

Topical Actinic Keratosis Products

Policy # 00579

Original Effective Date: 01/01/2018

Current Effective Date: 05/01/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider branded Fluorouracil 0.5% cream, Tolak^{®‡} (fluorouracil 4% cream), Fluoroplex^{®‡} (fluorouracil 1% cream), Efudex^{®‡} (fluorouracil 5% cream), Carac^{®‡} (fluorouracil 0.5% cream), Aldara^{®‡} (imiquimod 5% cream), Zyclara^{®‡} (imiquimod 3.75% cream and imiquimod 2.5% cream), branded Imiquimod 3.75% cream, Klisyri^{®‡} (tirbanibulin 1% ointment), Solaraze^{®‡} (diclofenac 3% gel), and generic diclofenac 3% gel to be **eligible for coverage**** when the patient selection criteria are met for the requested drug.

Patient Selection Criteria

Coverage eligibility for branded Fluorouracil 0.5% cream, Tolak (fluorouracil 4% cream), Fluoroplex (fluorouracil 1% cream), Efudex (fluorouracil 5% cream), Carac (fluorouracil 0.5% cream), Aldara (imiquimod 5% cream), Zyclara (imiquimod 3.75% cream and imiquimod 2.5% cream), branded Imiquimod 3.75% cream, Klisyri (tirbanibulin 1% ointment), Solaraze (diclofenac 3% gel), and generic diclofenac 3% gel will be considered when the following criteria are met for the requested drug:

- Branded Fluorouracil 0.5% cream, Tolak (fluorouracil cream 4%), Fluoroplex (fluorouracil 1% cream):
 - Patient has a diagnosis of actinic keratosis; AND
 - Patient has tried and failed (e.g., intolerance or inadequate response) TWO of the following products (one from each active ingredient) for at least ONE month each:
 - Generic topical fluorouracil products (2% or 5% topical solution, 5% cream); AND
 - Generic topical imiquimod products (e.g., 5% cream).
- Efudex (fluorouracil 5% cream):
 - Patient has a diagnosis of actinic keratosis; AND
 - Patient has tried and failed (e.g., intolerance or inadequate response) TWO of the following products (one from each active ingredient) for at least ONE month each:
 - ❖ Generic fluorouracil 2% or 5% topical solution; AND

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- ❖ Generic topical imiquimod products (e.g., 5% cream); AND
 - Patient has tried and failed (e.g., intolerance or inadequate response) its generic equivalent (fluorouracil 5% cream) for at least ONE month; OR
- Patient has a diagnosis of superficial basal cell carcinoma; AND
 - Patient has tried and failed (e.g., intolerance or inadequate response) its generic equivalent (fluorouracil 5% cream) for at least THREE months.
- Carac (fluorouracil 0.5%):
 - Patient has a diagnosis of actinic keratosis; AND
 - Patient has tried and failed (e.g., intolerance or inadequate response) ONE generic topical fluorouracil product (2% or 5% topical solution, 5% cream) for at least ONE month.
- Aldara (imiquimod 5% cream):
 - Patient has a diagnosis of actinic keratosis; AND
 - Patient has tried and failed (e.g., intolerance or inadequate response) the generic equivalent (imiquimod 5% cream) for at least FOUR months; AND
 - Patient has tried and failed (e.g., intolerance or inadequate response) ONE generic topical fluorouracil product (2% or 5% topical solution, 5% cream) for at least ONE month; OR
 - Patient has a diagnosis of external genital and/or perianal warts/condyloma acuminata; AND
 - Patient has tried and failed (e.g., intolerance or inadequate response) the generic equivalent (imiquimod 5% cream) for at least FOUR months; OR
 - Patient has a diagnosis of superficial basal cell carcinoma; AND
 - Patient has tried and failed (e.g., intolerance or inadequate response) generic imiquimod 5% cream for at least TWO months.
- Zyclara (imiquimod 3.75% cream) or branded Imiquimod 3.75% cream:
 - Patient has a diagnosis of actinic keratosis; AND
 - Patient has tried and failed (e.g., intolerance or inadequate response) generic imiquimod 5% cream for at least FOUR months; AND
 - Patient has tried and failed (e.g., intolerance or inadequate response) ONE generic topical fluorouracil product (2% or 5% topical solution, 5% cream) for at least ONE month; OR
 - Patient has a diagnosis of external genital and/or perianal warts/condyloma acuminata; AND
 - Patient has tried and failed (e.g., intolerance or inadequate response) generic imiquimod 5% cream for at least FOUR months.
- Zyclara (imiquimod 2.5% cream) or Klisyri (tirbanibulin 1% ointment):
 - Patient has a diagnosis of actinic keratosis; AND
 - Patient has tried and failed (e.g., intolerance or inadequate response) generic imiquimod 5% cream for at least FOUR months; AND

