplasia and facial aging is the submalar region. Many people think about "high cheek bones" when they discuss midface implants. Although this is an option, that is not what the average patient needs. The submalar region stretches from under the anterior cheek bone to the level of the nostrils. This is where the malar fat pad changes shape and position and leaves a facial hollow. Many patients with submalar hypoplasia actually have adequate cheek bone volume and basically need the submalar hollow area plumped. To illustrate this to a patient, hand them a mirror and ask them to smile. This elevates the ptotic tissues and fills the

Patients who require both submalar and malar fill benefit from the Combined Submalar Implant. The configuration of the implant has bulk in the anterior and the lateral cheek for this purpose.



FIGURE 4



FIGURE 5



FIGURE 6

deficiency where they could benefit from both submalar and malar augmentation. This is generally a smaller percentage of patients, but is an obvious finding if the surgeon pays close attention. Patients who require both submalar and malar fill benefit from the Combined Submalar Implant. The configuration of the implant has bulk in the anterior and the lateral cheek for this purpose. Figure 1B shows an example of the Combined Submalar Implant and its approximate position.

Finally, some patients actually have very adequate submalar anatomy but only require lateral malar fill. These patients are the ones who need or desire "high cheekbones." The malar shell implant is designed specifically for this purpose. This implant is placed higher and more laterally and only augments the lateral cheek. Figure 1C shows a malar shell implant and its approximate position. Although many other implant configurations exist, these three are the work horses of my practice.

SURGICAL IMPLANT PLACEMENT

The surgeon must be familiar with the midface anatomy, which is relatively simple compared with other areas in the face. The implants are always placed in the subperiosteal plane. The only significant anatomic structure in this area is the infraorbital nerve, which exits at the foramen about 5-8 mm inferior to the inferior orbital rim in the papillary midline. In reality, the dissection does not need to encroach on the nerve as all the implants are designed to be placed inferior or lateral to that area. Occasionally, the nerve is visualized during dissection and is easily protected. The surgical procedure is as follows.

I inject 5 cc of 2% lidocaine with 1:100,000 epinephrine in the subperiosteal plane across the submalar and malar regions. This is done percutaneously through the cheek. I inject another 2-3 cc of the same local anes-

thetic intraorally in the gingival sulcus above the canine tooth.

Next, I make a 10-15 mm incision just below the sulcus above the canine tooth through mucosa, muscle and periosteum. There are no significant anatomic structures in this area and the incision can be made directly to bone. At this point, I use a periosteal elevator to raise the periosteum off of

the anterior maxilla to a level beneath the infraorbital nerve. The dissection is then directed obliquely to tunnel out over the lateral malar area and slightly over the zygomatic arch, depending on the implant used (Figure 2A). The submalar implant requires the smallest dissection, and the combined submalar and malar shell implants require a larger pocket. The

dissection pocket is made to be only slightly larger than the actual implant to prevent shifting. Once the subperiosteal pocket is made, an implant size can be tried in to choose the proper size. This is more common for the novice surgeon; choosing the correct size

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Figure 3: A 47-year-old female before and after mini facelift, blepharoplasty and placement of medium submalar implants.

Figure 4: A 40-year-old female before and after placement of malar shell implants.

Figure 5: A 64-year-old female before and after facelift, blepharoplasty, laser resurfacing and placement of combined submalar implants.

Figure 6: A 46-year-old female before and after laser resurfacing and placement of medium submalar implants.

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comes with experience. The pocket is then irrigated with an antibiotic solution and the implant is placed in the pocket (figure 2B). It is imperative to place the implant passively so the flexible margins do not get folded over. The implants are designed to fit in the specific area and usually “self

seat” in the proper position. If the implant is too mobile (usually from over dissecting the pocket) they can be secured with a suture or a single fixation screw. After the implant is placed, the upper lip is pulled and the cheeks are compressed to see if the implant squeezes out of the pocket. If it does, the pocket is enlarged so the implant is not expressed when the surround-

ing tissues are mobilized. The incision is then closed in a single layer with 4-0 chromic suture. With experience, each cheek implant takes 10-15 minutes from incision to suture.

