Actinic Keratoses Treatments

Number: 0567

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers destruction of actinic keratoses lesions using either of the following methods medically necessary:

I. Cryosurgery with liquid nitrogen
II. Topical diclofenac, imiquimod, ingenol mebutate gel, or 5-fluorouracil (5-FU) with or without tretinoin cream.

Aetna considers either of the following methods of removal of actinic keratoses medically necessary when squamous cell carcinoma is suspected, and submission of a specimen for histological analysis is needed:

I. Curettage
II. Excision

Aetna considers the following methods of destruction of actinic keratoses medically necessary for members who have failed to adequately respond to topical imiquimod or 5-FU, or to cryosurgery:

Policy History

Last Review: 06/08/2017
Effective: 11/09/2001
Next Review: 06/07/2018

Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes
Chemical peel (chemoexfoliation)
- Dermabrasion
- Laser therapy
- Photodynamic therapy (e.g., Levulan Kerastick [aminolevulinic acid hydrochloride solution and blue light] or Metvixia photodynamic therapy [methyl aminolevulinate cream and the Aktilite CL128 (red light) lamp]).

Aetna considers the following experimental and investigational for the treatment of actinic keratoses because their safety and effectiveness for this indication has not been established (not an all-inclusive list):
- Intense pulsed light
- Lapatinib
- Topical calcipotriol
- Topical piroxicam
- Topical vitamin D and analogs

See also CPB 0031 - Cosmetic Surgery (../_1_99/0031.html), CPB 0251 - Dermabrasion, Chemical Peels, and Acne Surgery (../_200_299/0251.html), and CPB 0427 - Carbon Dioxide Laser for Actinic Lesions and Other Selected Indications (../_400_499/0427.html).

Background
Actinic keratoses (AKs), also known as solar keratoses, are common, sun-induced pre-cancerous skin lesions that are confined to the epidermis. The lesions typically appear as circumscribed, rough, scaly patches on sun exposed skin, ranging from flesh-colored to reddish-brown. Although most AKs are asymptomatic, some may exhibit signs and symptoms such as thickening, burning, tenderness, or itching. Actinic keratoses may also progress to squamous cell carcinoma (SCC), a form of skin cancer.

Actinic keratoses (AKs) most commonly occur in sun-exposed
Actinic cheilitis is a variant of AKs found on the lip. Actinic keratoses are most prevalent in fair-skinned individuals with a history of significant sun exposure. The prevalence of AKs increases with advancing age, and AKs are more common in men than women. Actinic keratoses are more common in immunosuppressed patients and in patients with some genetic disorders (such as xeroderma pigmentosum).

The overall reported prevalence of AKs has been reported to range from 23 to 61.1%, and the reported annual incidence of AK ranges from 12.6 to 43.4%. Due to these high rates of prevalence and incidence, destruction of AKs is the most commonly performed outpatient dermatologic procedure in the United States.

Several studies have demonstrated an association between the presence of AKs and the development of SCCs, and 2 studies suggest a progression rate of 1 to 2 SCCs per 1,000 AKs. There is consensus that immunosuppressed individuals, people with a prior history of skin cancer, and people with AKs of the lips, nose, ear or eyelid are at increased risk of developing SCC. Squamous cell carcinoma can and do metastasize, with reported rates of metastasis ranging from 0.5 to 16%.

Treatment for AKs involves selectively destroying skin lesions (growths) without harming the surrounding skin tissue. Various options exist for managing AKs, and clinicians may consider several factors to determine the most appropriate management strategy, including size, location or growth pattern of the lesion, patient preference, and patient medical history. Common treatments for AK include cryosurgery with liquid nitrogen, topical treatments, and curettage. Other less common treatments for AK include dermabrasion, excision, chemical peels, laser therapy, and photo-dynamic therapy (PDT).

Cryosurgery with liquid nitrogen, the most common treatment for AKs in the United States, is most appropriate when discrete AKs are present. With this procedure, liquid nitrogen is applied
directly to AK lesions as a method of destruction. The skin surface freezes, causing it and the lesion cells to slough off. New skin then forms. The procedure generally does not require the use of a local anesthetic and involves only mild pain and minor side effects, such as temporary post-procedural erythema.

With topical drug therapy, medicated creams, gels or lotions are applied to the surface of the skin to remove multiple lesions, above and below the surface of the skin. The patient applies the medication at home as directed. Topical treatments, such as the chemotherapeutic agent 5-fluorouracil (5-FU), are most commonly used for patients with multiple lesions. The 5-FU cream is applied to the entire region that is affected, and the recommended course of treatment involves several applications per day over a 2 to 4 week time span. 5-fluorouracil selectively targets the damaged skin, causing an inflammatory response with erythema, necrosis, and erosion. Numerous side effects are associated with 5-FU, including pain or irritation, tenderness, ulceration, burning, and inflammation. As a result, patient compliance is a significant concern with this treatment.

Experts suggest topical fluorouracil (5-FU) may be the most efficacious with comparable tolerability compared to imiquimod. The British Academy of Dermatology (BAD, 2007) has assigned a grade A recommendation with level 1 quality of evidence for 5-FU. A wide range of open trials, dose ranging studies, and manipulations of the vehicle has been reported over the last 35 years, as well as two randomized controlled trials, confirming efficacy. Witheiler et al. used 5% 5-FU cream on the face as control in a right/left comparison with a single application of Jessner’s solution (14% lactic acid, 14% salicylic acid, 14% resorcinol in ethanol) followed by a 35% TCA peel. There was a mean reduction in Aks on both sides of the face from 18 to 4 (78% reduction with 5-FU and 79% reduction with TCA. This benefit was sustained for 12 months. Alternative therapies such as imiquimod, have also been proven to be effective. However, there is limited long term data on relapse after treatment with imiquimod.

