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# Drug Class Review: Actinic Keratosis

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**Purpose for Class Review:**
Evaluate evidence for treatment of actinic keratosis (AK), which is not funded according to the 2025 Health Evidence Review Commission (HERC) List of Prioritized Health Services.[1] Develop prior authorization (PA) criteria to provide a medical necessity pathway to coverage for AK in people with the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit.

**Plain Language Summary:**
- Actinic keratosis is a skin condition caused by sun damage. Because sun damage builds up over time, actinic keratosis is more common in older people. It appears as scaly, rough, or bumpy spots on the skin. Actinic keratosis is most common in people who have fair skin, have blonde or red hair, have freckles, or sunburn easily.
- Anyone can get actinic keratosis, but it is more common in males than in females. Common places for actinic keratosis to appear include: the scalp in people who are bald or have thinning hair, face, neck, hands, and arms.
- Without treatment, actinic keratosis can grow, spread, and may turn into skin cancer. Doctors can freeze the actinic keratosis spots off with liquid nitrogen or use a special tool to burn off actinic keratosis spots. Doctors can also prescribe a medicated cream or gel to apply to actinic keratosis areas. The 3 most common treatments are 5-fluorouracil cream, imiquimod cream, and diclofenac gel. To be effective, these medicines must be applied to the actinic keratosis spots once or twice every day over several weeks. The most common side effects from these medicines are redness, tenderness, itching, burning, and skin irritation in areas where the medicine is applied.
- Providers must explain to the Oregon Health Authority why someone needs medicine for actinic keratosis before the Oregon Health Plan will pay for it. This process is called prior authorization.

**Research Questions:**
1. What is the evidence for the efficacy of self-administered topical 5-fluorouracil, imiquimod, diclofenac, and tirbanibulin and provider-administered aminolaevulinic acid in treating AK?
2. What is the comparative safety of topical 5-fluorouracil, imiquimod, diclofenac, tirbanibulin and aminolaevulinic acid in treating AK?
3. Are there specific subpopulations based on age, ethnicity, comorbidities, disease duration or severity for which one therapeutic agent is better tolerated or more effective than other available topical treatments when used to manage AK?

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**Conclusions:**

- Three systematic reviews[2-4] and 2 clinical guidelines[5,6] provide evidence for the safety and efficacy of topical drugs to treat AK. There is evidence to support the efficacy topical drugs for AK but insufficient evidence to directly compare treatments.[5,6] A summary of comparative randomized controlled trials (RCTs) is presented in **Table 2**. Overall, these studies are at high-risk of bias due to open-label study design and enrollment of small patient populations.
- A 2009 systematic review evaluated RCTs which compared the treatment of AK with 5% 5-fluorouracil cream compared to other treatments including imiquimod cream, cryotherapy, diclofenac 3% gel, facial resurfacing, photodynamic therapy (PDT), 5% 5-fluorouracil cream augmented with tretinoin, and 0.5% 5-fluorouracil cream.[2] This review provides low-quality evidence to indicate that about 50% of patients using 5% 5-fluorouracil cream for the treatment of AK lesions can expect complete clearance; overall, an 80% reduction in lesion count can be expected; and a 90% reduction in total lesion count is likely.[2] The duration of follow-up varied between studies; from 3 to 12 weeks.[2] Although few patients stop treatment as a result of adverse events, up to one-half may not be able to complete the full treatment course.[2] However, the quality of the studies providing this evidence is poor.[2] Evidence on alternative treatments studied head-to-head with topical 5-fluorouracil is limited.[2]
- A 2012 Cochrane review assessed the effects of topical, oral, mechanical, and chemical interventions for management of AK.[3] 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.[3] Low-quality evidence showed that the primary outcome, complete clearance of AK lesions, equally favored 4 topical treatments compared to vehicle or placebo: 3% diclofenac (risk ration [RR] 2.46, 95% confidence interval [CI] 1.66 to 3.66; 3 RCTs; n=420), 0.5% 5-fluorouracil (RR 8.86, 95% CI: 3.67 to 21.44; 3 RCTs; n=522), 5% imiquimod (RR 7.70, 95% CI 4.63 to 12.79; 9 RCTs; n=1871), and 0.025% to 0.05% ingenol gel (RR 4.50, 95% CI 2.61 to 7.74; 2 RCTs; n= 456).[3] Of note, ingenol gel is on longer commercially available in the United States. One RCT compared 0.5% and 5% 5-fluorouracil formulations and found comparable efficacy and safety between both agents.[3]
- A 2022 systematic review compared different therapeutic options for managing AK.[4] The treatments included imiquimod, 5-fluorouracil, diclofenac, PDT with aminolevulinic acid (ALA-PDT), and PDT with methyl-aminolevulinate (PDT-MAL).[4] The included studies were of low to moderate risk of bias.[4] Twenty-three studies investigated treatment with imiquimod as monotherapy, while two studies investigated imiquimod plus cryotherapy and one used imiquimod plus PDT-MAL.[4] Overall, the percent reduction in AKs was 67.5 ± 19.6% at 1–3 months, 64.0 ± 13.0% at 3–6 months and 68.0 ± 1.6% at 6–12 months after treatment with imiquimod.[4] Thirteen studies compared topical 5-fluorouracil as monotherapy, and several others investigated 5-fluorouracil in combination with another agent (salicylic acid, calcipotriol, cryotherapy, PDT-MAL, and PDT-ALA).[4] Overall, after treatment with 5-fluorouracil monotherapy, the number of AKs was reduced by 80.1% at 1–3 months, and 67.4% at 3–6 months.[4] Treatment success is ≥ 75% clearance of AK lesions. Four studies investigated the effectiveness of twice daily application of diclofenac sodium 3.0% gel in the treatment of AKs.[4] Percent clearance of AKs at 1–3 months post diclofenac treatment was 36.3 ± 9.5%, which was lower compared to 5-fluorouracil and imiquimod therapies.[4]
- In 2021, the American Academy of Dermatology (AAD) published guidelines to assist in clinical decision-making for the management of AK.[5] Topical agents, cryosurgery, and PDT are all recommended in the guidance.[5] Choice of treatment is based on a number of factors, including the site of the AKs, whether AKs are solitary, multiple, or within an affected field, and patient preferences and tolerability.[5] Specific recommendations for topical therapies and quality of evidence are as follows:
    - The AAD recommends field treatment with 5-fluorouracil cream or imiquimod cream (Strong Recommendation; Moderate-Quality Evidence).[5]
    - The AAD conditionally recommends the use of diclofenac gel (Low-Quality Evidence).[5]
    - The AAD conditionally recommends red light PDT with aminolevulinic acid over cryosurgery alone (Low-Quality Evidence).[5]
    - AAD conditionally recommends combination treatment cryosurgery with 5-fluorouracil or imiquimod over cryosurgery alone (based on Moderate- and Low-Quality Evidence, respectively).[5]

- In 2022 the AAD published a focused guideline update on management of AK.[6] The purpose of the focused update was to incorporate recently published evidence on the use of topical tirbanibulin to treat AK.[6] Tirbanibulin was approved for the topical, field-directed treatment of AK on the scalp or face by the Food and Drug Administration (FDA) in December 2020.[6] Two phase 3 trials were identified and analysis of this evidence resulted in one recommendation.[6] Although the AAD work group recognized that tirbanibulin cost may be prohibitive without adequate insurance coverage and other strongly recommended treatments for AK may be available for lower cost, they concluded that the use of tirbanibulin is likely acceptable to patients and providers and feasible to implement especially considering the abbreviated duration of tirbanibulin treatment compared with the duration of other available topically applied agents for the management of AK.[6]
    - AAD recommends field treatment with topical tirbanibulin (Strong Recommendation; High-Quality Evidence).[6]
- There is insufficient evidence to show that there are subgroups of patients based on demographics (based on age, ethnicity, comorbidities, disease duration or severity), for which one topical treatment for AK is more effective or associated with fewer adverse events.

**Recommendations:**

- Based on review of evidence, designate at least one topical formulation of 5-FU and imiquimod which are indicated for treatment of basal cell carcinoma and genital warts, as preferred on the preferred drug list (PDL).
- Maintain diclofenac 3% gel as non-preferred and add tirbanibulin 1% ointment and aminolevulinic acid gel as non-preferred agents to the PDL and create a PDL class called “Topical Agents for Actinic Keratosis”.
- Implement PA criteria for topical agents used in AK to provide a pathway to coverage for AK in people with the EPSDT benefit.
- After executive session, make 5% 5-FU cream and 5% imiquimod cream preferred and other products non-preferred.