Postoperatively, the patients are asked not to excessively animate for 48 hours and to stay on a soft diet. This region is prone to significant postoperative swelling in some patients; ice and

tapering steroids can be of benefit. The patient is also warned that their smile and pucker will be somewhat reduced for about 10 days while the muscles heal. The average recovery period is about one week. Temporary paresthesia is not uncommon and returns over several weeks. Any implant is subject to hematoma or infection. Meticulous hemostasis and antibiotic coverage with a cephalosporin for one week is recommended. Midfacial augmentations with various implants are shown in figures 3 through 6.

COMPLICATIONS

Like any implant, the possibility of over correction or under correction is a possibility. Initially, some patients may feel that the augmentation is too dramatic, but they should wait a full three months before removing or changing the implants. Placing a larger or smaller implant is a relatively easy procedure, as the original implant becomes encapsulated and the revision surgery is less invasive than the primary implant placement.

Hematoma from bleeding is possible but rare; adequate hemostasis will prevent excessive bleeding. Finally, infection is a possibility, but fortunately quite rare. Small infections may be treated by antibiotics and antibiotic irrigation. More significant infections require explanation.

CONCLUSION

Midface implants are an effective way to improve midfacial aging in any patient. The variety of available shapes and sizes along with the ability to reverse the procedure make cheek augmentation with implants an attractive and effective procedure for any surgeon that treats the aging face.

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TRI-LUMA[®] Cream
(fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%)
Brief Summary For External Use Only Not for Ophthalmic Use **Rx only**

INDICATIONS AND USAGE:

TRI-LUMA Cream is indicated for the short-term intermittent 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, was proven safe for the intermittent treatment of melasma, with cumulative treatment time of at least 180 days. Because melasma usually recurs upon discontinuation of TRI-LUMA Cream, patients can be retreated with TRI-LUMA until melasma is resolved. 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. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic 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 hypospemia 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 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, 15 women became pregnant during treatment with TRI-LUMA Cream. Of these pregnancies, 6 resulted in healthy babies, 6 outcomes still unknown, 2 were reported as miscarriages, and 1 case was lost to follow-up.

- 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. In the long-term clinical study, from a total of 314 patients treated with TRI-LUMA Cream for at least 180 cumulative days, there were 202 (64%) patients who experienced at least one treatment-related adverse event. No significant increase in severity or incidence of the adverse events was observed from long term use of TRI-LUMA Cream compared with events reported during the 8-week controlled clinical studies. The most frequently reported adverse events that were observed from the controlled clinical trials and the long term safety were erythema, desquamation, and burning, and at the site of application. The number and percentages of these events were markedly lower in the long-term study than in the controlled clinical studies. The great 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 and the long-term study are summarized (in decreasing order of frequency).

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.

Summary of Most Common Treatment-related Adverse Events (TRAE) ^a Study 29		
	Number (%) of Patients	
	Treatment Group	
	TRI-LUMA	
Preferred Term	All Patients (N=569)	Patients with at least 180 Cumulative Days of TRI-LUMA Treatment (N=314)
Total number of TRAE ^a	326 (57.29)	202 (64.33)
Application site erythema	166 (29.17)	105 (33.44)
Application site desquamation	145 (25.48)	91 (28.98)
Application site dryness	46 (8.08)	27 (8.60)
Application site burning	38 (6.68)	25 (7.96)
Application site inflammation	31 (5.45)	24 (7.64)
Application site reaction nos	31 (5.45)	17 (5.41)
Application site rash	30 (5.27)	18 (5.73)
Application site pruritus	24 (4.22)	18 (5.73)
Application site pigmentation changes	23 (4.04)	18 (5.73)

^a Defined as “probably” or “possibly” related to study medication

Data source: Section 14.3, Tables 8.1.1, 8.1.2, and 8.1.3

The severity, incidence and type of adverse events experienced from 6 months cumulative use were not significantly different from the events reported for all patients.

The incidence of application site pigmentation changes that occurred in both the controlled and long-term safety studies included 11 occurrences of hypopigmentation and 18 occurrences of hyperpigmentation in 27 patients.

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.

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Manufactured by:
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Reference: 1. Taylor SC, Torok H, Jones T, et al. Efficacy and safety of a new triple-combination agent for the treatment of facial melasma. *Cuts*. 2003;72:67-72.

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