After 4 weeks of treatment with 5% fluorouracil (5-FU) and a
2-month follow-up, 94% of treated actinic keratoses had resolved. Following 16 weeks of 5% imiquimod application and a 2 month follow-up, 66% of actinic keratoses had cleared (p<0.01). Complete clearance occurred in 63% of patients with 5% 5-FU and 24% of patients with 5% imiquimod at 2 months post-therapy completion (p<0.05). After one year of posttherapy follow-up, 87% of Aks were still cleared with 5% 5-FU, whereas 72% of actinic keratoses were cleared with 5% imiquimod, indicating a low recurrence rate with both therapies. The adverse event profile did not differ significantly between the two therapies. In this study, 5% 5-FU cream achieved faster and more complete clearance of actinic keratoses as compared to 5% imiquimod cream. The two modalities had comparable adverse event profiles (Tanghetti, et al., 2007).

Curettage, which involves the use of a curette to scrape away the lesion, is another common method of treatment for AKs. Curettage is a destructive technique which usually treats to a deeper level within the dermis than cryosurgery and is indicated for larger lesions, especially in immunocompromised patients with AKs likely to be more aggressive. In some instances, curettage may be used in combination with electrosurgery to stop bleeding or apply more damage to the affected area. The primary advantage of curettage is the ability to submit the specimen for histological analysis, particularly in cases where invasive SCC is suspected. Disadvantages of curettage include the need for local anesthesia and the potential for scarring.

Excision involves surgical removal or resection of tissue from the body. Like curettage, excision treats to a deeper level within the dermis than cryosurgery and is indicated for larger lesions, especially in immunocompromised patients with AKs likely to be more aggressive. Full-thickness elliptical excision for AK is rarely performed by dermatologists, but is regularly performed by plastic surgeons, general surgeons, and general practitioners.

Shave removal involves excision of a lesion using a razor. It is indicated for lesions suggestive of squamous cell carcinoma requiring histopathological examination. When performed on the lip, this procedure is called a vermilionectomy.
According to the American Academy of Dermatology, dermabrasion, chemical peels (utilizing alpha-hydroxy acids or trichloroacetic acid), and laser resurfacing by carbon dioxide laser have also been effective in the treatment of extensive AK.

Dermabrasion involves removal of skin blemishes by abrasion (as in sandpaper) which removes the surface of the epidermis of the skin.

With chemical peels (chemoexfoliation), a topical agent, such as an acid, is applied to the skin causing it to blister and peel. The top layers slough off and are usually replaced within seven days by new epidermis (the skin’s outermost layer). This technique requires local anesthesia and can cause temporary discoloration and irritation.

Laser therapy is a finely controlled treatment that uses a laser to burn away AKs and is an option for lesions in small or narrow areas. Laser surgery is useful for people taking blood thinners and as a secondary therapy when other techniques are unsuccessful. Local anesthesia is usually necessary and scarring and pigment loss may occur.

Photodynamic Therapy (PDT) is a two-step treatment that uses drugs, called photosensitizing agents, along with light to kill cells. The drugs only work after they have been activated by certain kinds of light. In the first step, a topical solution, such as aminolevulinic acid (Kerastick or Levulan) or methyl aminolevulinate (Metvixia), is applied to each lesion using an applicator. Once applied, exposure to a specific wavelength of light (blue or red) causes cellular destruction.

Photodynamic therapy with the topical agent 5-aminolevulinic acid (5-ALA) is used to selectively photosensitize the atypical cells of the AK lesion. Approximately 14 to 18 hours following application of the 5-ALA, the skin is exposed to a light source and the cells of the AK lesion are destroyed. Common side effects of PDT include erythema, stinging/burning, edema, and scaling or crusting of the lesion. The primary disadvantage of PDT is the need for treatment over a 2-day period. One PDT system
currently has approval for the treatment of AKs. In 1999, DUSA Pharmaceuticals, Inc. received Food and Drug Administration (FDA) approval for Levulan Kerastick. Levulan Kerastick involves the use of both a drug (20 % ALA topical solution) and a device (the Levulan Kerastick) for application of ALA and the BLU-U™ Illuminator as the light source). An interventional procedure assessment by the National Institute for Clinical Excellence (NICE, 2006) concluded that there is adequate evidence to support the use of PDT for AK, as well as for basal cell carcinoma and Bowen's disease. The assessment found insufficient evidence for PDT for invasive SCC of the skin.

There are few studies directly comparing the various treatments for AK to determine which are most effective. Although the evidence is limited, PDT and 5-FU appear to be equally effective in treatment of AKs. In 1999, Kurwa et al conducted a study to compare 5-FU (5 %) to PDT (5-ALA followed by irradiation with a halogen lamp emitting red light). A total of 17 patients with a long history of AKs on the forearms and hands were initially recruited for this study, and patients were randomized to apply 5-FU (twice-daily for 3 weeks) to one hand and receive PDT to the other hand. Clinical margins of the AKs on both hands were traced prior to treatment and at 1 week, 4 weeks and 6 months following the start of treatment; 14 of the original 17 patients completed the study and the mean lesional areas were compared pre- and post-treatment. The study reported a mean lesional reduction of 70 % for lesions treated with 5-FU and a 73 % reduction in lesions treated with PDT after 6 months of follow-up. The difference in response to the 2 treatments was not statistically significant. No patients exhibited a complete destruction of AKs with either treatment. Limitations included small sample size, lack of information on selection criteria, lack of information on assessment of patient compliance with 5-FU, and non-blinding study design. Further, results at 1 and 4 weeks of follow-up were not reported.