**Background:**

Actinic keratoses are rough scaly patches that arise on skin that is chronically exposed to ultraviolet (UV) radiation.[5] Patches range from pink, red, or brown and may present with tenderness, burning or itching, although most lesions are asymptomatic.[3] Actinic keratosis is the most frequently diagnosed premalignant skin disease in fair-skinned, Caucasian individuals.[7] Actinic keratosis is usually the initial lesion in a disease continuum that progresses to invasive, squamous cell carcinoma.[7] The real progression rate toward an invasive, squamous cell carcinoma, which has a metastatic risk of 0.5% to 3.3%, is unknown, varying from 0.025% to 20%.[8] The risk of progression in squamous cell carcinoma increases in patients with multiple AKs (more than five); for example it is 4-fold higher in patients with 6-20 AKs and 11-fold higher in those with more than 20 lesions.[9] However, this inability to predict which AK will transform into an invasive squamous cell carcinoma indicates that treatment of each visible AK is advisable.[8]

With a prevalence of 37.5% among white people 50 years of age or older, AK is one of the most frequent reasons for patients to visit a dermatologist.[7] Individual patients may have single or multiple lesions, but the average number of AKs per person is 6 to 8 when the patient first visits the dermatologist.[10] Actinic keratosis is more prevalent in males.[10] A meta-analysis of 60 observational studies reported an overall world-wide prevalence of AK of 14%, with an estimated incidence rate of 1.9 per 1000 person-years.[11] The highest prevalence of AK has been recorded in Australia, where it affects 40%–60% of white individuals aged ≥ 40 years.[12] Reported rates are lower in the United States, where studies have reported prevalence rates of 16% and 25%.[12] Prevalence may be as high as 55% in people 65-74 years of age with extensive sun exposure.[12] Increasing exposure to UV light during recreational pursuits and the decrease in the protective ozone layer are gradually increasing the incidence of AKs, even in individuals not exposed to sunlight through their occupations.[10]

Actinic keratoses are usually seen as multiple lesions in sun-exposed areas including the face, hands and forearms, neck, shoulders, and scalp in people with premature baldness.[10] Individuals who live in areas with high exposure to UV radiation with fair skin, particularly those with freckles, light-colored eyes (blue or

green), and blonde or red hair, are most at risk.[10] Occasionally, AKs may also result from exposure to X-rays and to repeated UV light from artificial sources.[10] Immunocompromised patients are also known to be at increased risk of AK, including organ transplant recipients taking immunosuppressive medications.[12] In patients with diffuse signs of skin photocarcinogenesis, AKs may be multiple and may be difficult to manage therapeutically, especially in people who, for professional or lifestyle reasons, are chronically photoexposed.[10] In these cases, lesions are usually widespread and tend to recur.[10]

Diagnosis of AK is based upon provider visual inspection and examination. A skin biopsy may be performed to exclude malignancy if any suspicious features (i.e., large size, rapid growth, ulceration, bleeding) are present. There are several treatments that are highly effective for AK, and cure rates are high.[10] Sun protection is recommended for all patients with AK including broad spectrum sunscreen, avoidance of high peak sun hours, and sun protective clothing. Nonpharmacologic treatments include curettage, liquid nitrogen cryosurgery, dermabrasion, PDT, and radiotherapy.[10] Self-administered topical medical treatments include 5-fluorouracil cream, imiquimod cream, diclofenac 3% gel, and tirbanibulin 1% ointment (see **Table 1**). The topical photosensitizer, aminolaevulinic acid, is applied prior to PDT and must be administered by a health care provider.[13] Cryosurgery (liquid nitrogen) should be considered the treatment of choice for patients with only a few lesions (1-6 lesions) or isolated lesions, or for patients who are noncompliant with topical agents.[9] Complete response rate for individual lesions to cryotherapy is around 98%, and the result depends on the duration of the freezing.[9]

Treatment can be directed either at individual lesions or to larger areas of the skin where several visible and less visible lesions occur (field-directed treatment).[14] The use of topical agents to promote reversal of neoplastic transformation in surrounding tissue may provide a field effect on subclinical disease and may contribute to the prevention of additional lesions in adjacent areas.[8] Clearance rates with topical medications are dependent upon patient adherence.[9] Duration of therapy varies, depending on the topical product that is prescribed (see **Table 1**). Adverse reactions including skin swelling, redness, burning and itching may make it difficult for patients to adhere to the prescribed topical regimen. Outcomes used to evaluate AK treatment efficacy include treatment success (≥ 75% reduction in the number of AK lesions from baseline), mean reduction in the number of AK lesions, change in lesion area, and proportion of patients with complete (100%) AK lesion clearance.[3] Frequency of adverse events, tolerability and impact on patient satisfaction have also been evaluated in comparative studies.[3]

In a study of Medicare claims data, 81.9% of people with a diagnosis of AK received treatment.[15] The most common treatment type was non-pharmacologic curettage or cryosurgery.[15] Only 1.5% of people had claims billed for PDT and 2.9% had claims for topical medications.[15] In the Oregon Medicaid fee-for-service (FFS) population, 1,302 people had a diagnosis of AK from 4/1/2023 to 3/31/2024. Because 5-fluorouracil and imiquimod creams have funded FDA-indications for treatment of basal cell carcinoma and genital warts, there is utilization of these products in the Oregon Medicaid population. In the fourth quarter of 2024 (September to December) there were 11 claims for imiquimod cream and no utilization of 5-fluorouracil cream in the Oregon Health Plan (OHP) fee-for-service (FFS) population.

A summary of relevant drug information is available in **Appendix 2**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings, and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

**Table 1. Topical Drugs for Treatment of Actinic Keratosis and Other Indications**

| Generic Drug Name (BRAND NAME) | Strength/ Formulation | FDA-Approved Indications | Patient or Health Care Provider Administered | AK Dosing Parameters |
|---|---|---|---|---|
| 5-fluorouracil | 0.5% cream | • Actinic Keratosis in adults | Patient | 0.5% and 4% cream: Apply once daily to lesions for 4 weeks. |

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| (CARAC, EFUDEX)[16] | 4% cream<br>5% cream<br>2% solution<br>5% solution | • Basal Cell Carcinoma in adults (5% cream and solution only) | | 5% cream, 2% solution and 5% solution: Apply twice daily to lesions for 2-4 weeks. |
| Imiquimod (ZYCLARA)[17] | 2.5% cream<br>3.75% cream<br>5% cream | • Actinic Keratosis in adults<br>• Basal Cell Carcinoma in adults (5% cream only)<br>• Genital and Perianal Warts approved in children and adolescents ≥ 12 years (3.75% and 5% cream only) | Patient | 2.5% and 3.75% cream: Apply once daily at bedtime for 2-week cycles (2 weeks on treatment, 2 weeks off, 2 weeks on) over 6 weeks. May repeat cycle up to 2 times. Leave on for 8 hours, then remove with soap and water.<br><br>5% cream: Apply to lesions to an involved area ≤ 25 $cm^2$ twice weekly for 16 weeks. Leave on for 8 hours, then remove with soap and water. |
| Diclofenac Sodium (SOLARAZE)[18] | 3% gel | • Actinic Keratosis in adults | Patient | Apply to lesions twice daily for 60-90 days. |
| Tirbanibulin (KLISYRI)[19] | 1% ointment | • Actinic Keratosis in adults | Patient | Apply once daily up to 100 $cm^2$ area for 5 days. |
| Aminolevulinic acid (AMELUZ, LEVULAN)[13] | 10% gel (red and blue light)<br>20% solution (red light) | • Actinic Keratosis prior to PDT in adults | Health Care Provider | Apply prior to blue-light or red-light PDT. May treat lesions that have not completely resolved 3 months after the initial treatment. |
| Abbreviations: FDA = Food and Drug Administration; PDT = photodynamic therapy | | | | |

**Methods:**

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Canada's Drug Agency (CDA-AMA), Scottish Intercollegiate Guidelines Network (SIGN), and Oregon Mental Health Clinical Advisory Group (MHCAG) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

**Systematic Reviews:**

*Effectiveness Of 5-Fluorouracil Treatment for Actinic Keratosis*

A 2009 systematic review evaluated RCTs which compared the treatment of AK with 5-fluorouracil versus placebo or another treatment.[2] Literature was searched through January 2008 and 13 RCTs met inclusion critiera.[2] Eight studies compared 5-fluorouracil 5% cream with other treatments including imiquimod cream, cryotherapy, diclofenac sodium 3% gel, facial resurfacing, PDT, 5-fluorouracil 5% cream augmented with tretinoin, and 5-fluorouracil 0.5% cream.[2] One study compared different dosing regimens of 5-fluorouracil 5% cream (twice daily for 3 weeks versus twice daily for 1 day per week for 12 weeks).[2] Three studies compared 5-fluorouracil 0.5% cream with placebo, and one study compared 5-fluorouracil 0.5% with aminolevulinic acid-PDT, activated with either blue light or pulsed laser light.[2]

