AETNA BETTER HEALTH®

Clinical Policy Bulletin:
Hypertrophic Scars and Keloids

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Policy

Aetna considers silicone products (e.g., sheeting, gels, rigid shells) experimental and investigational for the treatment of hypertrophic scars or keloids because there is inadequate evidence from prospective randomized clinical trials in the peer-reviewed published medical literature of the effectiveness of silicone products in alleviating symptoms of hypertrophic scars and keloids.

Aetna considers intralesional 5-fluorouracil, cryotherapy or corticosteroids medically necessary for treatment of keloids where medical necessity criteria for keloid removal are met. See CPB 0031 - Cosmetic Surgery, for medically necessary indications for keloid removal.

Aetna considers the following interventions experimental and investigational for the treatment of hypertrophic scars or keloids because of insufficient evidence in the peer-reviewed literature:

- Adipose-derived stem cell
- Basic fibroblast growth factor
- Dermal substitutes
- Etanercept (see CPB 0315 - Enbrel (Etanercept))
- Hyaluronidase
- Imiquimod cream
- Intense pulsed light
- Interferon alpha (see CPB 0404 - Interferons)
- Intralesional bleomycin
- Intralesional botulinum toxin type A injection
- Intralesional mitomycin
- Laser-assisted administration of corticosteroid
- Micro-needling (with Dermapen disposable tips or other devices/tools)
- Non-ablative fractional laser
- Radiofrequency treatment
- Topical calcipotriol
- Topical retinoids
Background

Keloids and hypertrophic scars develop as a result of a proliferation of dermal tissue following skin injury, and are common (keloids develop in 5 % to 15 % of wounds).

Topical silicone gel sheeting is a soft, slightly adherent, semi-occlusive covering which is fabricated from medical grade silicone polymers. Topical silicone gel sheeting is used to reduce the volume and increase the elasticity of hypertrophic and keloid scars, as a dressing for both donor and recipient sites in skin grafting, and as a treatment of burn wounds.

Examples of brands of silicone gel sheeting available over-the-counter include: Sil-K, Cica-Care, ReJuveness, DuraSil and Silastic Gel Sheeting. Epi-Derm brand of silicone gel sheeting is currently available only by prescription, although the manufacturer of Epi-Derm is pursing Food and Drug Administration (FDA) clearance for over-the-counter marketing.

Silicone has also been applied as a gel or as rigid custom-molded shell to scars, burns, and skin grafts. Although several case series have reported improvements in the appearance (scar size, erythema, elasticity) and symptoms (pruritus, burning pain) from the application of silicone sheets, gels, or shells to hypertrophic scars and keloids, these promising results have not been confirmed by subsequent prospective randomized controlled trials (RCTs). Prospective RCTs of silicone products in treatment of hypertrophic scars and keloids are limited, and the outcomes of these studies have not consistently demonstrated a clinically significant benefit of silicone products in treating hypertrophic scars or keloids over standard wound dressings.

In an open-label pilot study, Lacarrubba et al (2008) assessed the effectiveness and tolerability of a silicone gel in the treatment of hypertrophic scars. A topical self-drying silicone gel containing polysiloxane and silicone dioxide was applied twice-daily in 8 hypertrophic scars. After 6 months, all lesions showed evident clinical and/or ultrasound improvement, with a mean scar thickness reduction of 37 % (range of 20 % to 54 %). The authors stated that although controlled trials in larger series of patients are necessary, these findings suggested that the self-drying silicone gel may represent a safe and effective treatment for hypertrophic scars.

In a prospective, single-blind, RCT, Wittenberg et al (1999) evaluated the effectiveness of the 585-nm flashlamp-pumped pulsed-dye laser and silicone gel sheeting in the treatment of hypertrophic scars in lighter-skinned and darker-skinned patients: 19 completed the laser treatments and 18 completed the silicone gel sheeting treatments. Clinical measurements included hypertrophic scar blood
flow, elasticity, and volume. Patients' subjective complaints of pruritus, pain, and burning were also monitored. Histological assessment of fibrosis, number of telangiectasias, and number of mast cells was performed. Statistically significant improvements in clinical measurements and patients' subjective complaints determined treatment success. These investigators concluded that clinical results demonstrate that the improvements in scar sections treated with silicone gel sheeting and pulsed-dye laser were no different than those in control sections.

In a discussion of treatment of keloids, Quintal (2002) concluded that “[m]ore in-depth, controlled research is needed to prove or disclaim the therapeutic effect of silicone.” A recently published systematic review of the literature on treatment of keloid scars concluded that “[t]he effectiveness of silicone gel sheeting and other occlusive dressings in treating keloidal scars cannot be confirmed by existing studies” (Shaffer et al, 2002).

The FDA (2004) classified silicone sheeting intended for use in the management of closed hyper-proliferative (hypertrophic and keloid) scars into class I (general controls). As a class I device, the device will be exempt from premarket notification requirements.

In a prospective, randomized, placebo-controlled, clinical trial that examined the use of silicone gel in preventing hypertrophic scar development in median sternotomy wound, Chan et al (2005) concluded that the effect of silicone gel in the prevention of hypertrophic scar development in sternotomy wounds is promising. In a recent review on keloid pathogenesis and treatment, Al-Attar and colleagues (2006) noted that established treatment strategies for keloids include surgery, steroid, and radiation (silicone was not listed as an established treatment for keloids).