Medium-depth chemical peel has been shown to be about as effective as topical 5-FU. Lawrence et al (1995) initially reported on a study comparing a medium-depth chemical peel (Jessner's solution and 35 % trichloroacetic acid) to 5 % 5-FU in 15 patients.
Following a daily self-administration of 0.025 % tretinoin cream to both sides of the face for 2 weeks, each patient was subjected to the chemical peel on the left side of the face and 5-FU to the right side of the face. Actinic keratoses were counted prior to treatment and at 1, 6 and 12 months following treatment; 12 of the 15 patients completed the 12-month study, and reported results indicate that "both fluorouracil [5-FU] and the chemical peel induced almost identical percent reductions (75 %) in the number of AK". The study reports that this reduction in AKs was noted at the 1-month follow-up and persisted throughout the 12-month study period. As with earlier studies, methodological flaws included non-blinding study design, small sample size, lack on information on selection criteria and characteristics of the study setting, and a lack of information on whether patient compliance with 5-FU was assessed. Further, the results at 6 and 12 months of follow-up are confounded by intervening treatment of persistent AKs (35 % trichloroacetic acid and cryosurgery at 6 months, shaving at 12 months). Witehiler et al (1997) later reported a 32-month follow-up on the patients from the Lawrence study. Results indicated an increase in the mean number of AKs between 12 and 32 months. However, this study contained flaws in addition to those of the Lawrence study, including the availability of only 8 patients for follow-up and intervening treatment of some AKs during the study period (between 12 and 32 months).

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) of the acetic acid chemical class. The mechanism of action of topical diclofenac sodium in the treatment of actinic keratoses (AK) is unknown.

Imiquimod cream (Aldara, Zyclara) is indicated for the treatment of AK. Imiquimod is a Toll-7 like receptor agonist that activates immune cells. Its specific mechanism of action for treating actinic keratosis (AK), however, is unknown. A consensus panel on the treatment of AK (Berman et al, 2006) stated that imiquimod and 5-FU are the most effective field-directed therapies for AK (for multiple lesions or an entire area at risk).

Imiquimod was effective in the treatment of AK, preventing
potential development of SCC. In a meta-analysis, Hadley and colleagues (2006) evaluated benefit and harm associated with treating AK with imiquimod 5 % cream, an immune response modifier. Five randomized, double-blind trials lasted 12 to 16 weeks with 1,293 patients were studied. Complete clearance occurred in 50 % of patients treated with imiquimod, compared to 5 % treated with vehicle, and the number needed to treat (NNT) for 1 patient to have his/her keratosis completely cleared after 12 to 16 weeks was 2.2 (95 % confidence interval [CI]: 2.0 to 2.5). For partial (greater than or equal to 75 %) clearance the NNT was 1.8 (1.7 to 2.0). The proportion of patients with any adverse event, any local adverse event, or any treatment-related adverse event was substantially higher with imiquimod than with vehicle, and numbers needed to harm for 1 additional adverse event with imiquimod over 12 to 16 weeks ranged from 3.2 to 5.9. Particular local adverse events with imiquimod included erythema (27 %), scabbing or crusting (21 %), flaking (9 %), erosion (6 %), edema (4 %), and weeping (3 %).

McIntyre and colleagues (2007) stated that treatment options for AKs include ablative (destructive) therapies such as cryosurgery, curettage with electrosurgery, and PDT. Topical therapies are used in patients with multiple lesions. Fluorouracil has been the traditional topical treatment for AKs, although imiquimod 5 % cream and diclofenac sodium 3 % gel are effective alternative therapies. This is in agreement with the recommendations of Newman and Weinberg (2007). Furthermore, Iraji et al (2008) noted that the use of diclofenac is associated with a few side effects, which include pruritus, rashes, dry skin, and scaling. These side effects are usually minimal and tolerable. A meta-analysis of 3 randomized trials (n = 364) found that treatment with diclofenac gel resulted in complete resolution of AKs in approximately 40 % of patients as compared with 12 % with placebo. Thus, this topical medication is suggested as the first line treatment for AKs.

A systematic evidence review of PDT for actinic keratoses (ICES, 2009) found it to have similar response rates to other commonly used methods of treating AKs. Eight clinical trials met criteria for inclusion in the review; 4 of which compared PDT with
cryotherapy, 2 of which compared PDT with 5-FU, 1 of which compared PDT with aminolevulinic acid with PDT with methylaminolevulinate and 1 comparing PDT with placebo. The authors reported that the trials that compared PDT with surgery included a total number of 642 patients with 4,430 lesions with AK. In all the trials, each patient received both treatments, randomly assigning one treatment to each side. The authors stated that studies of PDT for AKs are limited by short durations of follow-up and a lack of evidence on the effectiveness in prevention of SCC. One trial assessed the result in the lesions with no specific location. No differences were observed in cure rate (69 % with PDT with methylaminolevulinate compared to 75 % with cryotherapy). Two trials compared the results in face and scalp lesions. In both studies, a higher response rate was observed at 3 months with PDT with methylaminolevulinate, with a range for PDT between 89 and 91 % and between 68 and 76 % for cryosurgery (p < 0.001). In addition, one of the 2 studies had a 6-month-follow-up, but no significant differences were observed. Finally, 1 study conducted by Kaufman et al (2008) compared the use of PDT with methyaminolevulinate with cryotherapy in patients with AK located in different areas of the face and scalp, observing a 78 % decrease in the number of lesions with PDT with methylaminolevulinate and 88 % with cryotherapy (p < 0.001) at 6 months. In all the studies, the cosmetic result assessed both by the physicians and patients was significantly higher for PDT with methylaminolevulinate against cryotherapy. Both studies comparing PDT with 5-FU included a total of 30 patients showing a similar result, with response rates ranging between 70 % and 90 %. The authors also reported that PDT is associated with a higher cost than other commonly used methods of treating AK.

The British Association of Dermatologists proposes in its clinical practice guidelines the use of only PDT with aminolevulinic acid (PTAA) or methyl aminolevulinate (PTMA) in patients with multiple AK lesions that do not respond to standard cryotherapy or 5-FU treatment (de Berker et al, 2007). The guidelines note that PDT may be particularly good for superficial and confluent AKs, but is likely to be more expensive than most other therapies. "Due to expense and inconvenience PDT is probably
best reserved for patients with extensive AKs that cannot be controlled with other therapies." The guidelines reviewed the evidence for PDT for actinic keratoses. Two studies compared PDT with cryotherapy; 1 showed a higher clearance rate with cryotherapy, whereas another showed a lower clearance rate with cryotherapy. Cryotherapy appeared to be superior to PDT for lesions of the face and scalp, and for thicker lesions. The investigators noted that local adverse reactions were reported by 44% of those receiving PDT and 26% of those given cryotherapy, although the assessment of cosmetic outcome in studies was higher (98%) for PDT than cryotherapy (91%). A right/left comparison of AK treatment on the back of the hands by PDT and 5-FU showed a similar response to both therapies, clearing 73% and 70%, respectively. The guidelines noted that responses remained similar at 6 months. The guidelines also noted that the cost-effectiveness of PDT is not established but its use is likely to be limited by the cost of the photo-sensitizing cream.

