LifeWise
Health Plan of Washington

PHARMACY POLICY – 5.01.623
Topical Drugs for Actinic Keratosis and Other Dermatologic Conditions

Effective Date:	Mar. 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Feb. 11, 2025	None
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

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Introduction

Actinic keratosis (AK) are rough, scaly patches on the skin (often the face, scalp, neck, or hands) that is a result of years of exposure to ultraviolet (UV) light. These lesions may be itchy or painful and are a common reason people visit a doctor who specializes in skin diseases (a dermatologist). These lesions are considered precancerous and can lead to skin cancer. Although most lesions do not develop into skin cancer, AK is routinely treated to reduce the risk of this occurring. There are many treatment options for AK such as medical procedures to remove or freeze the lesion, specialized light therapy (called photodynamic therapy), and topical drugs. This policy describes when topical drugs used to treat AK may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Carac (fluorouracil 0.5%)	**Carac (fluorouracil 0.5%) may be considered medically necessary for the topical treatment of actinic keratosis in adults when the following criteria are met:** • The individual is aged 18 years and older **AND** • Has tried generic imiquimod 5% first and had an inadequate response or intolerance to generic imiquimod 5% unless use is contraindicated **AND** • Has tried one generic topical fluorouracil product first and had an inadequate response or intolerance to topical fluorouracil
Fluorouracil, brand	**Brand fluorouracil may be considered medically necessary for the topical treatment of actinic keratosis in adults when the following criteria are met:** • The individual is aged 18 years and older **AND** • Has tried generic imiquimod 5% first and had an inadequate response or intolerance to generic imiquimod 5% unless use is contraindicated **AND** • Has tried one generic topical fluorouracil product first and had an inadequate response or intolerance to topical fluorouracil
Imiquimod 3.75%, Generic	**Generic imiquimod 3.75% may be considered medically necessary for the topical treatment of actinic keratosis in adults when the following criteria are met:** • The individual is aged 18 years and older **AND** • Has tried generic imiquimod 5% first and had an inadequate response or intolerance to generic imiquimod 5% **AND** • Has tried one generic topical fluorouracil product first and had an inadequate response or intolerance to topical fluorouracil unless use is contraindicated **Generic imiquimod 3.75% may be considered medically necessary for the topical treatment of external genital and perianal warts (EGW) when the following criteria are met:**

Drug	Medical Necessity
	• The individual is aged 12 years and older **AND** • Has tried generic imiquimod 5% first and had an inadequate response or intolerance to generic imiquimod 5%
Klisyri (tirbanibulin)	**Klisyri (tirbanibulin) may be considered medically necessary for the topical treatment of actinic keratosis in adults when the following criteria are met:** • The individual is aged 18 years and older **AND** • Has tried generic imiquimod 5% first and had an inadequate response or intolerance to generic imiquimod 5% unless use is contraindicated **AND** • Has tried one generic topical fluorouracil product first and had an inadequate response or intolerance to topical fluorouracil unless use is contraindicated
Tolak (fluorouracil 4%)	**Tolak (fluorouracil 4%) may be considered medically necessary for the topical treatment of actinic keratosis in adults when the following criteria are met:** • The individual is aged 18 years and older **AND** • Has tried generic imiquimod 5% first and had an inadequate response or intolerance to generic imiquimod 5% unless use is contraindicated **AND** • Has tried one generic topical fluorouracil product first and had an inadequate response or intolerance to topical fluorouracil
Zyclara (imiquimod 2.5% and 3.75%)	**Zyclara (imiquimod 2.5% and 3.75%) may be considered medically necessary for the topical treatment of actinic keratosis in adults when the following criteria are met:** • The individual is aged 18 years and older **AND** • Has tried generic imiquimod 5% first and had an inadequate response or intolerance to generic imiquimod 5% **AND**

Drug	Medical Necessity
	• Has tried one generic topical fluorouracil product first and had an inadequate response or intolerance to topical fluorouracil unless use is contraindicated **Zyclara (imiquimod 3.75%) may be considered medically necessary for the topical treatment of external genital and perianal warts (EGW) when the following criteria are met:** • The individual is aged 12 years and older **AND** • Has tried generic imiquimod 5% first and had an inadequate response or intolerance to generic imiquimod 5%

Drug	Investigational
As listed	**All other uses of the drugs for conditions not outlined in this policy are considered investigational.** **The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months.** **All other reviews for all drugs listed in policy may be approved up to 12 months.**
Re-authorization criteria	**Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.** **All other reviews for re-authorization of all drugs listed in policy may be approved up to 12 months as long as the drug-**

Length of Approval	
Approval	**Criteria**
	specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history

Coding

N/A

Related Information

Consideration of Age

The ages stated in this policy for brand fluorouracil, Carac (fluorouracil 0.5%), generic imiquimod 3.75%, Klisyri (tirbanibulin), Tolak (fluorouracil 4%), and Zyclara (imiquimod 2.5% and 3.75%) are considered medically necessary are based on the ages approved in the US Food and Drug Administration (FDA) labeling.