Several different outcome measures were used to determine the efficacy of treatment, including absolute and proportional changes in lesion counts per patient, changes in total lesion count, change in lesion area, tolerability, and patient preferences.[2] Nine studies reported the proportion of patients achieving 100% clinical clearance of the lesions.[2] The duration of follow-up varied between studies.[2] As the complete healing of lesions treated with 5-fluorouracil 5% cream may not be evident for up to 2 months following the cessation of active treatment, 8 weeks post-treatment was considered to be the minimum time period to evaluate short-term benefit.[2] The assessment in 7 studies was short, with outcomes being assessed 4 weeks after the cessation of treatment.[2] Three studies assessed outcomes at around 8 weeks, and long-term assessment data were reported in 4 studies, at 6 months and 12 months post-treatment.[2]

The majority of studies were poorly reported, with only 5 studies providing any detail about randomization methods and only 2 of these adequately describing allocation concealment.[2] Only one study was double-blind, and four were single-blind (outcome assessment only).[2] Although most studies claimed to undertake intention-to-treat analysis, only 5 included all randomized patients in the analysis.[2] Insufficient baseline data were provided in 2 studies, preventing the comparison of treatment groups.[2] Eight studies did not report fully on their pre-specified outcomes; commonly, studies reported percentages without giving either the denominator or numerator, or did not provide standard deviations or ranges for the data when reporting means or medians.[2] In summary, most of the included studies were at moderate to high risk of bias, and therefore the results should be interpreted with caution and few, if any, generalizations could be made.[2]

Treatment with 5-fluorouracil 5% cream resulted in an average reduction of 79.5% (range, 59.2%–100%) in the mean number of lesions, from an average of 24.0 at baseline (range, 10.3–61.8) to 4.0 (range, 0–8.8) at follow-up.[2] In comparison, treatment with 5-fluorouracil 0.5% cream resulted in an average reduction of 86.1% (range, 77.9%–91.7%) in the mean number of lesions, from an average of 13.9 lesions at baseline to 3.9 lesions at follow-up.[2] The average number of lesions was reduced by 94.5% (range, 92.9–96.6%) when treated by laser resurfacing, and 28.0% (range, 21.6–34.4%) when treated with placebo.[2] Clearance of. $\geq$ 75% of lesions from baseline is considered treatment success.[2]

Of the 8 studies that reported a reduction in the mean or median number of lesions per patient, only 3 provided sufficient data to enable assessment of the weighted mean difference (WMD) between agents.[2] There was no statistically significant difference in the WMD of 5-fluorouracil 5% cream compared with 5-fluorouracil 5% augmented with tretinoin (WMD, –0.8; 95% CI, 0.8 to 2.4), resurfacing with carbon dioxide laser compared to placebo (WMD, –3.3; 95% CI, –9.9 to 3.3) or 30% trichloroacetic acid peel compared to placebo (WMD, –1.1, 95% CI –6.0 to 3.8).[2] Treatment with 5-fluorouracil 0.5% cream for 1 week resulted in a statistically significant greater reduction in the mean number of lesions per patient than did placebo (WMD, 4.8; 95% CI, 3.1 to 6.5).[2]

Treatment with 5-fluorouracil 5% cream cleared 93.8% (606/646) of lesions at 24 weeks, and 98.0% (124/126) of lesions at 4 weeks, compared with 65.9% (323/490) of lesions cleared with imiquimod and 89% (111/125) of lesions cleared with diclofenac gel.[2] Across the studies, an average of 49.0% (range, 0%–96%) of patients treated with 5-fluorouracil 5% cream and 34.8% (range, 14.9–57.8%) of patients treated with 5-fluorouracil 0.5% cream were reported as achieving clearance of 100% of lesions.[2] In comparison, no patients reported 100% clearance treated with acid peel or aminolevulinic acid-PDT activated with red light.[2] One hundred percent clearance of AK lesions was reported In 4.3% of patients using placebo, in 37.5% of patients treated with carbon dioxide laser resurfacing, in 50% of patients treated with aminolevulinic acid-PDT activated by blue light, in 54.5% of patients treated with imiquimod, and in 68% of patients treated with cryotherapy.[2]

Treatment with 5-fluorouracil is associated with application site reactions, and most studies assessed the severity of these reactions, although the methods varied between studies making data synthesis difficult.[2] Cosmetic outcome was assessed in only one study, and at 3 months there was no difference between the groups treated with 5-fluorouracil 5% cream, cryotherapy, or imiquimod cream; however, at 12 months, 4% of patients treated with 5-fluorouracil 5% or cryotherapy and 81% of patients treated with imiquimod showed a positive cosmetic outcome (based on scarring, atrophy, and induration).[2] This is a very large difference, but it is unclear whether investigators were blind to the treatment groups, introducing a high risk of bias in these results.[2]

Only two studies assessed patient preferences for treatment.[2] In the study comparing 0.5% and 5% 5-fluorouracil, 85% (17/20) of patients preferred 5-fluorouracil 0.5% with the remaining 3 patients preferring 5-fluorouracil 5%.[2] The study comparing diclofenac gel and 5-fluorouracil 5% reported that 79% of patients were very or completely satisfied with diclofenac, compared with 68% with this level of satisfaction with 5-fluorouracil 5% cream.[2] However, the patients were not blind to the treatment in either of these studies, limiting the validity of this assessment.[2] Only 3 studies reported the number of patients withdrawing from the study as a result of adverse events: 1.9% (4/213) of patients using 5-fluorouracil 0.5% and 5.9% (1/17) of patients using 5-fluorouracil 5% cream.[2]

In summary, this systematic review provides low-quality evidence to indicate that about 50% of patients using 5-fluorouracil 5% for the treatment of AK lesions can expect complete clearance; overall, an 80% reduction in lesion count can be expected; and a 90% reduction in total lesion count is likely.[2] Although few patients stop treatment as a result of adverse events, up to one-half may not be able to complete the full treatment course.[2] Evidence on alternative treatments studied head-to-head with 5-fluorouracil is limited.[2]

*Cochrane: Interventions For Actinic Keratoses*

A 2012 Cochrane review assessed the effects of topical, oral, mechanical, and chemical interventions for AK.[3] Literature was searched through March 2011 for RCTs that compared treatment of AK with either placebo, vehicle, or active therapy.[3] Eighty-three RCTs met inclusion criteria, with a total of 10,036 participants.[3] The RCTs covered 18 topical treatments, 1 oral treatment, 2 mechanical interventions, and 3 chemical interventions, including PDT.[3] Sixty RCTs investigated topical treatments applied to a skin area by the participants: adapalene gel, aretinoid methyl sulfone, betulin-based oleogel, calcipotriol, colchicine, diclofenac, 2-(difluoromethyl)-dl-ornithine (DFMO), 5-fluorouracil, imiquimod, ingenol mebutate, isotretinoin, masoprocol, nicotinamide, resiquimod, sunscreen, vitamin E, and tretinoin.[14] One RCT evaluated oral etretinate.[3] Clinical staff administered 2 mechanical treatments (carbon dioxide and laser resurfacing) on a skin area (2 RCTs), and they administered 3 chemical treatments: cryotherapy on individual lesions, PDT on individual lesions or a skin area, and trichloroacetic acid peel on a skin area (37 RCTs).[3] Lesions were located on the head only (i.e. face, forehead, temples, cheeks, scalp, ear, lips, and neck) in 59 RCTs, on only non-head locations (i.e., upper and lower extremities, legs, arms, elbow, forearms, hands, dorsa of hands, shoulder, décolleté, chest, trunk, and back) in 9 RCTs and on both head and non-head locations in 22 RCTs.[3]

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.[3] Study comparison was difficult because of the multiple parameters used to report efficacy and safety outcomes, as well as statistical limitations.[3] No data was identified on the possible reduction of squamous cell carcinoma.[3]

The primary outcome, complete clearance of AK lesions, favored 4 field-directed treatments compared to vehicle or placebo: 3% diclofenac (RR 2.46, 95% CI 1.66 to 3.66; 3 RCTs; n=420), 0.5% 5-fluorouracil (RR 8.86, 95% CI: 3.67 to 21.44; 3 RCTs; n=522), 5% imiquimod (RR 7.70, 95% CI 4.63 to 12.79; 9 RCTs; n=1871), and 0.025% to 0.05% ingenol gel (RR 4.50, 95% CI 2.61 to 7.74; 2 RCTs; n= 456).[3] Of note, ingenol gel is on longer commercially available in the United States. The medication was withdrawn by LEO Pharma in 2020 from worldwide markets due to an increased risk of squamous cell carcinoma and other nonmelanoma skin malignancies associated with the drug's use when compared to other treatment options of AK.[14] One RCT compared 0.5% and 5% 5-fluorouracil and found comparable efficacy and safety between both agents.[3]