Guidelines on AK from the European Dermatology Forum (Stockfleth et al, 2006) also noted that the clinical experience in AK patients receiving PDT with methylaminolevulinate shows complete response rate of 70 to 78% after a single treatment session and 90% after 2 treatment sessions 1-week apart. The guidelines noted that negative effects of PDT are local pain, risk of photosensitivity (mainly for aminolevulinic acid) and time delay between application of cream and treatment. The guidelines note level 2b (individual cohort study) evidence of better cosmetic results with PDT than cryotherapy. The guidelines state that advantages of PDT include the selective absorption and treatment of subclinical lesions and the fluorescence of the photosensitiser can be visualised using Wood's light before the initiation of therapy. The guidelines note, on the other hand, the costs of PDT are considerably higher compared to cryotherapy.

Methyl aminolevulinate cream (Metvixia), a porphyrin precursor, in combination with the Aktilite CL128 lamp, a narrowband, red light illumination source, has been approved by the FDA for treatment of thin and moderately thick, non-hyperkeratotic, non-pigmented AK of the face and scalp in immunocompetent patients when used in conjunction with lesion preparation in the
physician's office when other therapies are considered medically less appropriate (Galderma, 2008).

Ortiz-Policarpio and Lui (2009) noted that methyl aminolevulinate (MAL)-hydrochloride cream in combination with PDT provides an effective treatment option for AK, superficial basal cell carcinoma (sBCC), and Bowen's disease (BD). Good clinical outcomes have been reported in the literature. Complete responses (CRs) in AK range from 69% to 93% at 3 months. In sBCC, reported CR rates were from 85% to 93% at 3 months and almost on par with cryosurgery at 60 months (75% versus 74%). In BD, CR rates were 93% at 3 months and 68% at 2 years. Current evidence has shown that this non-invasive treatment is superior in terms of cosmetic outcome to other management strategies such as surgery. It also offers the advantages of relative simplicity, low risk of side-effects and decreased complications due to scar formation.

Fai and associates (2009) reported the findings of a retrospective chart review showing the cumulative 4-year experience with MAL-PDT in a hospital outpatient setting. The medical records selected concerned all patients who completed the MAL-PDT regimen (1 single session for AK and 2 sessions 1 week apart for non-melanoma skin cancers [NMSCs]) and who underwent post-treatment assessments over a follow-up period of at least 12 months. Present case series included a total of 462 patients: 210 patients with AK, 228 subjects with 348 BCCs, 213 of nodular type BCC (nBCC) and 135 of sBCC, 17 patients with BD and 7 with SCC. On the whole, following a single session, complete clearance of AK was achieved in 79% of patients at 3 months and in 68.1% at 12 months. As concerns BCCs, regardless of the clinical type, a CR was observed in 71% of lesions at 3 months, with a rate of recurrence at 12 months of 15%. The risk of both initial treatment failure and recurrence was higher for nBCCs than sBCCs. These findings, even if obtained in very few cases, indicate that BD is very responsive to MAL-PDT, unlike micro-invasive or invasive SCC. Treatment was generally well-tolerated. The authors concluded that these findings confirmed that MAL-PDT is a valid approach to patients with AK, BCC and BD, with an acceptable tolerability profile and a very low risk of
In an investigator-blinded, half-side comparison study, Seckin et al (2009) examined if AK may benefit from the anti-proliferative and pro-differentiative effects of topical vitamin D. Patients applied calcipotriol cream to 1 side and Ultrabase cream as placebo to the other side of the scalp and/or face for 12 weeks. The total number of AK and diameters and total scores of the target lesions were determined at each visit. A total of 9 patients were included, 8 of whom completed the treatment. There was a statistically significant difference between the total number of AK at baseline and at week 12 on calcipotriol applied side whereas no difference was detected on placebo applied side (p = 0.028 versus p = 1.00). The mean total score of the target lesions reduced significantly at week 12 on calcipotriol side; however, no significant reduction was found on placebo side (p = 0.017 versus p = 0.056). Although side effects were more common on calcipotriol side, the difference was not statistically significant. The authors concluded that topical calcipotriol may show promise in the treatment of AK. Moreover, they stated that more studies are needed to confirm its efficacy.

Ingenol mebutate (Picato) is a dermatologic agent indicated for the topical treatment of actinic keratosis. The mechanism of action by which Picato (ingenol mebutate) induces cell death in treating actinic keratosis lesions is unknown. Siller et al (2009) noted that the sap of the plant Euphorbia peplus is a traditional remedy for skin conditions, including AKs. The active constituent of the sap is ingenol mebutate (ingenol-3-angelate), formerly known as PEP005. In a phase II clinical trial, these researchers investigated the safety (and secondarily the efficacy) of 2 applications of ingenol mebutate gel in 58 patients with biopsy-confirmed AKs. Five pre-selected lesions were treated with ingenol mebutate gel, 0.0025 %, 0.01 % or 0.05 %, or vehicle gel, on days 1 and 2 (Arm A) or days 1 and 8 (Arm B). There were no significant differences in tolerability or efficacy between Arms A and B. Treatment was well-tolerated. The most common local skin responses were dose-related erythema, flaking/scaling/dryness and scabbing/crusting. Efficacy was greatest with ingenol mebutate gel, 0.05 %, which resulted in complete clinical
clearance of 71% of treated lesions (p < 0.0001 vs vehicle gel). In addition, 67% of patients treated with ingenol mebutate gel, 0.05% had clinical clearance of at least 4 of 5 treated lesions (p = 0.0185 versus vehicle gel). Ingenol mebutate gel is being developed as a short-course topical therapy for AKs and non-melanoma skin cancer.