A structured assessment of the evidence of silicone gel sheeting for preventing and treating hypertrophic scars and keloids prepared for the Cochrane Collaboration reached the following conclusions (O'Brien and Pandit, 2006): “Trials evaluating silicon gel sheeting as a treatment for hypertrophic and keloid scarring are of poor quality and highly susceptible to bias. There is weak evidence of a benefit of silicon gel sheeting as a prevention for abnormal scarring in high risk individuals but the poor quality of research means a great deal of uncertainty prevails.”

Stavrou et al (2010) stated that hypertrophic and keloid scars still are among the banes of plastic surgery. In the treatment arsenal at the disposal of the plastic surgeon, topical silicone therapy usually is considered the first line of treatment or as an adjuvant to other treatment methods. Yet, knowledge concerning its mechanisms of action, clinical efficacy, and possible adverse effects is rather obscure and sometimes conflicting. The author summarized the existing literature regarding the silicone elastomer's mechanism of action on scars, the clinical trials regarding its efficacy, a description of some controversial points and contradicting evidence, and possible adverse effects of this treatment method. Topical silicone therapy probably will continue to be the preferred first-line treatment for hypertrophic scars due to its availability, price, ease of application, lack of serious adverse effects, and relative efficacy. Hopefully, future RCTs will help to clarify its exact clinical efficacy and appropriate treatment protocols to optimize treatment results.
In a single-center placebo-controlled double-blind trial, Stoffels et al (2010) examined the impact of silicone spray on scar formation. These investigators reported that after 3 months of treatment the Patient Scar Assessment Scale demonstrated that patient satisfaction with the silicone application was significantly higher compared to placebo. However, when treatment was stopped after 3 months, the topical silicone spray did not exhibit any lasting long-term impact on the objective results of scar formation.

In a review on "Prevention and management of keloid scars", Lutgendorf et al (2011) noted that "[a]lthough silicone gel sheeting is a well-accepted treatment modality, the studies to date provide level IV evidence, with a lack of controls and increased susceptibility to bias. A recent Cochrane systematic review on the use of silicone gel sheeting for preventing and treating hypertrophic and keloid scars found that any effects were obscured by the poor quality of research".

Several clinical trials have demonstrated the effectiveness of intralesional 5-fluorouracil in the treatment of keloid scarring (Asilian et al, 2006; Nanda and Reddy, 2004; and Manuskiatti and Fitzpatrick, 2002). Asilian and colleagues (2006) examined the effectiveness of a combination of intralesional steroid, 5-fluorouracil (5-FU), and pulsed-dye laser in the treatment of hypertrophic scars and keloids. A total of 69 patients were randomly assigned to treatment with intralesional triamcinolone acetonide (TA), intralesional TA plus intralesional 5-FU, and TA, 5-FU and pulse-dye laser treatment. The investigators reported that, after 12 weeks, good to excellent improvements were reported by a blinded observer in 15% of subjects treated with TA alone, 40% of subjects treated with TA plus 5-FU, and 70% of subjects treated with all 3 modalities.

Tosa et al (2009) stated that because intralesional injection of TA, a widely used for the treatment of keloid, is painful, many patients discontinue treatment. These researchers evaluated the effects of pre-treatment with topical 60% lidocaine tape on the pain and tolerability of intralesional TA treatment in patients with keloid. The subjects were 42 patients with keloid who had been treated with intralesional injection of TA but had discontinued treatment owing to intolerable pain. All patients were pre-treated with 60% lidocaine tape placed on the keloids for more than 120 mins before intralesional injection of TA. Patients assessed pain with a 100-mm visual analog scale (VAS) with 0 mm for "no pain" and 100 mm for "worst possible pain". Pain was assessed with the VAS immediately after TA injection. Finally, the patients assessed the tolerability of this treatment. The mean VAS score during intralesional TA injection therapy without pre-treatment with lidocaine tape was 82.6 +/- 14.4 mm. In contrast, the mean VAS score during intralesional TA injection therapy in the same patients after pre-treatment with lidocaine tape was 18.9 +/- 11.3 mm, which was significantly lower (p < 0.05), and 30 (71.4%) of the patients tolerated this therapy well. Pre-treatment with 60% lidocaine tape significantly reduces the pain associated with intralesional injection of TA. This approach increases patient comfort and should enable patients to continue the treatment.

Pai and Cummings (2011) examined if surgical excision with or without adjuvant treatment beneficial in reducing the size of the scar in patients with hypertrophic and keloid scarring of the sternotomy wound. More than 15 papers were found using the reported search, of which 9 represented the best evidence to address
this clinical issue. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers were tabulated. One of the studies showed no difference between surgery and adjunctive TA or colchicine. One study showed that incomplete excision resulted in higher recurrence rates. Post-operative radiation was found to be useful in 2 of the studies, although 1 study showed that it was not useful. One RCT showed improvement after laser compared to no treatment; 2 other trials showed no difference between laser, silicone gel, intralesional steroid or 5-FU. One trial showed that peri-operative systemic steroid application gave rise to no improvement but in fact worsened scar formation. The authors concluded that small keloids can be treated radically by surgery with adjuvant therapy (radiation or corticosteroid injections) or by non-surgical therapy (corticosteroid injections, laser and anti-tumour/immunosuppressive agents, such as 5-FU). Large and multiple keloids are difficult to treat radically and are currently only treatable by multi-modal therapies that aim to relieve symptoms.