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- Patient has tried and failed (e.g., intolerance or inadequate response) ONE generic topical fluorouracil product (2% or 5% topical solution, 5% cream) for at least ONE month.
- Solaraze (diclofenac 3% gel)/generic diclofenac 3% gel:
 - Patient has diagnosis of actinic keratosis; AND
 - Patient has tried and failed (e.g., intolerance or inadequate response) TWO of the following products (one from each active ingredient) for at least ONE month each:
 - Generic topical fluorouracil products (2% or 5% topical solution, 5% cream); AND
 - Generic topical imiquimod products (e.g., 5% cream); AND
 - For brand Solaraze, patient has tried and failed (e.g., intolerance or inadequate response) the generic equivalent (diclofenac 3% gel) for at least THREE months.

*(Note: The patient selection criteria that requires use of alternative products for a particular amount of time prior to the requested product are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*

(Note: The patient selection criteria require use of alternative products unless there is clinical evidence or patient history that suggests the use of the alternative products will be ineffective or cause an adverse reaction to the patient)

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of branded Fluorouracil 0.5% cream, Tolak (fluorouracil 4% cream), Fluoroplex (fluorouracil 1% cream), Efudex (fluorouracil 5% cream), Carac (fluorouracil 0.5% cream), Aldara (imiquimod 5% cream), Zyclara (imiquimod 3.75% cream and imiquimod 2.5% cream), branded Imiquimod 3.75% cream, Klisyri (tirbanibulin 1% ointment), Solaraze (diclofenac 3% gel), and generic diclofenac 3% gel when the required alternative products are not tried and failed for the allotted amount of time to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers branded Fluorouracil 0.5% cream, Tolak (fluorouracil 4% cream), Fluoroplex (fluorouracil 1% cream), Efudex (fluorouracil 5% cream), Carac (fluorouracil 0.5% cream), Aldara (imiquimod 5% cream), Zyclara (imiquimod 3.75% cream and imiquimod 2.5% cream), branded Imiquimod 3.75% cream, Klisyri (tirbanibulin 1% ointment), Solaraze (diclofenac 3% gel), and generic diclofenac 3% gel for indications other than those listed in the policy for the requested drug to be **investigational.***

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Background/Overview

Actinic Keratosis

Actinic keratosis is a common skin condition involving proliferation of atypical keratinocytes in the epidermis in response to prolonged exposure to ultraviolet radiation. The lesions that form may be a harmless cosmetic concern, but may also progress to squamous cell carcinoma (SCC). Because those lesions that will progress to SCC cannot be distinguished from those that will spontaneously resolve, treatment is warranted for all cases of actinic keratosis. Treatment for actinic keratosis depends on patient factors such as the number and location of lesions, lesion characteristics, and patient preference. Options include surgical or cryogenic removal of the lesion (generally preferred for isolated lesions) and various medical therapies. Recommended medical therapies include topical fluorouracil, topical imiquimod, and topical diclofenac.

Topical fluorouracil is available as 0.5%, 1%, 4%, and 5% creams and 2% and 5% topical solutions. It works by inhibiting deoxyribonucleic acid (DNA) synthesis in the fast-growing dysplastic cells of the lesion. Because this mechanism involves causing inflammation and destruction of the lesions, the treatment course typically involves erythema, blistering, necrosis with erosion, and reepithelialization over a course of 4-6 weeks. All strengths have been used successfully in patients with multiple lesions, but the 0.5% preparation may be better tolerated, especially when lesions are on sensitive areas such as the face or anterior scalp.