In a randomized, double-blinded study, Anderson et al (2009) evaluated the safety and effectiveness of ingenol mebutate gel at 3 dosing regimens for the treatment of AKs. Patients with non-facial AKs applied vehicle gel for 3 days, ingenol mebutate gel, 0.025% for 3 days, or ingenol mebutate gel, 0.05% for 2 or 3 days, with an 8-week follow-up period. All 3 active treatments were significantly more effective than vehicle at clearing AKs lesions, with a dose-response observed. The partial clearance rate (primary efficacy end point) for patients treated with ingenol mebutate gel ranged from 56.0% to 75.4% compared with 21.7% for vehicle gel (p = 0.0002 to p < 0.0001 versus vehicle). The complete clearance rate was also significantly higher (p < or = 0.0006) for patients in the ingenol mebutate gel treatment groups (range of 40.0% to 54.4%) compared with vehicle (11.7%), as was the baseline clearance rate (range of 42.0% to 57.9% for ingenol mebutate gel compared with 13.3% for vehicle, p < 0.0001 to 0.0007 versus vehicle). The median percentage reduction in baseline AKs lesions for patients treated with ingenol mebutate gel ranged from 75% to 100% compared with 0% for vehicle gel (p < 0.0001 versus vehicle). Active treatment was well-tolerated at all dosages. The mechanism of action of this agent is the localized induction of necrosis followed by a transient inflammatory response, and this was manifested in most patients as transient local skin responses consisting primarily of erythema, flaking/scaling, and crusting. There was no evidence of treatment-related scarring. The authors concluded that short-course, field-directed therapy with ingenol mebutate gel for AKs on non-facial sites seems to be effective with a favorable safety profile and potential benefits over topical agents that require a more prolonged course of treatment.

Lebwohl et al (2012) examined the safety and effectiveness of a
new topical field therapy for AKs, ingenol mebutate gel (0.015 % for face and scalp and 0.05 % for trunk and extremities). In 4 multi-center, randomized, double-blind studies, these investigators randomly assigned patients with AKs on the face or scalp or on the trunk or extremities to receive ingenol mebutate (n = 503) or placebo (n = 502), self-applied to a 25-cm(2) contiguous field once-daily for 3 consecutive days for lesions on the face or scalp or for 2 consecutive days for the trunk or extremities. Complete clearance (primary outcome) was assessed at 57 days, and local reactions were quantitatively measured. In a pooled analysis of the 2 trials involving the face and scalp, the rate of complete clearance was higher with ingenol mebutate than with placebo (42.2 % versus 3.7 %, p < 0.001). Local reactions peaked at day 4, with a mean maximum composite score of 9.1 on the local-skin-response scale (which ranges from 0 to 4 for 6 types of reaction, yielding a composite score of 0 to 24, with higher numbers indicating more severe reactions), rapidly decreased by day 8, and continued to decrease, approaching baseline scores by day 29. In a pooled analysis of the 2 trials involving the trunk and extremities, the rate of complete clearance was also higher with ingenol mebutate than with placebo (34.1 % versus 4.7 %, p < 0.001). Local skin reactions peaked between days 3 and 8 and declined rapidly, approaching baseline by day 29, with a mean maximum score of 6.8. Adverse events were generally mild-to-moderate in intensity and resolved without sequelae. The authors concluded that ingenol mebutate gel applied topically for 2 to 3 days is effective for field treatment of AKs.

Rosen et al (2012) noted that current topical agents for field therapy of AKs have single mechanisms of action and must be applied for weeks. Ingenol mebutate gel appears to have a dual mechanism of action: (i) rapid lesion necrosis and (ii) specific neutrophil-mediated, antibody-dependent cellular cytotoxicity. Because of the rapid destruction of AKs lesions after application of ingenol mebutate gel, treatment is necessary for only 2 or 3 days. The subsequent immune-mediated response targets any residual dysplastic epidermal cells. This dual mechanism of action should provide efficacy equivalent to that of current topical agents with a substantially shorter treatment period.
On January 25, 2012, the FDA ingenol mebutate gel (Picato; 0.015 %, 0.05 %) for the topical treatment of AKs. The gel is applied once-daily on the face and scalp for 3 consecutive days, and the 0.05 % gel is used once-daily on the trunk and extremities for 2 consecutive days (Spencer, 2012).

Nashan et al (2012) defined the state of art for destructive and topical treatment options for AKs based on randomized trials that meet criteria like greater than 30 patients in an intention-to-treat analysis, an easily reproducible study design with responses rated towards treatment as the major objective, measured as complete remission. Epidemiological data included grades and location of treated AKs, operational procedures, cryotherapy (CRYO), laser therapy, 3 % diclofenac in 2.5 % hyaluronic acid ([DCF/HA]), 2.5 %, 3.75 % and 5 % imiquimod (IMI), 0.5 % and 5 % 5-FU, PDT including ALA-patches.