An UpToDate review on "Keloids" (Goldstein and Goldstein, 2012) states that "[i]ntralesional corticosteroids are first-line therapy for most keloids. A systematic review found that up to 70 percent of patients respond to intralesional corticosteroid injection with flattening of keloids, although the recurrence rate is high in some studies (up to 50 percent at five years)".

Meshkinpour et al (2005) examined the safety and effectiveness of the ThermaCool TC radiofrequency system for treatment of hypertrophic and keloid scars and assessed treatment associated collagen changes. Six subjects with hypertrophic and 4 with keloid scars were treated with the ThermaCool device: 1/3 of the scar received no treatment (control), 1/3 received one treatment and 1/3 received 2 treatments (4-week interval). Scars were graded before and then 12 and 24 weeks after treatment on symptoms, pigmentation, vascularity, pliability, and height. Biopsies were taken from 4 subjects with hypertrophic scars and evaluated with hematoxylin and eosin (H & E) staining, multi-photon microscopy, and pro-collagen I and III immunohistochemistry. No adverse treatment effects occurred. Clinical and H & E evaluation revealed no significant differences between control and treatment sites. Differences in collagen morphology were detected in some subjects. Increased collagen production (type III > type I) was observed, appeared to peak between 6 and 10 weeks post-treatment and had not returned to baseline even after 12 weeks. The authors concluded that use of the thermage radiofrequency device on hypertrophic scars resulted in collagen fibril morphology and production changes. ThermaCool alone did not achieve clinical hypertrophic scar or keloid improvement. They noted that the collagen effects of this device should be studied further to optimize its therapeutic potential for all indications.

Davison et al (2006) ascertained the effectiveness of interferon alpha-2b in keloid management. These investigators prospectively assessed the effects of interferon alpha-2b as post-excisional adjuvant therapy for keloids. A total of 39 keloids in 34 patients were photographed, measured, and surgically excised. The wound bed was injected twice with either interferon alpha-2b (treatment group; n = 13 keloids) or TA (control group; n = 26 keloids) at surgery and 1 week later. The patients were followed-up in the plastic surgery clinic. The trial protocol was terminated at mid-trial surveillance. Among the 13 keloids that were treated with
post-operative intralesional interferon alpha-2b, 7 recurred (54 % recurrence rate).

In contrast, in the 26 keloids that received TA (control group), only 4 recurred (15 % recurrence rate). Recurrence in either group did not correlate with location of the keloid or race. The authors concluded that interferon does not appear to be effective in the clinical management of keloids. This finding is consistent with an earlier controlled trial which also found a lack of effectiveness of intralesional interferon alpha in the treatment of keloids (al-Khawajah, 1996).

Al-Attar et al (2006) reviewed the major concepts of keloid pathogenesis and the treatment options stemming from them. They noted that mechanisms for keloid formation include alterations in growth factors, collagen turnover, tension alignment, and genetic and immunologic contributions. Treatment strategies for keloids include established (e.g., surgery, steroid, radiation) and experimental (e.g., interferon, retinoid) regimens. The authors concluded that combination therapy, using surgical excision followed by intra-dermal steroid or other adjuvant therapy, currently appears to be the most effective and safe current regimen for keloid management.

Sharma and colleagues (2007) compared the effectiveness of liquid nitrogen cryosurgery alone with liquid nitrogen cryosurgery plus intralesional TA combination in the treatment of keloids (n = 21; 60 clinically diagnosed lesions of keloids). The statistical analysis showed synergistic action of cryosurgery and corticosteroids may offer promise in the treatment. Karrer (2007) noted that keloids are a therapeutic challenge for dermatologists. Although multiple therapeutic options are available, a reliably effective approach with few side effects remains elusive. High quality research in evaluating the effectiveness of keloid therapy is also lacking. This is in agreement with the findings of Durani and Bayat (2008) who reported that the level of evidence (LOE) of cryosurgery in the treatment of keloids is 4 (LOE-1 denotes highest quality while LOE-5 denotes lowest quality).

Berman et al (2008) evaluated the tolerability and efficacy of etanercept as compared to TA for the treatment of keloids. A total of 20 subjects were randomly assigned to receive monthly intralesional injections of either 25 mg of etanercept or 20 mg of TA for 2 months. Keloids were evaluated at baseline, week 4, and week 8 by subjects and investigators in a blinded fashion using physical, clinical, and cosmetic parameters. Photographs were taken and adverse events were noted during each evaluation. Etanercept improved 5/12 parameters including significant pruritus reduction, while TA improved 11/12 parameters at week 8, although no statistical difference was observed as compared to baseline. There was no significant difference between the 2 treatment groups. The authors concluded that etanercept was safe, well-tolerated, improved several keloid parameters, and reduced pruritus to a greater degree than TA therapy. However, they noted that further studies are needed before it can be recommended for the treatment of keloids.

Berman (2010) stated that the potential of various biological agents to reduce or prevent excessive scar formation has now been evaluated in numerous in-vitro studies, experimental animal models and preliminary clinical trials, in some cases with particularly promising results. Perhaps prominent among this group of biological agents, and, to some degree, possibly representing marketed
compounds already being used "off label" to manage excessive scarring, are the tumor necrosis factor alpha antagonist, etanercept, and immune-response modifiers such as interferon-alpha2b and imiquimod. The author noted that additional assessment of these novel agents is now justified with a view to reducing or preventing hypertrophic scars, keloid scars and the recurrence of post-excision keloid lesions.