Benefit Application

This policy is managed through the pharmacy benefit.

Evidence Review

Background

Actinic keratosis (aka solar keratosis, sunspots, or precancerous spots) are the most common epithelial precancerous lesions, particularly among individuals with light complexions. AKs present as dry, scaly, or crusty bumps on the skin that are more easily felt than seen. They most commonly occur on sun exposed areas such as the face, ears, bald scalp, lips, neck, back of hands, and forearms. Five to 20% of AK lesions will transform into squamous cell carcinoma (SCC) within 10 to 25 years, with reported annual transformation rates ranging widely, from 0.25% to 16%. Consequently, aggressively treating AK before progression is believed prudent. In the US, approximately 4 million individuals are treated each year for this condition, and at least 1 in every 6 persons will develop at least one AK lesion over their lifetime.

Choice of therapy depends primarily on two factors, efficacy of the therapeutic option and number of target lesions present. Cryotherapy is generally used in cases with few lesions. Topical therapies, including photodynamic therapy (PDT) are generally employed in individuals with more than 15 lesions. Anatomic location of the lesions impacts the response time to topical treatments. AK on the face responds the quickest (more quickly than on the scalp), and lesions on the arms usually take the longest to respond. After topical treatment, actinic keratoses may recur on the treated area.

Treatments Available

5-Flourouracil (Carac, Efudex, Tolak): Topical 5-FU is the standard to which other topical treatments are compared. 5-FU is a cytotoxic antimetabolite. Fluorouracil is administered twice daily for 2-4 weeks. The cure rate is approximately 75%. Application is associated with local irritation presenting as dryness, erythema, erosion, pain, or edema.

Aminolevulinic acid (Ameluz, Levulan Kerastick): Aminolevulinic acid is a porphyrin precursor. Photoactivation following topical application occurs when aminolevulinic acid (prodrug) is metabolized to protoporphyrin IX (PpIX), a photoactive compound which accumulates in the skin. When exposed to red light of a suitable wavelength and energy, PpIX is activated resulting in an excited state of porphyrin molecules. In the presence of oxygen, reactive oxygen species are formed which causes damage to cellular components and eventually destroys the cells. There are two PDT therapies approved for use in the United States. Both

modalities have a cure rate of approximately 75%. Ameluz and Levulan Kerastick are administered only by a health care provider as part of the procedure. Most commonly, these therapies are associated with local erythema and stinging or burning.

Imiquimod (Aldara, Zyclara): Imiquimod is an immunomodulator that is applied once daily for two or three days a week, for 16 weeks. In two double-blind placebo-controlled trials of imiquimod 5%, complete clearance of AK lesions was found in 46% and 44% of individuals compared with 3% and 4% with vehicle. Partial clearing was reported with 60% and 58% versus 10% and 14% respectively. Local reactions (e.g., erythema, scabbing or crusting, erosions or ulceration) are common with topical imiquimod therapy. Topical imiquimod also has been reported to rarely produce systemic adverse effects, including fatigue, flu-like symptoms, and angioedema.

Diclofenac: Diclofenac is an anti-inflammatory that is applied twice daily for 8 to 16 weeks. A randomized, double-blind, vehicle-controlled study, participants applied the treatments twice daily for 90 days, with follow-up 30 days after the end of treatment. Approximately 50% of participants in the treatment group had complete resolution compared with 20% in the vehicle group. Adverse effects associated with topical diclofenac include pruritus, dry skin, application site reactions, rash, and erythema. It appears to be as effective as 5-FU without the burning and irritation. However, like 5-FU, the longer treatment time can make patient compliance a factor.

Tirbanibulin (Klisyri): Tirbanibulin is a microtubule inhibitor that inhibits tubulin polymerization and disrupts Src kinase signaling, which are upregulated in actinic keratosis. Tirbanibulin is applied once daily for 5 consecutive days. Two double-blind, vehicle-controlled clinical trials were conducted with 702 adult subjects with actinic keratosis on the face or scalp. Subjects enrolled had 4 to 8 clinically typical, visible, and discrete AK lesions in a contiguous area of 25 cm^2 on the face or scalp. Both studies met the primary endpoint, with 44% and 54% of individuals achieving complete clearance at Day 57 within the face or scalp treatment areas. The secondary outcome evaluating a partial response (≥75% clearance of AK lesions) was also met. Most common adverse reactions (incidence ≥2%) are local skin reactions, application site pruritus, and application site pain.

Practice Guidelines and Position Statements

American Academy of Dermatology (AAD): Guidelines of care for the management of actinic keratosis (2021, focus update 2022)

The ADD strongly recommends use of ultraviolet protection, topical imiquimod, topical 5-fluorouracil, tirbanibulin, and cryosurgery for AK. Photodynamic therapy and diclofenac are conditionally recommended, both individually and as part of combination therapy regimens.