In a Cochrane review, Gupta et al (2012) evaluated the effects of topical, oral, mechanical, and chemical interventions for AK. These investigators searched the following databases up to March 2011: the Cochrane Skin Group Specialised Register, CENTRAL in The Cochrane Library, MEDLINE (from 2005), EMBASE (from 2010), and LILACS (from 1982). They also searched trials registers, conference proceedings, and grey literature sources. Randomized controlled trials (RCTs) comparing the treatment of AKs with placebo, vehicle, or another active therapy. At least 2 authors independently abstracted data, which included adverse events, and assessed the quality of evidence. They performed meta-analysis to calculate a weighted treatment effect across trials, and we expressed the results as risk ratios (RR) and 95 % CI for dichotomous outcomes (e.g., participant complete clearance rates), and mean difference (MD) and 95 % CI for continuous outcomes (e.g., mean reduction in lesion counts). These researchers included 83 RCTs in this review, with a total of 10,036 participants. The RCTs covered 18 topical treatments, 1 oral treatment, 2 mechanical interventions, and 3 chemical interventions, including PDT. Most of the studies lacked descriptions of some methodological details, such as the generation of the randomization sequence or allocation concealment, and half of the studies had a high-risk of reporting
bias. Study comparison was difficult because of the multiple parameters used to report efficacy and safety outcomes, as well as statistical limitations. They found no data on the possible reduction of SCC. The primary outcome 'participant complete clearance' significantly favored four field-directed treatments compared to vehicle or placebo: DCF/HA (RR 2.46, 95 % CI: 1.66 to 3.66; 3 studies with 420 participants), 0.5 % 5-FU (RR 8.86, 95 % CI: 3.67 to 21.44; 3 studies with 522 participants), 5 % IMI (RR 7.70, 95 % CI: 4.63 to 12.79; 9 studies with 1,871 participants), and 0.025 % to 0.05 % ingenol mebutate (IMB) (RR 4.50, 95 % CI: 2.61 to 7.74; 2 studies with 456 participants). It also significantly favored the treatment of individual lesions with PDT compared to placebo-PDT with the following photo-sensitisers: ALA (blue light: RR 6.22, 95 % CI: 2.88 to 13.43; 1 study with 243 participants, ALA (red light: RR 5.94, 95 % CI: 3.35 to 10.54; 3 studies with 422 participants), and MAL (red light: RR 4.46, 95 % CI: 3.17 to 6.28; 5 studies with 482 participants). ALA-PDT was also significantly favored compared to cryotherapy (RR 1.31, 95 % CI: 1.05 to 1.64). The corresponding comparative risks in terms of number of participants completely cleared per 1,000 were as follows: 313 with 3 % diclofenac compared to 127 with 2.5 % hyaluronic acid; 136 with 0.5 % 5-FU compared to 15 with placebo; 371 with 5 % IMI compared to 48 with placebo; 331 with IMB compared to 73 with vehicle; 527 to 656 with ALA/MAL-PDT treatment compared to 89 to 147 for placebo-PDT; and 580 with ALA-PDT compared to 443 with CRYO. 5 % 5-FU efficacy was not compared to placebo, but it was comparable to 5 % IMI (RR 1.85, 95 % CI: 0.41 to 8.33). A significant number of participants withdrew because of adverse events with 144 participants affected out of 1,000 taking DCF/HA, compared to 40 participants affected out of 1,000 taking 2.5 % hyaluronic acid alone, and 56 participants affected out of 1,000 taking 5 % IMI compared to 21 participants affected out of 1,000 taking placebo. Based on investigator and participant evaluation, IMI treatment and PDT resulted in better cosmetic outcomes than CRYO and 5-FU. The authors concluded that for individual lesions, PDT appears more effective and has a better cosmetic outcome than CRYO. For field-directed treatments, diclofenac, 5-FU, IMI, and IMB had similar efficacy, but their associated adverse events and cosmetic outcomes are different. More direct comparisons between these treatments are needed to determine
Gupta and Paquet (2013) performed a network meta-analysis for 8 treatments [ALA-PDT, CRYO, DCF/HA, 0.5 % or 5.0 % 5-FU, 5 % IMI, 0.015 to 0.05 % IMB, MAL-PDT, and placebo/vehicle (including placebo-PDT)] to determine their relative efficacies. As part of a prior Cochrane systematic review, different databases and grey literature were searched for RCTs up to April 2012. The inclusion criteria were parallel-group studies with non-immunosuppressed participants: (i) reporting "participant complete clearance" and (ii) comparing at least 2 of the interventions. A total of 32 publications met the criteria and they included the following number of individual or pooled studies (n) and total number of participants (N) for the different interventions: 0.5 % 5-FU (n = 4, N = 169), 5.0 % 5-FU (n = 2, N = 44), ALA-PDT (n = 6, N = 739), CRYO (n = 2, N = 174), DCF/HA (n = 5, N = 299), IMI (n = 14, N = 1,411), IMB (n = 3, N = 560), MAL-PDT (n = 7, N = 557), and placebo (n = 32, N = 2520). Network analyses using a random effects Bayesian model were carried out with the software ADDIS v1.16.1. The interventions were ranked as followed based on calculated probabilities and odd ratios: 5-FU > ALA-PDT ~ IMI ~ IMB ~ MAL-PDT > CRYO > DCF> placebo. This efficacy ranking was obtained based on the current available data on "participant complete clearance" from RCTs and the analysis model used. However, several other factors should also be considered when prescribing a treatment for AK.

In a systematic review, Wat and colleagues (2014) provided evidence-based recommendations to guide physicians in the application of intense pulsed light (IPL) for the treatment of dermatologic disease. 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 was conducted. 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. Level 1 evidence was found for the use of IPL for the treatment of melasma, acne vulgaris, and telangiectasia. Level 2 evidence was found for the treatment of lentiginous
disease, rosacea, capillary malformations, AKs, and sebaceous gland hyperplasia. Level 3 or lower evidence was found 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.

Wat and Dytoc (2014) provided evidence-based clinical guidelines for the off-label use of topical vitamin D in the treatment of dermatologic disease. A systematic literature review was conducted via the MEDLINE, Embase, and CENTRAL databases for off-label uses of topical vitamin D analogs in the treatment of dermatologic disease other than psoriasis. The data were synthesized, and evidence-based recommendations were rendered according to the highest level of evidence available. A total of 165 articles met the inclusion criteria. A moderate to strong recommendation was given for the use of topical vitamin D in combination with corticosteroids and phototherapy in vitiligo and as monotherapy for various ichthyoses, morphea, pityriasis alba, prurigo nodularis, and polymorphous light eruption. There is evidence showing that topical vitamin D is ineffective in the treatment of AK, seborrheic keratosis, lichen planus, seborrheic dermatitis, alopecia areata, chemotherapy-induced alopecia, and hypertrophic scars. The authors concluded that topical vitamin D analogs have an important role in the off-label treatment of dermatologic disease, but higher quality studies are still needed.