Lesion clearance was also favored with PDT compared to placebo-PDT with the following photosensitizers: aminolevulinic acid (blue light: RR 6.22, 95% CI 2.88 to 13.43; 1 study with 243 participants, aminolevulinic acid (red light: RR 5.94, 95% CI 3.35 to 10.54; 3 studies with 422 participants).[3] Aminolevulinic acid-PDT was also favored compared to cryotherapy (RR 1.31, 95% CI 1.05 to 1.64).[3]

A significant number of participants withdrew because of adverse events with 144 participants affected out of 1000 taking 3% diclofenac in 2.5% hyaluronic acid; compared to 40 participants affected out of 1000 taking 2.5% hyaluronic acid alone; and 56 participants affected out of 1000 taking 5% imiquimod compared to 21 participants affected out of 1000 taking placebo.[3] In general, 5-fluorouracil treatment did not lead to withdrawal because of adverse events; however, substantial skin irritation was associated with this intervention.[3]

The authors concluded that for individual lesions, photodynamic therapy appears more effective in lesion clearance than cryotherapy (low-quality evidence).[3] For field directed therapy, topical diclofenac, 5-fluorouracil, and imiquimod, low-quality evidence shows topical agents had similar efficacy in complete clearance of AK lesions, but their associated adverse events were different.[3] More comparative evidence is needed to determine the best therapeutic approach in managing AK.[3]

*Treatment Of Actinic Keratosis*

A 2022 systematic review compared different therapeutic options for managing AK.[4] Literature was searched through December 2019 and 80 RCTs (n=6,748) met inclusion criteria.[4] The most commonly studied modalities were imiquimod (n=23 studies), 5-fluorouracil (n=13), ALA-PDT (n=19 studies), and PDT-MAL (n=17 studies).[4] Among all included studies, the proportion of male to female patients was 3.5:1, and the mean age was 69 years.[4] The included studies were of low to moderate risk of bias.[4] Homogeneity in the primary outcome by $I^2$ was > 50% and, therefore, meta-analysis was not possible.[4]

The percent clearance of AKs after treatment with all types of PDT was 67.0 ± 16.2% at 1–3 months, 76.1 ± 10.8% at 3–6 months, and 59.8 ± 9.7% at 6–12 months.[4] Subgroup analysis revealed that PDT-ALA had mean lesion reduction rates of 66.2 ± 17.0% at 1–3 months, 75.2 ± 9.9% at 3–6 months, and 64.2 ± 6.2% at 6–12 months; whereas PDT-MAL had lesion reduction of 72.2 ± 10.6%, 77.7 ± 12.8%, and 51.1% at 1–3, 3–6, and 6–12 months, respectively. PDT-ALA and PDT-MAL were not significantly different at 1–3 months and 3–6 months, but PDT-ALA was significantly more effective than PDT-MAL at 1 year.[4] All participants who were treated with PDT (100%) experienced erythema.[4] A fair percent (47.6%) experienced severe pain, which was higher than with other treatment modalities.

Twenty-three studies investigated treatment with imiquimod as monotherapy, while two studies investigated imiquimod plus cryotherapy and one used imiquimod plus PDT-MAL.[4] The most common application methods were 3 applications of 5% imiquimod per week for 4–6 weeks, or daily application of 3.75% imiquimod alternating 2 weeks on and 2 weeks off. Overall, the percent reduction in AKs was 67.5 ± 19.6% at 1–3 months, 64.0 ± 13.0% at 3–6 months and 68.0 ± 1.6% at 6–12 months after treatment with imiquimod. Compared to other treatments included in this analysis, imiquimod was non-inferior to any other treatment and superior only to diclofenac.[4] Commonly reported side effects included erythema (53.3%), stinging/itching (41.6%), and crusting (33.5%).[4]

Thirteen studies compared topical 5-fluorouracil as monotherapy, and several others investigated 5-fluorouracil in combination with another agent (salicylic acid, calcipotriol, cryotherapy, PDT-MAL, and PDT-ALA).[4] Most studies of 5-fluorouracil monotherapy implemented the standard twice daily application of 5% 5-fluorouracil for 3 weeks, whereas shorter application durations were implemented in combination therapy studies.[4] Two studies investigated lower strength (0.5%) 5-fluorouracil, while the remainder used the standard 5% concentration.[4] Overall, after treatment with 5-fluorouracil monotherapy, the number of AKs was reduced by 80.1% at 1–3 months, and 67.4% at 3–6 months.[4] Relative to the efficacy of other treatments included in this analysis, 5-fluorouracil was superior compared only to diclofenac at both 1–3 months and 3–6 months.[4] Only one included study evaluated the long-term effectiveness of 5-fluorouracil at 12 months and found that long-term percent clearance rates were comparable to 1–3 months and 3–6 months time points.[4] Overall, the recurrence rate of AKs at one year post-treatment with 5-fluorouracil monotherapy was 27%.[4] A vast majority of patients included in this analysis (90.7%) reported discomfort with 5-fluorouracil application, which is a significant disadvantage of this treatment method compared to other modalities.[4]

Four studies investigated the effectiveness of twice daily application of diclofenac sodium 3.0% gel in the treatment of AKs.[4] Percent clearance of AKs at 1–3 months post-treatment was 36.3 ± 9.5%, which was lower compared to most other treatment modalities.[4] Only one study included in the analysis reported sustained clearance of 45% at 6 months.[4] In summary, based on the results of this analysis, all treatments except for diclofenac were non-inferior to each other in the treatment of AKs.[4]

After review, 8 systematic reviews were excluded due to poor quality (e.g., network meta-analyses),[20-25] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled),[26,27] or outcome studied (e.g., non-clinical).

**Guidelines:**

High Quality Guidelines:

*American Academy Of Dermatology Guidelines Of Care For The Management Of Actinic Keratosis*

In 2021, the AAD published guidelines to assist in clinical decision-making for the management of AK.[5] Topical agents, cryosurgery, and PDT are all recommended.[5] Choice of treatment is based on a number of factors, including the site of the AKs, whether AKs are solitary, multiple, or within an affected field, and patient preferences and tolerability.[5] Lesion-directed treatments are used to manage few or isolated AKs.

Treating individual AKs in the office setting with physical modalities such as liquid nitrogen cryosurgery or destructive modalities such as curettage offers the patient a treatment that is completed within a single visit and requires only that the patient participate in post-procedural skincare.[5] Cryosurgery is recommended for solitary AK lesions.[5]

Field directed treatments, such as topical agents or PDT, can be used to manage multiple AKs and keratinocyte changes in a contiguous area and may provide benefits in reducing the risk of developing new AKs, limiting AK recurrence, and mitigating subclinical damage.[5] Topical agents can be used focally or in broad areas and are advantageous when AKs occur in areas of high density or areas with indistinct clinical borders.[5] The recommended topical agents all have the

potential for generating local skin reactions.[5] As skin reactions can result in the termination of treatment without reaching the desired therapeutic outcome, the clinician should work with the patient to tailor an individual treatment program that achieves the desired results.[5] A few small studies directly compared the efficacy and safety of topical medications to treat AK.[5] This limited evidence was considered by the AAD Work Group to be insufficient to form recommendations on the comparative efficacy and safety of topical therapies for AK (see **Table 2**).[5]

AAD topical treatment recommendations for patients with AK and quality of evidence:

- The AAD recommends field treatment with 5-fluorouracil cream or imiquimod cream (Strong Recommendation; Moderate-Quality Evidence).[5]
- The AAD conditionally recommends the use of diclofenac gel (Low-Quality Evidence).[5]
- The AAD conditionally recommends red light PDT with aminolevulinic acid over cryosurgery alone (Low-Quality Evidence).[5]
- AAD conditionally recommends combination treatment cryosurgery with 5-fluorouracil or imiquimod over cryosurgery alone (based on Moderate- and Low-Quality Evidence, respectively).[5]

*American Academy of Dermatology Focused Update: Management of Actinic Keratosis*

In 2022 the AAD published a focused guideline update on management of AK.[6] The purpose of the focused update was to incorporate recently published evidence on the use of topical tirbanibulin to treat AK.[6] A first-in-class microtubule inhibitor, tirbanibulin, was approved for the topical, field-directed treatment of AK on the scalp or face by the FDA in December 2020.[6] Two trials were identified and analysis of this evidence resulted in one recommendation.[6] Two phase 3 randomized, double-blinded, parallel-group, placebo-controlled trials (n=702) compared a standard regimen of topical tirbanibulin 1% or a placebo vehicle applied once daily to a 25 $cm^2$ treatment field containing 4 to 8 AKs on the face or scalp for 5 consecutive days.[28] The primary outcome was the percentage of patients with a complete (100%) reduction in the number of lesions in the application area at day 57.[28] The secondary outcome was the percentage of patients with a partial (≥75%) reduction in the number of lesions within the application area at day 57.[28] The incidence of recurrence was evaluated at 1 year.[28]