In a meta-analysis, Anzarut et al (2009) evaluated the effectiveness of pressure garment therapy (PGT) for the prevention of abnormal scarring after burn injury. Randomized control trials were identified from CINHAL, EMBASE, MEDLINE, CENTRAL, the "grey literature" and hand searching of the Proceedings of the American Burn Association. Primary authors and pressure garment manufacturers were contacted to identify eligible trials. Bibliographies from included studies and reviews were searched. Study results were pooled to yield weighted mean differences or standardized mean difference and reported using 95 % confidence interval (CI). The review incorporated 6 unique trials involving 316 patients. Original data from 1 unpublished trial were included. Overall, studies were considered to be of high methodological quality. The meta-analysis was unable to demonstrate a difference between global assessments of PGT-treated scars and control scars [weighted mean differences (WMD): -0.46; 95 % CI: -1.07 to 0.16]. The meta-analysis for scar height showed a small, but statistically significant, decrease in height for the PGT-treated group standardized mean differences (SMD): -0.31; 95 % CI: -0.63 to 0.00. Results of meta-analyses of secondary outcome measures of scar vascularity, pliability and colour failed to demonstrate a difference between groups. The authors concluded that PGT does not appear to alter global scar scores. It does appear to improve scar height, although this difference is small and of questionable clinical importance. The beneficial effects of PGT remain unproven, while the potential morbidity and cost are not insignificant. Given current evidence, additional research is needed to examine the effectiveness, risks and costs of PGT.

In a prospective, randomized, clinical trial, Xiao et al (2009) examined the effectiveness of intralesional botulinum toxin type A (BTX-A) injections in the treatment of hypertrophic scars. A total of 19 patients were enrolled in this study. At 1-month intervals, BTX-A (2.5 U per cubic centimeter of lesion) was injected in these patients for a total of 3 months. All the patients were followed-up for at least half a year. Therapeutic satisfaction was recorded, and the lesions were assessed for erythema, itching sensation, and pliability. At the half-year follow-up visits, all the patients showed acceptable improvement, and the rate of therapeutic satisfaction was very high. The erythema score, itching sensation score, and pliability score after the BTX-A injection all were significantly lower than before the BTX-A injection. The differences all were statistically significant (p < 0.01). The authors concluded that for the treatment of hypertrophic scars, doctors and patients both found BTX-A acceptable because of its better therapeutic results. Its effect of eliminating or decreasing hypertrophic scars was promising. The findings of this preliminary report need to be validated by further investigation.

In a randomized, double-blind, placebo-controlled trial using the reduction mammoplasty wound-healing model, van der Veer et al (2009) assessed the effectiveness of topical application of calcipotriol (a synthetic derivative of calcitriol or vitamin D) to healing wounds in preventing or reducing hypertrophic
scar formation and investigated the biochemical properties of the epidermis associated with hypertrophic scar formation. A total of 30 women who underwent bilateral reduction mammoplasty were included in this study. For 3 months, scar segments were treated with either topical calcipotriol or placebo. Three weeks, 3 months, and 12 months post-operatively, the scars were evaluated and punch biopsy samples were collected for immuno-histochemical analysis. No significant difference in the prevalence of hypertrophic scars was observed between the placebo-treated and calcipotriol-treated scars. Only scars with activated keratinocytes 3 weeks post-operatively became hypertrophic (p = 0.001). The authors concluded that topical application of calcipotriol during the first 3 months of wound healing does not affect the incidence of hypertrophic scar formation.

Hayashida and Akita (2012) stated that pediatric burn wounds present unique challenges. Second-degree burns may increase in size and depth, raising concerns about healing and long-term scarring. Results of a clinical study in adults with second-degree burn wounds suggested that application of basic fibroblast growth factor may reduce time to second-intention healing and result in a more cosmetically acceptable scar. These investigators evaluated the effect of this treatment on pediatric patients with deep second-degree burn wounds, 20 pediatric patients ranging in age from 8 months to 3 years (average of 1 year, 3 months [±/ 6 months]) with a total of 30 burn wounds from various causes were allocated either the growth factor (treatment, n = 15) or an impregnated gauze treatment (control, n = 15). Wounds, which still exudative (not healed) after 21 days, were covered with a split-thickness skin graft. All wounds were clinically assessed until healed and after 1 year. A moisture meter was used to assess scars of wounds healing by secondary intention. A color meter was used to evaluate grafted wounds. Five wounds in each group required grafting. Skin/scar color match was significantly closer to 100 % in the treatment than in the control group (p <0.01). Wounds not requiring grafting were no longer exudative after 13.8 (+/- 2.4) and 17.5 (+/- 3.1) days in the treatment (n = 10) and control group (n = 10), respectively (p <0.01). After 1 year, scar pigmentation, pliability, height, and vascularity were also significantly different (p <0.01) between the groups. Hypertrophic scars developed in 0 of 10 wounds in the treatment and in 3 of 10 wounds in the control group, and effective contact coefficient, trans-epidermal water loss, water content, and scar thickness were significantly greater in control group (p <0.01). The authors concluded that both the short- and long-term results of this treatment in pediatric burn patients are encouraging and warrant further research.