Furthermore, an UpToDate review on “Treatment of actinic keratosis” (Jorizzo, 2014) does not mention the use of intense pulsed light and vitamin D as therapeutic options.

*Topical Piroxicam:*

In a proof of concept study, Babino et al (2016) conducted an 18-month exploratory open-label study on AK to evaluate the tolerability and effectiveness of a new topical formulation of piroxicam and sunscreen. Enrolled subjects applied a galenic
formulation of piroxicam 0.8 %, vehiculated in a topical product containing sun filters with high (50+) and broad spectrum (UVA) actions, twice-daily for 6 months. Subjects were then followed-up for additional 12 months. A total of 38 subjects with a total of 69 AK lesions participated in the trial. The primary outcome was the evolution of the Actinic Keratosis Erythema Scale Atrophy (A.K.E.S.A) score assessing erythema, scale, and atrophy of a target AK lesion. Secondary outcomes were the percentage of treated lesions with complete (100 %) or partial (greater than or equal to 75 %) clearance and the evaluation skin tolerability. A.K.E.S.A. mean (S.D.) score at baseline was 7.5 (1.2). After 6 months of treatment, A.K.E.S.A. score decreased to 0.9 (1.1), a -88 % reduction versus baseline. At the end of follow-up, A.K.E.S.A. score was 0.8 (1.2). A complete response was achieved in 38 of the 69 lesions (55 %, 95 % CI: 43 % to 66 %) and clearance was maintained 1 year post-treatment. A partial clearance was observed in 57 of 69 treated lesions (83 %, 95 % CI: 73 % to 91 %); adverse events were limited to mild local irritation. The authors concluded that their experience suggested that 6-month topical piroxicam 0.8 % was effective and well-tolerated in AK; clinical effectiveness was maintained 1 year post-treatment. The main drawback of this study was that it was an open-label, non-controlled trial. They stated that future controlled trials are needed to compare the tolerability and effectiveness of this topical piroxicam preparation with standard treatments in the management of AK.

Furthermore, an UpToDate review on “Treatment of actinic keratosis” (Jorizzo, 2016) does not mention piroxicam as a therapeutic option.

Topical Corticosteroid for Ingenol Mebutate-Induced Local Skin Responses:

Erlendsson et al (2016) noted that ingenol mebutate (IngMeb) is approved for treatment of AK and may cause unpredictable local skin responses (LSR). These investigators examined if IngMeb-induced LSR, pain, and pruritus could be alleviated with a topical glucocorticoid and, further, evaluated effectiveness, cosmetic outcome, and patient satisfaction in patients with severe photo-
damage. In this blinded, RCT, patients with multiple AK and field cancerization of the face or scalp were treated in 2 areas with IngMeb (0.015 %) daily for 3 days. After finalized IngMeb treatment, 1 area was randomized to receive topical clobetasol propionate (0.05 %) twice-daily for 4 days. Assessments included LSR (0 to 24; days 1, 4, 8, 15, 57), pain (0 to 10) and pruritus (0 to 3; days 1 to 15), AK clearance (days 15, 57), and cosmetic outcome (0 to 3; day 57). Clobetasol propionate application had no influence on LSR (p = 0.939), pain (p = 0.500), pruritus (p = 0.312), or AK cure rate (p = 0.991). Overall, IngMeb cleared 86 % of all AK lesions, exerting a therapeutic effect on all AK severity grades; cure rates were 88 %, 70 %, and 60 % for grade I, II, and III AK, respectively. Skin texture improved significantly in remedied areas (2.0 versus 1.0; p < 0.001); no hypo-pigmentation, hyper-pigmentation, or scarring were observed. The authors concluded that application of clobetasol propionate did not alleviate IngMeb-induced LSR after 3 days of IngMeb treatment.

**Lapatinib:**

In a phase II clinical trial, Jenni and colleagues (2016) examined the effects of lapatinib on cutaneous SCC (cSCC) scheduled for resection and in co-existing precursor lesions (AK and BD). These researchers initiated a prospective single-center, open-label, non-controlled clinical study with translational intentions to investigate changes in size and histopathological features in cSCC after a 14-day period of neoadjuvant lapatinib therapy at a dose of 1,500 mg/day prior to surgery, to quantify the impact on AK and BD in the same patient after 56 days and to evaluate the tolerability in patients with cSCC and precursor lesions. A total of 10 immunocompetent male patients were included with a mean age of 73 years (range of 59 to 87); 8 patients were treated with the study medication lapatinib 1,500 mg/day for a total duration of 56 days according to the protocol and were available for full analysis, whereas 2 patients had to discontinue treatment during the first 2 weeks because of adverse events (AEs -- diarrhea, pancreatitis). Tolerability was acceptable with only 1 related grade III AE. A reduction in tumor size of cSCC was documented in 2 of 8 evaluable patients after 14 days of treatment. The mean regression of captured precursor lesions was 30 % after 56 days.
of treatment and 36 % 28 days after therapy cessation. The authors concluded that short-term lapatinib resulted in a cSCC tumor reduction in 2 of 8 patients. In addition, there was a clinically documented reduction of AK in 7 of 8 patients encouraging larger clinical trials, especially in high-risk patients with cSCC such as organ transplant recipients.