On day 57, the participants treated with tirbanibulin experienced higher rates of complete clearance of AKs in the treatment area (pooled clearance rate 49.3%) than those treated with the vehicle (pooled clearance rate, 8.6%; RR, 6.14; 95% CI, 2.73 to 13.80; P<0.0001).[6] The participants treated with tirbanibulin also experienced significantly higher rates of partial clearance (≥75% reduction in the number of treated AKs) than those treated with the vehicle (pooled partial clearance rate, (72.2% vs. RR, 3.99; 95% CI, 3.16 to 5.04; P<0.00001).[6] At 12 months, the estimated percentage of previously cleared participants with recurrent lesions in the treatment area was 47% and the estimate of those with recurrent or new lesions in the treatment area was 73%.[6] The most common local reactions to tirbanibulin were erythema in 91% of the patients and flaking or scaling in 82% of patients.[28] The most common adverse events reported through day 57 of the phase III trials were application site pruritus (reported in 9.1% of tirbanibulin-treated participants vs 6.0% of vehicle-treated participants) and pain (reported in 9.9% of tirbanibulin-treated participants vs 3.2% of vehicle-treated participants).[6]

Trials comparing tirbanibulin with conventional treatments with longer follow-up are needed to determine the effects of tirbanibulin therapy on AK.[28] Although the AAD work group recognized that tirbanibulin cost may be prohibitive without adequate insurance coverage and other strongly recommended treatments for AK may be available for lower cost, they concluded that the use of tirbanibulin is likely acceptable to patients and providers and feasible to implement especially considering the abbreviated duration of tirbanibulin treatment compared with the duration of other available topically applied agents for the management of AK.[6]

Recommendation:

- AAD recommends field treatment with topical tirbanibulin (Strong Recommendation; High-Quality Evidence).[6]

**Randomized Controlled Trials:**
A total of 101 citations were manually reviewed from the initial literature search. After further review, 95 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 6 trials are summarized in **Table 2** below. Full abstracts are included in **Appendix 3**.

**Table 2. Description of Randomized Comparative Clinical Trials.**

| Study | Comparison | Population | Primary Outcome | Results | Notes/Limitations |
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| Krawtchenko, et al[29] (2007)<br><br>Single-center, open-label trial<br><br>Patients randomized to 1 of 3 active treatment arms | 1. 5-fluorouracil 5% cream applied twice a day over 4 weeks<br><br>2. Imiquimod 5% cream applied for 8 hours 3 times a week over 4 weeks (for 1 or 2 treatment courses)<br><br>3. Cryosurgery (liquid nitrogen spray) applied 20 to 40 sec for each lesion and repeated in 2 weeks for insufficiently cleared lesions. | Caucasian patients with ≥ 5 typical, visible AK lesions at head, neck, and chest.<br><br>1. n=24<br>2. n=26<br>3. n=25<br><br>Total enrollment: 75 patients<br>Male = 62<br>Female = 13<br>Mean age =74 years<br>Mean number of AK lesions: 8 | Complete clearance of AK lesions 6 weeks after last cryosurgery, 4 weeks after last 5-fluorouracil application, and 8 weeks after last application of imiquimod and at 12-month follow-up. | <u>Total clearance 4 to 8 weeks after last application:</u><br>1. n=23 (96%)<br>2. n=22 (85%)<br>3. n=17 (68%)<br><br>1 vs 3 : p=0.03<br>2 vs 3: p=0.03<br>()<br><br><u>Total clearance 12 months after last application:</u><br>1. n=13 (57%)<br>2. n=19 (86%)<br>3. n=7 (41%)<br><br>1 vs 3 : p=0.01<br>2 vs 3: p=0.01 | 1. Unclear if patients and investigators were blinded to treatment assignment.<br>2. Unclear how many patients received additional treatments with imiquimod or cryosurgery.<br>3. Small patient population, study not powered to detect significant differences between treatment arms.<br>4. 59% of patients had received previous treatment - type of treatment not reported. Could introduce bias in terms of treatment response to active comparators in this trial.<br>5. Statistical analysis only completed for imiquimod compared to 5FU or cryosurgery. |
| Jansen, et al[7] (2019)<br><br>MC, Single-Blind, Phase IV RCT | 1. 5-fluorouracil 5% cream applied twice daily for 4 weeks<br><br>2. Imiquimod 5% cream applied 3 times a week for 4 weeks | Adults with ≥ 5 AK lesions on the head, involving one continuous area of 25 to 100 $cm^2$<br><br>1.155<br>2.156<br>3.156 | Proportion of patients with a reduction ≥ 75% in the number of AK lesions from baseline to 12 months after the end of treatment. | <u>Treatment success at 12 months:</u><br>1. n=108 (82.4%)<br>2. n=76 (71.0%)<br>3. n=57 (49.6%)<br>4. n=42 (42.9%)<br><br><u>Probability of treatment success 12 months after end of treatment:</u><br>1. 74.7%; 95% CI 66.8 to 81.0 | 1. Single-blind study. Investigator who determined treatment outcome was blinded to treatment assignment.<br>2. Protocol included retreatment if patient had initial treatment failure at 3 months. More than one-third of patient population had initial |

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| | 3. Methyl aminolevulinate-PDT for one session<br><br>4. Ingenol gel 0.015% applied once a day for 3 days total*<br>*removed from market in 2020 | 4.157<br><br>Total enrollment: 624 patients,<br>90% were male,<br>mean age 75 years | | 2. 53.9%; 95% CI 45.4 to 61.6<br>3. 37.7%; 95% CI 30.0 to 45.3<br>4. 28.9%; 95% CI 21.8 to 36.3<br><br><u>Treatment failure after one treatment cycle:</u><br>1. 14.8% (n=23/155)<br>2. 7.2% (n=58/156)<br>3. 34.6% (n=54/156)<br>4. 47.8% (n=75/157)<br><br><u>Percentage of patients who were retreated:</u><br>1. 83% (n=19/23)<br>2. 76% (n=44/58)<br>3. 76% (n=41/54)<br>4. 80% (n=60/75)<br><br><u>HR for treatment failure compared to 5-fluorouracil:</u><br>1 vs. 2<br>HR = 2.03; 95% CI 1.36 to 3.04; p<0.001<br>1 vs 3<br>HR = 2.73; 95% CI 1.87 to 3.99; p<0.001<br>1 vs 4<br>HR = 3.33; 95% CI 2.39 to 4.85; p<0.001 | treatment failure and received 2 courses of treatment.<br>3. All treatment arms included pretreatment curettage, which is not always the standard of care.<br>4. Of the 10 authors, 5 reported potential conflicts of interest, including the blinded investigator. |
| Akarsu, et al[30] (2011)<br><br>Single center, open-label, evaluator-blinded study | 1. Diclofenac 3% gel applied twice daily for 12 weeks<br><br>2. Imiquimod 5% cream applied twice a week for 16 weeks<br><br>3. Base cream applied twice daily for 12 weeks | Adults with 1 AK lesion.<br>1. 21<br>2. 20<br>3. 20<br><br>Baseline TTS score<br>1. $3.85 \pm 0.37$<br>2. $3.95 \pm 0.22$<br>3. $3.80 \pm 0.41$ | Treatment efficacy as assessed by investigator assessed by 5-point TTS and self-reported 7-point PGII scores<br><br>Higher TTS scores = worse total skin thickness score<br>0 = complete clearance<br>1 = lesion visible but not palpable | <u>Change from baseline in TTS score at 24 weeks:</u><br><br><u>TTS score:</u><br>1. 2.00<br>2. 1.15<br>3. 3.40<br><br>2 vs 3:<br>MD = 1.4<br>95% CI 0.52 to 2.27 | 1. Not clear if TTS has been validated in other trials.<br>2. MCID not reported for either score (TTS or PGII).<br>3. Small patient population, not clear if study was powered to detect differences between treatment arms. |