Verhaeghe et al (2013) noted that non-ablative fractional laser (NAFL) therapy is a non-invasive procedure that has been suggested as a treatment option for hypertrophic scars. These researchers evaluated the safety and effectiveness of 1,540-nm NAFL therapy in the treatment of hypertrophic scars. An intra-individual RCT with split lesion design and single-blinded outcome evaluations was performed. Patients received 4 NAFL treatments at monthly intervals. Primary end-point was a blinded on-site visual and palpable Physician Global Assessment (PhGA). Adverse event registration and pain evaluation were used to evaluate safety. Patient global assessment (PGA) was a secondary endpoint to additionally evaluate effectiveness. The PhGA did not find a statistically significant difference between the treated and untreated control side of 18 patients, although there was significant difference on the PGA at 1 month (p = 0.006) and 3 months (p = 0.02).
after last treatment (Wilcoxon signed rank test). Patients experienced moderate pain during treatment and mild adverse events. The authors concluded that in this trial, blinded PhGA could not confirm the clinical effectiveness of 1,540-nm non-ablative fractional laser in the treatment of hypertrophic scars, but the treatment is safe, and patients judged that the treated part had a better global appearance.

Waibel et al (2013) stated that hypertrophic scars and contractures are common following various types of trauma and procedures despite skilled surgical and wound care. Following ample time for healing and scar maturation, many millions of patients are burdened with persistent symptoms and functional impairments. Cutaneous scars can be complex and thus the approach to therapy is often multimodal. Intralesional corticosteroids have long been a staple in the treatment of hypertrophic and restrictive scars. Recent advances in laser technology and applications now provide additional options for improvements in function, symptoms, and cosmesis. Fractional ablative lasers create zones of ablation at variable depths of the skin with the subsequent induction of a wound healing and collagen remodeling response. Recent reports suggested these ablative zones may also be used in the immediate post-operative period to enhance delivery of drugs and other substances. These researchers presented a case series evaluating the effectiveness of a novel combination therapy that incorporates the use of an ablative fractional laser with topically applied triamcinolone acetonide suspension in the immediate post-operative period. This was a prospective case series including 15 consecutive subjects with hypertrophic scars resulting from burns, surgery or traumatic injuries. Subjects were treated according to typical institutional protocol with 3 to 5 treatment sessions at 2- to 3-month intervals consisting of fractional ablative laser treatment and immediate post-operative topical application of triamcinolone acetonide suspension at a concentration of 10 or 20 mg/ml. Three blinded observers evaluated photographs taken at baseline and 6 months after the final treatment session. Scores were assigned using a modified Manchester quartile score to evaluate enhancements in dyschromia, hypertrophy, texture, and overall improvement. Combination same session laser therapy and immediate post-operative corticosteroid delivery resulted in average overall improvement of 2.73/3.0. Dyschromia showed the least amount of improvement while texture showed the most improvement. The authors concluded that combination same-session therapy with ablative fractional laser-assisted delivery of triamcinolone acetonide potentially offers an efficient, safe and effective combination therapy for challenging hypertrophic and restrictive cutaneous scars. The main drawbacks of this study were its small sample size and the lack of a control arm. These preliminary findings need to be validated by well-designed studies.

Jin and colleagues (2013) performed a meta-analysis to evaluate the effectiveness of various laser therapies for prevention and treatment of pathologic excessive scars. The pooled response rate, pooled standardized mean difference of Vancouver Scar Scale scores, scar height, erythema, and pliability were reported. A total of 28 well-designed clinical trials with 919 patients were included in the meta-analysis. The overall response rate for laser therapy was 71 % for scar prevention, 68 % for hypertrophic scar treatment, and 72 % for keloid treatment. The 585/595-nm pulsed-dye laser and 532-nm laser subgroups yielded the best responses among all laser systems. The pooled estimates of hypertrophic scar studies also showed that laser therapy reduced total Vancouver Scar Scale
scores, scar height, and scar erythema of hypertrophic scars. Regression analyses of pulsed-dye laser therapy suggested that the optimal treatment interval is 5 to 6 weeks. In addition, the therapeutic effect of pulsed-dye laser therapy is better on patients with lower Fitzpatrick skin type scores. The authors concluded that this study presented the first meta-analysis to confirm the safety and effectiveness of laser therapy in hypertrophic scar management. The level of evidence for laser therapy as a keloid treatment is low. Moreover, they stated that further research is needed to determine the mechanism of action for different laser systems and to examine the effectiveness in quantifiable parameters, such as scar erythema, scar texture, degrees of symptom relief, recurrence rates, and adverse effects.

In a Cochrane review, O’Brien and Jones (2013) examined the effectiveness of silicone gel sheeting for: (i) prevention of hypertrophic or keloid scarring in people with newly healed wounds (e.g., post-surgery); (ii) treatment of established scarring in people with existing keloid or hypertrophic scars. In May 2013 these investigators searched the Cochrane Wounds Group Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL); Ovid MEDLINE; Ovid MEDLINE (In-Process & Other Non-Indexed Citations); Ovid EMBASE; and EBSCO CINAHL for this second update. Any randomized or quasi-RCTs, or controlled clinical trials, comparing silicone gel sheeting for prevention or treatment of hypertrophic or keloid scars with any other non-surgical treatment, no treatment or placebo were selected for analysis. These researchers assessed all relevant trials for methodological quality. Three review authors extracted data independently using a standardized form and cross-checked the results. They assessed all trials meeting the selection criteria for methodological quality. The authors included 20 trials involving 873 people, ranging in age from 1.5 to 81 years. The trials compared adhesive silicone gel sheeting with no treatment; non silicone dressing; other silicone products; laser therapy; triamcinolone acetonide injection; topical onion extract and pressure therapy. In the prevention studies, when compared with a no treatment option, while silicone gel sheeting reduced the incidence of hypertrophic scarring in people prone to scarring (risk ratio (RR) 0.46, 95 % CI: 0.21 to 0.98) these studies were highly susceptible to bias. In treatment studies, silicone gel sheeting produced a statistically significant reduction in scar thickness (MD -2.00, 95 % CI: -2.14 to -1.85) and color amelioration (RR 3.49, 95 % CI: 1.97 to 6.15) but again these studies were highly susceptible to bias. The authors concluded that there is weak evidence of a benefit of silicone gel sheeting as a prevention for abnormal scarring in high-risk individuals but the poor quality of research means a great deal of uncertainty prevails. Moreover, they stated that trials evaluating silicone gel sheeting as a treatment for hypertrophic and keloid scarring showed improvements in scar thickness and scar color, but were of poor quality and highly susceptible to bias.