Topical imiquimod cream stimulates local cytokine induction to destroy actinic keratoses. It should be applied to the affected area twice per week for 16 weeks, with treatment-free intervals extended if the patient is unable to tolerate the adverse effects of erythema, scabbing, and flaking. However, the full treatment course should not exceed 16 weeks. A meta-analysis of randomized trials evaluating topical imiquimod for actinic keratosis treatment found that approximately 50% of patients treated had complete resolution of disease compared to only 5% in the control groups.

Despite an unclear mechanism of action, topical diclofenac 3% gel is indicated for the treatment of actinic keratosis. It is thought that the drug's inhibition of prostaglandins may disrupt the development of the ultraviolet B-induced skin cancers such as squamous cell carcinoma. While topical diclofenac is better tolerated than topical fluorouracil, it may be less effective and requires a substantially longer treatment time (60-90 days vs 30 days).

Klisyri is a new product containing tirbanibulin, a microtubule inhibitor, for the treatment of actinic keratosis on the face or scalp. Although it does have a unique mechanism of action, there are many other topical therapies for the treatment of actinic keratosis that may represent more studied and more economical options for treatment.

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Condylomata Acuminata

Condylomata acuminata, also known as genital or perianal warts, are caused by human papillomavirus (HPV) infection and may cause the patient negative psychosocial effects as well as physical symptoms of pruritus, pain, and bleeding. Treatment options include topical imiquimod and topical podofilox, both of which are considered first line agents. Imiquimod stimulates the immune system to destroy the warts and has exhibited a clearance rate of 35-75% in clinical trials. Podofilox is an antimitotic drug that destroys the tissues on which it is applied. It is indicated for the treatment of external genital warts, but not perianal or mucous membrane warts.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The patient selection criteria presented in this policy takes into consideration clinical evidence or patient history that suggests generic alternatives to the requested drug will be ineffective or cause an adverse reaction to the patient. Based on a review of the data, in the absence of the above mentioned caveats, there is no advantage of using the above listed products before their generic equivalents/alternatives. The purpose of this policy is to assure that these products are being used appropriately and that the most cost effective, yet equally efficacious products are tried and failed prior to utilization of the requested product.

References

1. UpToDate. Treatment of Actinic Keratosis. Accessed 8/2017.
2. UpToDate. Condylomata acuminata (anogenital warts): Management of External Condylomata Acuminata in Men. Accessed 8/2017.
3. UpToDate. Treatment of Vulvar and Vaginal Warts. Accessed 8/2017.
4. Tolak [package insert]. Hill Dermaceuticals, Inc. Sanford, FL. Updated 9/2015
5. Fluoroplex [package insert]. Aqua Pharmaceuticals. West Chester, PA. Updated 3/2012
6. Efudex [package insert]. Valeant. Bridgewater, NJ. Updated 2016
7. Carac [package insert]. Valeant. Bridgewater, NJ. Updated 5/2017
8. Aldara [package insert]. Strides Pharma Inc. East Brunswick, NJ. Updated 7/2016
9. Solaraze [package insert]. PharmaDerm. Melville, New York. Updated 5/2016
10. Zyclara [package insert]. Valeant. Bridgewater, NJ. Updated 2/2018
11. Klisyri [package insert]. Almirall, LLC. Exton, PA. Updated 12/2020
12. Klisyri Drug Evaluation. Express Scripts. Updated 1/2021

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09/07/2017 Medical Policy Committee review
09/20/2017 Medical Policy Implementation Committee approval. New policy.
09/06/2018 Medical Policy Committee review
09/19/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/05/2019 Medical Policy Committee review
09/11/2019 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/03/2020 Medical Policy Committee review
09/09/2020 Medical Policy Implementation Committee approval. Added Zyclara and Branded Imiquimod to the policy with criteria.
04/01/2021 Medical Policy Committee review
04/14/2021 Medical Policy Implementation Committee approval. Added new drug, Klisyri, with relevant background information.
04/07/2022 Medical Policy Committee review
04/13/2022 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/06/2023 Medical Policy Committee review
04/12/2023 Medical Policy Implementation Committee approval. No change to coverage.
04/04/2024 Medical Policy Committee review
04/10/2024 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/03/2025 Medical Policy Committee review
04/09/2025 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 04/2026

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

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- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.