### CPT Codes / HCPCS Codes / ICD-10 Codes

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":*

**ICD-10 codes will become effective as of October 1, 2015:**

**CPT codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>11300</td>
<td>Shaving of epidermal or dermal lesion, single lesion, trunk, arms or leg; lesion diameter 0.5 cm or less</td>
</tr>
<tr>
<td>11301</td>
<td>lesion diameter 0.6 to 1.0 cm</td>
</tr>
<tr>
<td>11302</td>
<td>lesion diameter 1.1 to 2.0 cm</td>
</tr>
<tr>
<td>11303</td>
<td>lesion diameter over 2.0 cm</td>
</tr>
<tr>
<td>11305</td>
<td>Shaving of epidermal or dermal lesion, single lesion, scalp, neck, hands, feet, genitalia; lesion diameter 0.5 cm or less</td>
</tr>
<tr>
<td>11306</td>
<td>lesion diameter 0.6 to 1.0 cm</td>
</tr>
<tr>
<td>11307</td>
<td>lesion diameter 1.1 to 2.0 cm</td>
</tr>
<tr>
<td>11308</td>
<td>lesion diameter over 2.0 cm</td>
</tr>
<tr>
<td>11310</td>
<td>Shaving of epidermal or dermal lesion, single lesion, face, ears, eyelids, nose, lips, mucous membrane; lesion diameter 0.5 cm or less</td>
</tr>
<tr>
<td>11311</td>
<td>lesion diameter 0.6 to 1.0 cm</td>
</tr>
<tr>
<td>11312</td>
<td>lesion diameter 1.1 to 2.0 cm</td>
</tr>
<tr>
<td>11313</td>
<td>lesion diameter over 2.0 cm</td>
</tr>
<tr>
<td>11400</td>
<td>Excision, benign lesion including margins, except skin tag (unless listed elsewhere), trunk, arms or legs; excised diameter 0.5 cm or less</td>
</tr>
<tr>
<td>11401</td>
<td>excised diameter 0.6 to 1.0 cm</td>
</tr>
<tr>
<td>11402</td>
<td>excised diameter 1.1 to 2.0 cm</td>
</tr>
<tr>
<td>11403</td>
<td>excised diameter 2.1 to 3.0 cm</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
</tr>
<tr>
<td>11404</td>
<td>excised diameter 3.1 to 4.0 cm</td>
</tr>
<tr>
<td>11406</td>
<td>excised diameter over 4.0 cm</td>
</tr>
<tr>
<td>11420</td>
<td>Excision, benign lesion including margins, except skin tag (unless listed elsewhere), scalp, neck, hands, feet, genitalia; excised diameter 0.5 cm or less</td>
</tr>
<tr>
<td>11421</td>
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</tr>
<tr>
<td>11422</td>
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<tr>
<td>11423</td>
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<tr>
<td>11426</td>
<td>excised diameter over 4.0 cm</td>
</tr>
<tr>
<td>11440</td>
<td>Excision, other benign lesion including margins, except skin tag (unless listed elsewhere), face, ears, eyelids, nose, lips, mucous membrane; excised diameter 0.5 cm or less</td>
</tr>
<tr>
<td>11441</td>
<td>excised diameter 0.6 to 1.0 cm</td>
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<tr>
<td>11442</td>
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<tr>
<td>11443</td>
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<td>11446</td>
<td>excised diameter over 4.0 cm</td>
</tr>
<tr>
<td>15780</td>
<td>Dermabrasion; total face (e.g., for acne scarring, fine wrinkling, rhytids, general keratosis)</td>
</tr>
<tr>
<td>15781</td>
<td>segmental, face</td>
</tr>
<tr>
<td>15782</td>
<td>regional other than face</td>
</tr>
<tr>
<td>15783</td>
<td>superficial, any site (e.g., tattoo removal)</td>
</tr>
<tr>
<td>15786</td>
<td>Abrasion; single lesion (e.g., keratosis, scar)</td>
</tr>
<tr>
<td>+ 15787</td>
<td>each additional four lesions or less (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>15789</td>
<td>Chemical peel, facial; dermal</td>
</tr>
<tr>
<td>15793</td>
<td>Chemical peel, nonfacial; dermal</td>
</tr>
<tr>
<td>17000</td>
<td>Destruction (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), premalignant lesions (e.g., actinic keratoses); first lesion</td>
</tr>
<tr>
<td>+ 17003</td>
<td>second through 14 lesions, each (List separately in addition to code for first lesion)</td>
</tr>
</tbody>
</table>
Destruction (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), pre-malignant lesions (e.g., actinic keratoses); 15 or more lesions

Photodynamic therapy by external application of light to destroy pre-malignant and/or malignant lesions of the skin and adjacent mucosa (e.g., lip) by activation of photosensitive drug(s), each phototherapy exposure session

**HCPCS codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J7308</td>
<td>Aminolevulinic acid HCL for topical administration, 20%, single unit dosage form (354 mg)</td>
</tr>
<tr>
<td>J7309</td>
<td>Methyl aminolevulinate (MAL) for topical administration, 16.8%, 1 gram</td>
</tr>
</tbody>
</table>

**ICD-10 codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L57.0</td>
<td>Actinic keratosis</td>
</tr>
</tbody>
</table>

*Intense pulsed light, topical calcipotriol, topical vitamin D and analogs:*

No specific code

The above policy is based on the following references:

3. Center for Medicare and Medicaid Services (CMS). Actinic...


16. English D, Armstrong B, Kricker A. Demographic


27 of 34

40. Pearlman D. Weekly pulse dosing: Effective and


52. Gupta AK, Weiss JS, Jorizzo JL. 5-fluorouracil 0.5% cream for multiple actinic or solar keratoses of the face and anterior scalp. Skin Therapy Lett. 2001;6(9):1-4.


63. National Institute for Health and Clinical Excellence (NICE). Photodynamic therapy for non-melanoma skin tumours (including premalignant and primary non-metastatic skin


82. Anderson L, Schmieder GJ, Werschler WP, et al. Randomized, double-blind, double-dummy, vehicle-controlled study of ingenol mebutate gel 0.025% and 0.05% for actinic keratosis. J Am Acad Dermatol.


93. Vegter S, Tolley K. A network meta-analysis of the relative


Amendment to
Aetna Clinical Policy Bulletin Number: 0567 Actinic Keratoses Treatments

Pennsylvania Medicaid uses Aetna Better Health Pharmacy Guidelines for most medications. Please see https://www.aetnabetterhealth.com/pennsylvania/providers/pharmacy.