Malhotra et al (2007) evaluated the safety and effectiveness of imiquimod 5 % cream in preventing the recurrence of pre-sternal keloids after excision (3 keloids in 2 patients). After excision with radiofrequency (RF), imiquimod 5 % cream was applied once-daily at bedtime for 8 weeks, and the defect was left to heal by secondary intention. In all the treated keloids, the defect healed in 6 to 8 weeks, and no recurrence was seen while on imiquimod application; however, all keloids completely recurred within 4 weeks of stopping imiquimod. Side effects were mild
and acceptable in the form of burning and pain. The authors concluded that imiquimod did exert an anti-fibrotic action but it was short-lived.

In a prospective, double-blind, placebo-controlled pilot study, Berman et al (2007) determined the tolerability and compare the effectiveness of imiquimod 5 % and vehicle cream in lowering keloid recurrence after shaving. A total of 20 randomized, shaved keloids were administered imiquimod 5 % or vehicle cream nightly for 2 weeks, and then given 3 times a week under occlusion for 1 month. Pain, tenderness, pruritus and keloid recurrence were evaluated at baseline, week 2, week 6 and 6 months. Tenderness and pain were significantly (p = 0.02 and p = 0.02, respectively) higher at week 2 in the imiquimod group than for those treated with vehicle cream. Pruritus did not attain statistical difference between the groups. At 6 months, keloid recurrence rates were 37.5 % (3/8) in the imiquimod group and 75 % (3/4) in the vehicle group (p = 0.54). The authors concluded that imiquimod was well-tolerated. However, there was not enough statistical power to detect a significant difference in 6-month keloid recurrence rates between the imiquimod-treated group and the vehicle-treated group.

Cacao et al (2009) evaluated the effectiveness of topical imiquimod 5 % cream applied after surgical excision and primary closure of trunk keloids in the prevention of recurrence. A total of 9 patients with a keloid lesion on the trunk were treated with surgical excision and primary closure. Daily application of imiquimod 5 % cream for 8 weeks was initiated the night of surgery. The patients were evaluated 2, 4, 8, 12, and 20 weeks after. Keloid recurrence occurred in 8 patients, 7 of them 12 weeks after surgery. These researchers lost track of 1 patient. The authors concluded that the results of this study suggested that imiquimod 5 % cream is not effective in preventing recurrence of trunk keloids after surgical excision. They stated that although this was a small case series, results strongly discouraged other studies using imiquimod 5 % cream in the prevention of surgically excised trunk keloids.

Viera et al (2012) stated that there is very limited evidence on the best wound management for minimizing scarring. Multiple available therapeutic modalities have been used for the treatment of keloids; however, high-recurrence rates continue to be reported. Currently, there are biological and anti-neoplastic agents that can potentially treat and prevent excessive scar formation. Some of them have been used as "off-label" therapies, and others are still in the experimental phase (e.g., interferon alpha (IFN-α), imiquimod, and transforming growth factor beta1 (TGF-β1)). The use of IFN-α2b showed 18 % recurrence rate when applied to post-surgical excised keloids. Imiquimod 5 % can lower recurrence rate on post -shaved keloids to 37.5 % at 6-month and to 0 % at a 12-month follow-up period. Transforming growth factor beta1 oligonucleotides have shown effective and long-lasting inhibition of TGF-β-mediated scarring in-vitro as well as in animal models. Daily injections of neutralizing antibodies against TGF-β1 and -β2 have shown successful reductions in scarring. The authors concluded that latest discoveries in the use of novel agents suggested therapeutic alternatives for the prevention of recurrences of hypertrophic scars and post-excision keloid lesions.

Gold et al (2014) reviewed available data on methods for preventing and treating cutaneous scarring. Relevant scientific literature was identified through a comprehensive search of the MEDLINE database. Additional data and published
studies were submitted for consideration by members of the International Advisory Panel on Scar Management. One of the most significant advances in scar management over the past 10 years has been the broader application of laser therapy, resulting in a shift in status from an emerging technology to the forefront of treatment. Accumulated clinical evidence also supports a greater role for 5-FU in the treatment of hypertrophic scars and keloids, particularly in combination with intralesional corticosteroids. The authors stated that encouraging data have been reported for newer therapies, including bleomycin, onion extract-containing preparations, imiquimod, and mitomycin C, although methodological limitations in available studies merit consideration.