British Association of Dermatologists (BAD): Guidelines for the care of patients with actinic keratosis

In 2017, the British Association of Dermatologists (BAD) published their guidelines on the management of AK. This set of recommendations note that in some instances, management may entail little or no medical treatment and that the most appropriate management plan should be determined by the individual's preferences and clinical circumstances, which should consider the extent, duration and presence of symptoms, severity of lesions and other associated risk factors for skin cancer. BAD also notes that a European AK guideline achieved consensus and that there remains a preference for cryosurgery for isolated lesions and curettage for larger ones. Otherwise, preferences revolved largely around different strengths of the common main agents, namely 5-fluorouracil (5-FU), imiquimod, ingenol mebutate, and variants of PDT. Diclofenac and imiquimod at 2.5% were not favored. For immunosuppressed individuals the preference was for stronger formulations of all products and laser was not considered a good choice for any circumstance other than treatment of field disease.

2022 Update

Reviewed prescribing information for Aldara, Carac, Klisyri, Solaraze, Tolak, Fluoroplex and Zyclara. Removed discontinued products Solaraze and Fluoroplex from medical policy. Reviewed guidelines added 2021 and 2022 American Academy of Dermatology actinic keratosis guidelines. Minor updates made to evidence review section.

2023 Update

Reviewed prescribing information for all drugs in this policy. No new evidence found that would change the policy statements.

2024 Update

Reviewed prescribing information for all drugs in this policy. No new evidence found that would change the policy statements.

2025 Update

Reviewed prescribing information for all drugs in this policy. Removed Aldara (imiquimod 5%) and brand imiquimod 3.75% from policy as the products have been discontinued and are no longer commercially available. Added coverage criteria for generic imiquimod 3.75% for the treatment of actinic keratosis and EGW. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

References

1. Berker B De, McGregor JM, Mustapa MF. Guidelines for the Care of Patients with Actinic Keratosis 2017. Br J Dermatol 2017 Jan;176(1):20-43.
2. Martin G. The impact of the current United States guidelines on the management of actinic keratosis: is it time for an update? J Clin Aesthet Dermatol 2010;3(11):20-25.
3. Carac cream prescribing information. Valeant Pharmaceuticals; Bridgewater, NJ. Updated May 2022.
4. Klisyri ointment prescribing information. Almirall LLC; Exton, PA. Updated June 2024.
5. Tolak cream prescribing information. Hill Dermaceuticals, Inc.; Sanford, Fl. Updated August 2022.
6. Zyclara cream prescribing information. Valeant Pharmaceuticals; Bridgewater, NJ. Updated September 2024.
7. Kempers S, DuBois J, Forman S, et al. Tirbanibulin ointment 1% as a novel treatment for actinic keratosis: phase 1 and 2 results. J Drugs Dermatol. 2020;19(11):1093-1100. doi:10.36849/JDD.2020.5576
8. Eisen DB, Asgari MM, Bennet DD, et al. Guidelines of care for the management of actinic keratosis. J Am Acad Dermatol 2021 Oct; 85(4): E209-233. doi: **https://doi.org/10.1016/j.jaad.2021.02.082.** Last accessed January 30, 2025.
9. Eisen DB, et al. Focused update: Guidelines of care for the management of actinic keratosis. J Am Acad Dermatol 2022 Aug; 87(2): 373-374. doi: **https://doi.org/10.1016/j.jaad.2022.04.013.** Last accessed January 30, 2025.

History

Date	Comments
04/01/21	New policy, approved March 9, 2021, effective for dates of service on or after April 1, 2021. Add to Prescription Drug section. Added coverage criteria for Aldara (imiquimod 5%), brand fluorouracil, brand imiquimod 3.75%, Carac (fluorouracil 0.5%), Fluoroplex (fluorouracil 1%), Klisyri (tirbanibulin), Solaraze (diclofenac 3%), Tolak (fluorouracil 4%), and Zyclara (imiquimod 2.5% and 3.75%) for the treatment of actinic keratosis. Added coverage criteria for Aldara for the treatment of sBCC. Added coverage criteria for Aldara, brand imiquimod 3.75%, and Zyclara for the treatment of EGW.
09/29/22	Minor update. Coding section was corrected; no codes apply to this policy. The coding table listed was for demonstrative purposes only and did not contain applicable content to the policy.
11/01/22	Annual Review approved October 24, 2022. Removed Fluoroplex and Solaraze as products have been discontinued by the manufacturer. Changed the wording from "patient" to "individual" throughout the policy for standardization.
08/01/23	Annual Review approved July 24, 2023. No changes to the policy statements.
09/01/24	Annual Review, approved August 26, 2024. No changes to the policy statements.
03/01/25	Annual Review, approved February 11, 2025. Removed Aldara (imiquimod 5%) and brand imiquimod 3.75% from policy as the products have been discontinued. Added coverage criteria for generic imiquimod 3.75% for the treatment of actinic keratosis and EGW. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.