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| | | Baseline PGII scores not reported<br><br>Total of 61 patients:<br>37 men<br>31 women<br><br>Mean age: 65.8 years | 2 = lesion visible and palpable<br>3 = lesion raised with visible scaling<br>4 = lesion hyperkeratotic and > 1 mm in thickness<br>MCID not available<br><br>Higher PGII scores = more improvement<br>0 = significantly worse<br>1 = slightly worse<br>2 = no change<br>3 = slightly improved<br>4 = moderately improved<br>5 = significantly improved<br>6 = completely improved<br>MCID not available | 1 vs 3:<br>MD = 2.25<br>95% CI 1.36 to 3.13<br><br>1 vs 2:<br>MD = 0.85<br>95% CI 0.36 to 1.66<br>P=0.034<br><br><u>Change from baseline in PGII score at 24 weeks:</u><br>1. 4.40<br>2. 4.43<br>3. 2.70<br><br>2 vs. 3<br>MD = -1.72<br>95% CI -2.88 to -0.57<br><br>1 vs 3<br>MD = -1.70<br>95% CI -2.86 to -0.53<br><br>1 vs 2<br>MD = 0.02<br>95% CI -0.99 to 1.05<br>NS | |
| Kose, et al[31] (2007)<br><br>Single center, open-label study | 1. Diclofenac 3% gel applied once a day for 12 weeks<br><br>2. Imiquimod 5% cream applied 3 times a week for 12 weeks | Adults with ≥ 3 AK lesions on the face and scalp<br>1. n=24<br>2. n=25<br><br>Total of 49 patients<br>Male = 29<br>Female = 21<br>Average age = 56.4 years | Global improvement (7-point) IGII and PGII scores were used to assess efficacy. Higher scores on both scales indicate improvement. | <u>Percent improvement on the IGII score at the end of therapy:</u><br><br>Moderate Improvement<br>1. 36%<br>2. 5%<br>P value NR<br><br>Significant Improvement<br>1. 52%<br>2. 73%<br>P value NR | 1. One of the clinical efficacy metrics was patient self-reported (PGII) which may be subject to bias.<br>2. Open-label study design introduces bias in investigator assessment and patient response.<br>3. Small patient population, not clear if study was powered to detect differences between treatment arms.<br>4. Results reported as percentages, specific patient data not reported |

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| | | | | Complete Improvement<br>1. 12%<br>2. 22%<br>p> 0.05<br><br><u>Percent improvement on the PGII score at the end of therapy:</u><br><br>Moderate Improvement<br>1. 27%<br>2. 12%<br>P value NR<br><br>Significant Improvement<br>1. 45%<br>2. 65%<br>P value NR<br><br>Complete Improvement<br>1. 28%<br>2. 23%<br>p> 0.05 | 5. Statistical analysis only completed for assessment of complete improvement. |
| Tanghetti et al[32] (2015)<br><br>Randomized 1:1:1 to one of three treatment arms. Single-blind (investigator) | 1. 5-fluorouracil 5% cream for 6-7 days followed by aminolevulinic acid 20% followed by PDT x1 application<br><br>2. 5-fluorouracil 5% cream applied twice daily for 6-7 days<br><br>3. Aminolevulinic acid 20% followed by PDT x 1 | Total enrollment: 30 patients<br><br>1. 10<br>2. 10<br>3. 10 | AK counts at 1- and 3-months post treatment<br><br>Mean Baseline AK counts<br>1. 23.0<br>2. 25.9<br>3. 38.9 | <u>Mean AK counts 1 month after treatment:</u><br>1. 2.8<br>2. 3.5<br>3. 5.8<br>p-values not reported<br><br><u>Mean AK counts 3 months after treatment:</u><br>1. 2.3<br>2. 4.2<br>3. 8.2<br>p-values not reported | 1.Baseline AK counts were not equal across all 3 treatment arms. Baseline aminolevulinic acid group had more lesions than the other 2 groups.<br>2. Inclusion and exclusion criteria not reported.<br>3. Statistical analysis not reported.<br>4. Small patient population, not clear if study was powered to detect differences between treatment arms. |
| Segatto et al[33] (2013)<br><br>Randomized, parallel group study | 1. Diclofenac 3% gel applied twice daily for 12 weeks | Adults with $\geq$ 5 AK lesions on the face, hands, and scalp<br><br>1. n=15<br>2. n=13 | Average number of lesions 8 weeks after treatment.<br><br>Baseline number of AK lesions<br>1. 13.6 $\pm$ 4.5 | <u>Average number of lesions after 8 weeks of treatment:</u><br><br>1. 6.6 $\pm$ 2.94 (MD before and after treatment: 7; p<0.001) | 1. Assessment investigator was blinded to treatment assignment.<br>2. Small patient population, not clear if study was powered to detect differences between treatment arms. |

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| | 2. 5-fluorouracil 5% cream applied twice daily for 4 weeks | Total enrollment: 28 patients<br>Male = 13<br>Female = 15<br>Mean age = 72 years<br>Average number of AK lesions = 15 | 2. 17.4 ± 6.69 | 2. 3.15 ± 2.15 (MD before and after treatment: 14.25; p<0.001)<br><br>1 vs 2 change in number of lesions (7 vs. 14.25; p<0.001) | 3. Number of baseline AK lesions was not balanced between groups. |
| Abbreviations: 5-fluorouracil = 5-fluorouracil; AK = Actinic Keratosis; CI = confidence interval; HR = hazard ratio; IGII= Investigator Global Improvement Index; MC = multi-center; MCID = minimal clinically important difference; MD = mean difference; PDT = photodynamic therapy; PGII = Patient Global Improvement Index; PDT = photodynamic therapy; RCT = randomized controlled trial; TTS = Total Thickness Score | | | | | |

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**Appendix 1:** PDL Status

| GENERIC NAME | BRAND NAME | FORM | PDL STATUS |
|---|---|---|---|
| diclofenac sodium | DICLOFENAC SODIUM | GEL (GRAM) | N |
| aminolevulinic acid HCl | AMELUZ | GEL (GRAM) | |
| aminolevulinic acid HCl | LEVULAN | SOL W/APPL | |
| fluorouracil | FLUOROURACIL | CREAM (G) | |
| fluorouracil | EFUDEX | CREAM (G) | |
| fluorouracil | FLUOROURACIL | SOLUTION | |
| imiquimod | IMIQUIMOD | CREAM PACK | |
| imiquimod | ZYCLARA | CREAM PACK | |
| imiquimod | IMIQUIMOD | CRM MD PMP | |
| imiquimod | ZYCLARA | CRM MD PMP | |

**Appendix 2:** Specific Drug Information

**Table 3. Clinical Pharmacology and Pharmacokinetics.**

| Drug Name | Mechanism of Action | Absorption | Metabolism/Excretion | Pharmacokinetics (mean) |
|---|---|---|---|---|
| 5-fluorouracil[16] | Pyrimidine antimetabolite that interferes with DNA synthesis to prevent cell proliferation. | 6% of topical dose is systemically absorbed. Tmax: ~1 hour | N/A | • Cmax: 1.03 hours<br>• AUC: 22.39 ng/hr/mL |
| Imiquimod[17] | Immune response modifier: toll-like receptor 7 agonist that activates immune cells and cytokines. Unknown mechanism of action in AK. | Tmax: 9-12 hours | Renal Excretion: < 3% | • Half-life: 20 to 24.1 hours |
| Diclofenac Sodium[18] | Unknown in the treatment of AK. | Tmax: 4.5 hours | Primarily Renal Excretion | • Half-life: 79 hours |

| | | | | |
|---|---|---|---|---|
| Tirbanibulin[19] | Microtubule inhibitor, unknown mechanism of action in AK. | Tmax: ~6 hours | Hepatic Metabolism by CYP3A4 and CYP2C8<br><br>Excretion has not been fully characterized in humans | N/A |
| Aminolaevulinic acid[13] | Porphyrin precursor, which optimizes photosensitization prior to illumination with red or blue light photodynamic therapy. | Tmax: 2 hours | N/A | N/A |
| Abbreviations: AK = Actinic Keratosis; AUC = area under the curve; Cmax = maximum plasma concentration; hr = hours; mL = milliliters; N/A = Not Available; Tmax = time to peak absorption | | | | |

**Table 4. Use in Specific Populations**

| | Fluorouracil[16] | Imiquimod[17] | Diclofenac[18] | Tirbanibulin[19] | Aminolaevulinic acid[13] |
|---|---|---|---|---|---|
| Contraindicated in pregnancy | X | | | | |
| Contraindicated in patients with dihydropyridine dehydrogenase (DPD) deficiency | X | | | | |
| Contraindicated in pregnancy after 30 weeks of gestation | | | X | | |
| Safe to use in pregnancy | | Unknown | | Unknown | Unknown |

**Drug Safety:**

Diclofenac Topical Gel: Black Boxed Warning for the risk of serious cardiovascular and gastrointestinal events.

- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.[18]
- Diclofenac gel is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.[18]
- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.[18]

**Table 5. Summary of Warnings and Precautions.**

| Warning/Precaution | 5-Fluorouracil[16] | Imiquimod[17] | Diclofenac[18] | Tirbanibulin[19] | Aminolaevulinic acid[13] |
|---|---|---|---|---|---|
| Hypersensitivity | X | | X | | |
| Local Skin Reactions | X | X | X | X | |
| Photosensitivity | X | X | X | | X |
| Systemic Reactions (Flu-like signs and symptoms) | | X | | | |
| Use on damaged skin (eczema, infected lesions, burns or wounds) | | | X | | |
| History of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs | | | X | | |
| Hepatotoxicity | | | X | | |
| Severe Heart Failure | | | X | | |
| Porphyria | | | | | X |

**Appendix 3:** Abstracts of Randomized Clinical Trials

**A Randomized Study of Topical 5% Imiquimod Vs. Topical 5-Fluorouracil Vs. Cryosurgery In Immunocompetent Patients With Actinic Keratoses: A Comparison Of Clinical And Histological Outcomes Including 1-Year Follow-Up[29]**

**Background:** Actinic keratoses (AK) frequently occur on sun-exposed skin and are considered as in situ squamous cell carcinoma. To date, no treatment algorithm exists for first- or second-line therapies due to the lack of comparative studies.
**Objective:** This study compared the initial and 12-month clinical clearance, histological clearance, and cosmetic outcomes of topically applied 5% imiquimod (IMIQ) cream, 5% 5-fluorouracil (5-fluorouracil) ointment and cryosurgery for the treatment of AK.
**Patients/methods:** Patients were randomized to one of the following three treatment groups: one or two courses of cryosurgery (20-40 s per lesion), topical 5-fluorouracil (twice daily for 4 weeks), or one or two courses of topical imiquimod (three times per week for 4 weeks each).
**Results:** Sixty-eight per cent (17/25) of patients treated with cryosurgery, 96% (23/24) of patients treated with 5-fluorouracil, and 85% (22/26) of patients treated with IMIQ achieved initial clinical clearance, $p = 0.03$. The histological clearance rate for cryosurgery was 32% (8/25), 67% (16/24) for 5-fluorouracil, and 73% (19/26) in the IMIQ group, $p = 0.03$. The 12-month follow-up showed a high rate of recurrent and new lesions in the 5-fluorouracil and cryosurgery arms. The sustained clearance rate of initially cleared individual lesions was 28% (7/25) for cryosurgery, 54% (13/24) for 5-fluorouracil and 73% (19/26) for IMIQ ($p < 0.01$). Sustained clearance of the total treatment field was 4% (1/25), 33% (8/24), and 73% (19/26) of patients after cryosurgery, 5-fluorouracil, and IMIQ, respectively ($p < 0.01$). The patients in the IMIQ group were judged to have the best cosmetic outcomes ($p = 0.0001$).
**Conclusion:** Imiquimod treatment of AK resulted in superior sustained clearance and cosmetic outcomes compared with cryosurgery and 5-fluorouracil. It should be considered as a first line therapy for sustained treatment of AK.

**Randomized Trial of Four Treatment Approaches for Actinic Keratosis[7]**

**Background:** Actinic keratosis is the most frequent premalignant skin disease in the white population. In current guidelines, no clear recommendations are made about which treatment is preferred.
**Methods:** We investigated the effectiveness of four frequently used field-directed treatments (for multiple lesions in a continuous area). Patients with a clinical diagnosis of five or more actinic keratosis lesions on the head, involving one continuous area of 25 to 100 $cm^2$, were enrolled at four Dutch hospitals. Patients were randomly assigned to treatment with 5% fluorouracil cream, 5% imiquimod cream, methyl aminolevulinate photodynamic therapy (MAL-PDT), or 0.015% ingenol mebutate gel. The primary outcome was the proportion of patients with a reduction of 75% or more in the number of actinic keratosis lesions from baseline to 12 months after the end of treatment. Both a modified intention-to-treat analysis and a per-protocol analysis were performed.
**Results:** A total of 624 patients were included from November 2014 through March 2017. At 12 months after the end of treatment, the cumulative probability of remaining free from treatment failure was significantly higher among patients who received fluorouracil (74.7%; 95% confidence interval [CI], 66.8 to 81.0) than among those who received imiquimod (53.9%; 95% CI, 45.4 to 61.6), MAL-PDT (37.7%; 95% CI, 30.0 to 45.3), or ingenol mebutate (28.9%; 95% CI, 21.8 to 36.3). As compared with fluorouracil, the hazard ratio for treatment failure was 2.03 (95% CI, 1.36 to 3.04) with imiquimod, 2.73 (95% CI, 1.87 to 3.99) with MAL-PDT, and 3.33 (95% CI, 2.29 to 4.85) with ingenol mebutate ($P \leq 0.001$ for all comparisons). No unexpected toxic effects were documented.
**Conclusions:** At 12 months after the end of treatment in patients with multiple actinic keratosis lesions on the head, 5% fluorouracil cream was the most effective of four field-directed treatments. (Funded by the Netherlands Organization for Health Research and Development; ClinicalTrials.gov number, NCT02281682.).

**Comparison Of Topical 3% Diclofenac Sodium Gel And 5% Imiquimod Cream For The Treatment Of Actinic Keratoses[30]**
**Background**. There is a wide spectrum of treatments available for actinic keratosis (AK). Topical diclofenac sodium and imiquimod are two topical treatments, which are noninvasive, easily applied, well-tolerated and effective.
**Aim.** To compare the effects of topical 3% diclofenac sodium plus hyaluranon (DFS) gel, 5% imiquimod (IMQ) cream, and base cream (BC) in patients with AK.
**Methods.** In total, 61 patients, diagnosed clinically and histopathologically as having AK, were randomized into three treatment groups to receive topical treatment with either DFS (twice daily for 12 weeks), IMQ (twice per week for 16 weeks) or BC (twice daily for 12 weeks). Patients were evaluated clinically at 0, 4, 8, 12, 16, 20 and 24 weeks. Treatment efficacy was assessed by Total Thickness Score (TTS) and Patient Global Improvement Index (PGII).
**Results.** Complete clearance rates for DFS, IMQ and BC at the end of the treatment and at the end of the total follow-up period were 19.1%, 20% and 0%, and 14.3%, 45% and 0%, respectively. Although the average TTS value of the DFS group at week 24 was significantly higher than that of the IMQ group, the PGII values were not significantly different.
**Conclusions**. Although DFS and IMQ each had considerable efficacy in the treatment of AK, the efficacy of DFS seemed to decrease after cessation of treatment.

**Comparison Of the Efficacy And Tolerability Of 3% Diclofenac Sodium Gel And 5% Imiquimod Cream In The Treatment Of Actinic Keratosis[31]**
**Background:** Topical diclofenac and imiquimod have been reported to be effective in the treatment of actinic keratosis, but a study to compare these two drugs has not been reported yet.
**Objective:** To compare the efficacy and safety of topical 3% diclofenac gel plus hyaluronic acid and 5% imiquimod cream in the treatment of actinic keratosis.
**Methods**: Forty-nine patients with actinic keratosis were enrolled in this randomized comparative open-label study. Twenty-four patients applied 3% diclofenac gel once a daily to their lesions, while the other 25 patients were treated with a 5% imiquimod cream three times a week for 12 weeks. Patients were examined before treatment and every month of the treatment. Assessments were made by investigators according to the Investigator and the Patient Global Improvement Indices (IGII) and (PGII).

**Results:** According to the IGII results, a complete response was observed in 12% of the diclofenac group and 22% of the imiquimod group. For the PGII scores, a complete response was observed in 28% of the diclofenac group and 23% of the imiquimod group. There were no significant differences between the two groups (p>0.05). Both treatments were well tolerated, with most adverse events related to skin.
**Conclusion:** The two drugs were found to be equally effective and safe in the treatment of actinic keratosis but complete remission was very low. Therefore, topical treatments with these two drugs were not seen to be completely effective, and combined therapies and further studies are needed.

**A Controlled Comparison Study of Topical Fluorouracil 5% Cream Pre-Treatment of Aminolevulinic Acid/Photodynamic Therapy for Actinic Keratosis[32]**
**Introduction:** Topical Fluorouracil 5% cream (5-fluorouracil) and 20% aminolevulinic acid (ALA)/ photodynamic therapy (PDT) are both FDA approved for the treatment of Actinic Keratosis (AK). We have studied the use of these 2 agents alone and in a sequential manner. We have also used a 5-fluorouracil re-challenge 3 months after treatment to highlight the efficacy of these treatments.
**Methods:** This was an investigator-blinded randomized study in which 30 patients were randomized 1:1:1 into the following groups: Group 1 patients pretreated for 6-7 days with 5-fluorouracil, ALA applied with incubation of 2 hours, ALA removed with wet gauze, illuminated treated areas with 10 J/cm(2) with Blu-U device; Group 2 patients treated with 5-fluorouracil BID for 6-7 days and no ALA/PDT; Group 3 patients received no pretreatment, ALA applied with incubation of 2 hours, ALA removed with wet gauze, illuminated treated areas with 10 J.cm2 with Blu-U device. Patients were seen at screening/baseline, treatment for ALA/PDT, 24 hours post treatment, 1 week post treatment and 3 months post treatment. All subjects were then given a re-challenge course of 5-fluorouracil for 6 days and reassessed.
**Results:** AK counts in all groups were dramatically decreased and similar at 1- and 3-months post treatment. The re-challenge brought a significant difference with many subclinical lesions in the area of activity in the ALA and 5-fluorouracil alone groups.