An UpToDate review on “Keloids and hypertrophic scars” (Goldstein and Goldstein, 2015) states that “Imiquimod -- A few small observational studies have reported that postoperative use of imiquimod with daily or alternate day applications may reduce the rate of recurrence of keloids. However, other studies have provided conflicting results …. Other therapies that have been used for keloids include intralesional bleomycin, mitomycin C, and topical imiquimod cream. There is insufficient evidence to make definitive recommendations about these therapies when used alone, although they may provide benefit when used after surgical excision”.

Ledon et al (2013) provided a comprehensive review of current intralesional treatment modalities for keloids and hypertrophic scars. These researchers performed a PubMed search for literature pertaining to intralesional treatment modalities for keloids and hypertrophic scars. References from retrieved articles were also considered for review. These investigators noted that many intralesional therapies for keloids and hypertrophic scars are currently available to physicians and patients. Mechanisms of action and side effect profiles vary between these agents, and new approaches to keloids and hypertrophic scars are frequently being explored. The authors concluded that RCTs are needed to evaluate these new and promising modalities fully.

Song (2014) noted that hypertrophic scars and keloids remain a challenge in surgery. Although the bench to bedside conundrum remains, the science of translational research calls for an even higher level of cooperation between the scientist and the clinician for the impetus to succeed. The clinicians alerted the possible theories in the pathogenesis of keloid formation, inter alia, the ischemia theory, mast cell theory, immune theory, TGB-β interaction, mechanical theory, and the melanocyte stimulating hormone theory. All of the above presupposed a stimulus that would result in an uncontrolled up-regulation of collagen and extracellular matrix expression in the pathogenesis of the keloid. This bedside to bench initiative, as in true science, realized more ponderables than possibilities. By the same token, research into the epidermal-mesenchymal signaling, molecular biology, genomics, and stem cell research holds much promise in the bench top arena. To assess efficacy, many scar assessment scores exist in the literature. The clinical measurement of scar maturity can aid in determining end-points for therapeutics. Tissue oxygen tension and color assessment of scars by standardized photography proved to be useful. In surgery, the use of dermal substitutes holds some promise as these researchers surmised that quality scars that arise from dermal elements, molecular and enzyme behavior, and balance. Although a systematic review showed some benefit for earlier closure and healing
of wounds, no such review exists at this point in time for the use of dermal substitutes in scars. Adipose-derived stem cell, as it pertains to scars, will hopefully realize the potential of skin regeneration rather than by repair in which the researchers were familiar with as well as the undesirable scarring as a result of healing through the inflammatory response. The author concluded that translational research will bear the fruit of coordinating bench to bedside and vice-versa in the interest of progress into the field of regenerative healing that will benefit the patient who otherwise suffers the myriad of scar complications.

Wat and associates (2014) provided evidence-based recommendations to guide physicians in the application of intense pulsed light (IPL) devices for the treatment of dermatologic disease. These investigators performed a literature search of the CENTRAL (1991 to May 6, 2013), EMBASE (1974 to May 6, 2013), and MEDLINE in-process and non-indexed citations and MEDLINE (1964 to present) databases. Studies that examined the role of IPL in primary dermatologic disease were identified, and multiple independent investigators extracted and synthesized data. Recommendations were based on the highest level of evidence available. These researchers found Level 1 evidence for the use of IPL for the treatment of melasma, acne vulgaris, and telangiectasia; Level 2 evidence for the treatment of lentiginous disease, rosacea, capillary malformations, actinic keratoses, and sebaceous gland hyperplasia; and Level 3 or lower evidence for the treatment of poikiloderma of Civatte, venous malformations, infantile hemangioma, hypertrophic scars, superficial basal cell carcinoma, and Bowen’s disease. The authors concluded that IPL is an effective treatment modality for a growing range of dermatologic disease and in some cases may represent a treatment of choice. It is typically well-tolerated. Moreover, they stated that further high-quality studies are needed.

Dogra and colleagues (2014) evaluated the safety and effectiveness of micro-needling treatment for atrophic facial acne scars. A total of 36 patients (26 females, 10 males) with post-acne atrophic facial scars underwent 5 sittings of derma-roller under topical anesthesia at monthly intervals. Objective evaluation of improvement was performed by recording the acne scar assessment score at baseline and thereafter at every visit. Pre- and post-treatment photographs were compared, and improvement was graded on quartile score. Final assessment was performed 1 month after the last sitting. Patients were asked to grade the improvement in acne scars on VAS (0 to 10 point scale) at the end of study. Of 36 patients, 30 completed the study. The age group ranged from 18 to 40 years, and all patients had skin phototype IV or V. There was a statistically significant decrease in mean acne scar assessment score from 11.73 ± 3.12 at baseline to 6.5 ± 2.71 after 5 sittings of derma-roller. Investigators’ assessment based on photographic evaluation showed 50 to 75% improvement in majority of patients. The results on VAS analysis showed “good response” in 22 patients and “excellent response” in 4 patients, at the end of study. The procedure was well-tolerated by most of the patients, and chief complications noted were post-inflammatory hyperpigmentation in 5 patients and tram-trek scarring in 2 patients. The authors concluded that micro-needling with derma-roller is a simple and cheap, means of treatment modality for acne scars re-modulation with little downtime, satisfactory results and peculiar side effects in Asian skin type. The findings of this small (n = 36) uncontrolled study need to be validated by well-designed studies.
In a retrospective study, Chandrashekar et al (2014) assessed the safety and effectiveness of micro-needling fractional radiofrequency in the treatment of acne scars. A total of 31 patients of skin types III to V with moderate and severe facial acne scarring received 4 sequential fractional RF treatments over a period of 6 months with an interval of 6 weeks between each session. Goodman & Baron's acne scar grading system was used for assessment by a side by side comparison of pre-operative and post-operative photographs taken at their first visit and at the end of 3 months after the last session. Estimation of improvement with Goodman and Baron's Global Acne Scarring System showed that by qualitative assessment of 31 patients with grade 3 and grade 4 acne scars, 80.64 % showed improvement by 2 grades and 19.35 % showed improvement by 1 grade. Quantitative assessment showed that 58 % of the patients had moderate, 29 % had minimal, 9 % had good and 3 % showed very good improvement. Adverse effects were limited to transient pain, erythema, edema and hyperpigmentation. The authors concluded that micro-needling fractional RF is effective for the treatment of moderate and severe acne scars. The findings of this small (n = 31) retrospective study need to be validated by well-designed studies.

Furthermore, UpToDate reviews on “Keloids and hypertrophic scars” (Goldstein and Goldstein, 2015), “Management of keloid and hypertrophic scars following burn injuries” (Gauglitz, 2015), and “Management of acne scars” (Saedi and Uebelhoer, 2015) do not mention micro-needling as a therapeutic option.

Goyal and Gold (2014) noted that keloids and hypertrophic scars remain one of the more difficult treatment concerns for clinicians. A variety of therapies have been used in the past with moderate success. On occasion, combination therapy has been used to treat these lesions, in an attempt to lessen the symptoms of pain and pruritus that often accompanies keloids and hypertrophic scars, as well as treating the actual lesions themselves. These researchers introduced a novel triple combination injection process in an attempt to further reduce the signs and symptoms of these lesions. The combination includes 5-FU, triamcinolone acetonide, and hyaluronidase. All 3 agents supposedly work in concert to treat keloids and hypertrophic scars, and this was the first work at looking at these medicines given together, at the same time, in a series of recalcitrant keloids and hypertrophic scars. The authors concluded that the positive results warrant further investigation and hope for those with keloids and hypertrophic scars.

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria are met:

- 11900 Injection, intraliesional; up to and including 7 lesions [corticosteroids]
- 11901 more than 7 lesions [corticosteroids]
- 17110 Destruction (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), of benign lesions other
than skin tags or cutaneous vascular proliferative lesions; up to 14 lesions

17111  15 or more lesions

Other CPT codes related to the CPB:

11042 - 11047  Debridement; subcutaneous tissue, muscle/fascia, bone

15852  Dressing change (for other than burns) under anesthesia (other than local)

HCPCS codes covered for indications listed in the CPB:

J0702  Injection, betamethasone acetate 3 mg and betamethasone sodium phosphate 3mg

J1020  Injection, methylprednisolone acetate, 20 mg

J1030  Injection, methylprednisolone acetate, 40 mg

J1040  Injection, methylprednisolone acetate, 80 mg

J1100  Injection, dexamethasone sodium phosphate, 1 mg

J1700  Injection, hydrocortisone acetate, up to 25 mg

J1710  Injection, hydrocortisone sodium phosphate, up to 50 mg

J1720  Injection, hydrocortisone sodium succinate, up to 100 mg

J2650  Injection, prednisolone acetate, up to 1 ml

J3300  Injection, triamcinolone acetonide, preservative free, 1 mg

J3301  Injection, triamcinolone acetonide, not otherwise specified, 10 mg

J3302  Injection, triamcinolone diacetate, per 5 mg

J3303  Injection, triamcinolone hexacetonide, per 5 mg

J7638  Dexamethasone, inhalation solution, compounded product, administered through DME, unit dose form, per milligram

J9190  Fluorouracil, 500 mg

HCPCS codes not covered for indications listed in the CPB:

A6025  Gel sheet for dermal or epidermal application, (e.g., silicone, hydrogel, other), each

J0585  Injection, onabotulinumtoxinA, 1 unit [Botox]

J0586  Injection, abobotulinumtoxinA, 5 units [Dysport]
J1438  Injection, etanercept, 25 mg

J3470  Injection, hyaluronidase, up to 150 units

J3471  Injection, hyaluronidase, ovine, preservative free, per 1 USP unit (up to 999 USP units)

J3472  Injection, hyaluronidase, ovine, preservative free, per 1,000 USP units

J3473  Injection, hyaluronidase, recombinant, 1 USP unit

J9040  Injection, bleomycin sulfate, 15 units

J9212  Injection, interferon Alfacon-1, recombinant, 1 mcg

J9213  Interferon alfa-2A, recombinant, 3 million units

J9214  Interferon alfa-2B, recombinant, 1 million units

J9215  Interferon alfa-N3, (human leukocyte derived), 250,000 IU

J9280  Injection, mitomycin, 5 mg

ICD-9 codes covered if selection criteria are met:

701.4  Keloid scar

The above policy is based on the following references:

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59. Goldstein BG, Goldstein AO. Keloids. Last reviewed February 2012. UpToDate Inc. Waltham, MA.
76. Goldstein BG, Goldstein AO. Keloids and hypertrophic scars. UpToDate Inc., Waltham, MA. Last reviewed January 2015.
77. Gauglitz GG. Management of keloid and hypertrophic scars following burn injuries. UpToDate Inc., Waltham, MA. Last reviewed January 2015.