**Conclusions:** All three arms appeared equal in treating visible AKs. These data strongly suggests a synergistic role of 5-fluorouracil with ALA/PDT over ALA/PDT or 5-fluorouracil alone in treating the subclinical lesions demonstrated on a 5-fluorouracil re-challenge. Treatment of these subclinical lesions should result in a longer remission. The data also suggests that a 5-fluorouracil re-challenge could be a clinical tool to judge the efficacy of treatment for AK if these subclinical lesions are proven to be an AK precursor.

**Comparative Study of Actinic Keratosis Treatment With 3% Diclofenac Sodium And 5% 5-Fluorouracil[33]**
**BACKGROUND:** Actinic keratosis is a frequent lesion which occurs in sunlight exposed areas. Diclofenac sodium and 5-Fluorouracil are effective, non-invasive and easy-to-apply topical treatment options.
**OBJECTIVES:** To assess and compare the effectiveness of 3% diclofenac sodium associated with 2.5% hyaluronic acid and of 5% 5-Fluorouracil for the treatment of actinic keratosis, as well as the patient's degree of satisfaction and tolerability.
**METHODS**: 28 patients with a clinical diagnosis of actinic keratosis were randomized to receive diclofenac sodium or 5-Fluorouracil and were clinically assessed before and after treatment as well as 8 weeks after the end of treatment. Modified versions of the Investigator and Patient Global Improvement Scores were used.
**RESULTS:** The average number of lesions in the diclofenac sodium group before and after treatment was 13.6 and 6.6 (p<0,001), respectively, while it was 17.4 and 3.15 (p<0.001) in the 5-Fluorouracil group. There was a significant reduction in the number of lesions in the 5-Fluorouracil group in relation to the diclofenac sodium group (p<0.001). To the non-blinded physician, there was a higher satisfactory therapeutic response in the 5-Fluorouracil group (p<0.001); to the blinded physician, there was a higher satisfactory response in this same group, although not statistically significant (p=0.09). There was a high degree of satisfaction in

both groups (73% in the diclofenac sodium group and 77% in the 5-Fluorouracil group; p=0.827). Regarding adverse effects, the diclofenac sodium group presented a higher degree of satisfaction (93.3% vs 38.4%; p=0.008). Erythema, edema, crusts and itching were significantly higher in the 5-Fluorouracil group. **CONCLUSION:** We concluded that 5-Fluorouracil was more effective; however, it showed lower tolerability than diclofenac sodium

**Appendix 4:** Medline Search Strategy
Ovid MEDLINE(R) ALL <1946 to March 05, 2025>

| | | |
|---|---|---|
| 1 | exp Keratosis, Actinic/ | 2675 |
| 2 | 5 fluorouracil.mp. or Fluorouracil/ | 59928 |
| 3 | Imiquimod/ | 3597 |
| 4 | Diclofenac/ | 9202 |
| 5 | tirbanibulin.mp. | 108 |
| 6 | Aminolevulinic Acid/ | 6889 |
| 7 | 2 or 3 or 4 or 5 or 6 | 79299 |
| 8 | Administration, Topical/ | 41448 |
| 9 | 7 and 8 | 1900 |
| 10 | 1 and 9 | 107 |
| 11 | limit 10 to (english language and humans) | 101 |

**Appendix 5:** Key Inclusion Criteria

| | |
|---|---|
| **Population** | Adults with actinic keratosis |
| **Intervention** | Topical 5-fluorouracil, imiquimod, diclofenac, tirbanibulin, and aminolaevulinic acid |
| **Comparator** | Other topical agents or placebo |
| **Outcomes** | Clearance of actinic keratoses |
| **Timing** | 2 to 6 months after treatment |

| | |
|---|---|
| **Setting** | Outpatient application, except for aminolaevulinic acid which is provider administered prior to photodynamic therapy |

# Topical Therapies for Actinic Keratosis

## Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature. Allow case-by-case review for members covered under the EPSDT program.

## Length of Authorization:

- Up to 3 months

## Requires PA:

- Non-preferred agents for pharmacy claims
- Aminolevulinic ointment for provider administered claims

## Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

**Table 1**. Topical Medications FDA-Approved in Actinic Keratosis and Other Indications

| Generic Drug Name (BRAND NAME) | Strength/ Formulation | FDA-Approved Indications in Adults | Patient or Health Care Provider Administered | Dosing Guidance |
|---|---|---|---|---|
| 5-fluorouracil (TOLAK, EFUDEX) | 0.5% cream<br>4% cream<br>5% cream<br>2% solution<br>5% solution | • Actinic Keratosis<br>• Basal Cell Carcinoma (5% cream or solution) | Patient | Maximum duration of therapy: 2 months<br><br>Actinic Keratosis:<br>• Fluorouracil 0.5% and 4% cream: Apply once daily up to 4 weeks.<br>• Fluorouracil 1% cream: Apply twice daily for an average of 2-6 weeks.<br>• Fluorouracil 5% cream: Apply twice daily for an average of 2-4 weeks.<br>• Fluorouracil 2% and 5% solution: Apply twice daily for an average of 2-4 weeks.<br>Basal Cell Carcinoma:<br>• Fluorouracil 5% cream or solution: Apply twice daily for an average of 2-4 weeks. |

| | | | | |
|---|---|---|---|---|
| Imiquimod (ALDARA, ZYCLARA)[1] | 2.5% cream<br>3.75% cream<br>5% cream | • Actinic Keratosis in adults (2.5%, 3.75%, and 5% cream)<br>• Basal Cell Carcinoma in adults (5% cream only)<br>• Genital and Perianal Warts (3.75% cream & 5% cream) approved in children and adolescents ≥ 12 years) | Patient | Actinic Keratosis:<br>• Imiquimod 2.5% and 3.75% cream: Apply at bedtime (remove in 8 hours) x 2 weeks, off for 2 weeks then repeat x 2 weeks. Apply up to 0.5 grams per application.<br>• Imiquimod 5% cream: Apply once daily before bedtime 2 times per week for 16 weeks. Apply no more than 1 packet per application.<br>Basal Cell Carcinoma:<br>• Imiquimod 5% cream: Apply once daily before bedtime 5 times per week for 6 weeks. Amount of cream used is based on target tumor diameter.<br>Genital Warts:<br>• Imiquimod 3.75% cream: Apply once daily (remove in 8 hours) up to 8 weeks. Apply up to 0.25 grams per application.<br>• Imiquimod 5% cream: Apply once daily before bedtime 3 times per week until total clearance or for a maximum of 16 weeks. |
| Diclofenac Sodium (SOLARAZE) | 3% gel | • Actinic Keratosis | Patient | • Apply twice daily for 60 to 90 days. |
| Tirbanibulin (KLISYRI) | 1% ointment | • Actinic Keratosis | Patient | • Apply once daily (max one single dose packet) x 5 consecutive days. |
| Aminolevulinic acid (AMELUZ, LEVULAN) | 10% gel (red or blue light)<br>20% solution (red light) | • Actinic Keratosis prior to photodynamic therapy | Health Care Provider | • 10% gel: Apply a maximum of 6 grams (3 tubes) at one time. Retreat lesions that have not completely resolved 3 months after the initial treatment.<br>• 20% gel: Apply one treatment and may repeat after 8 weeks. |

| Approval Criteria | | |
|---|---|---|
| 1. What diagnosis is being treated? | Record ICD10 code. | |
| 2. Is this an FDA approved indication (see **Table 1**)? | **Yes**: Go to #3 | **No:** Pass to RPh. Deny; medical appropriateness. |
| 3. Has the patient tried a preferred agent and do they have a contraindication, intolerance, or failure with this therapy? | **Yes**: Go to #4 | **No:** Pass to RPh. Deny; medical appropriateness. |
| 4. Is the diagnosis funded by OHP? | **Yes:** Go to #5 | **No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP.<br><br>If eligible for EPSDT review: Go to #5. |
| 5. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.) | **Yes:** Approve for up to 4 months based on dosing parameters in Table 1. | **No:** Pass to RPh. Deny; medical necessity. |

*P&T/DUR Review: 6/25 (DM)*
*Implementation: 8/1/25*