Pharmacy Policy Bulletin

Title:	Actinic Keratosis agents and Zyclara®
Policy #:	Rx.01.148

Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, quantity, or formulary restrictions (ie limits on non-preferred drugs). Individual member benefits must be verified.

This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.

Members are advised to use participating pharmacies in order to receive the highest level of benefits.

Intent:

The intent of this policy is to communicate the medical necessity criteria for **ingenol mebutate (Picato®), diclofenac 3% (Solaraze®), tirbanibulin (Klisyri®)**, and **imiquimod (Zyclara™)** as provided under the member's prescription drug benefit.

Description:

Actinic keratoses (AKs or solar keratoses) are keratotic macules, papules, or plaques resulting from the intraepidermal proliferation of atypical keratinocytes in response to prolonged exposure to ultraviolet radiation. AKs are a concern because the majority of cutaneous squamous cell carcinoma (SCCs) arise from pre-existing AKs, and AKs that will progress to SCC cannot be distinguished from AKs that will spontaneously resolve or persist.

Cutaneous T cell lymphoma (CTCL) describes a heterogeneous group of neoplasms of skin-homing T cells. CTCL represent approximately 75 to 80 percent of all primary cutaneous lymphomas. Mycosis fungoides (MF) and primary cutaneous $CD30^+$ lymphoproliferative disorders (LPD) account for approximately 90 percent of CTCL.

Ingenol mebutate (Picato®) is indicated for the topical treatment of actinic keratosis (AK).

Ingenol mebutate (Picato®) is an inducer of cell death. The mechanism of action by which ingenol mebutate gel induces cell death in treating AK lesions is unknown.

Diclofenac 3% gel (Solaraze®) is indicated for the topical treatment of AK.

The mechanism of action of diclofenac 3% gel (Solaraze®) in the treatment of AK is unknown.

Tirbanibulin (Klisyri™) is indicated for the topical treatment of actinic keratosis on the face or scalp.

Tirbanibulin is a microtubule inhibitor. The mechanism of action of KLISYRI for the topical treatment of actinic keratosis is unknown.

Imiquimod (Zyclara**™)** is indicated for the topical treatment of clinically typical visible or palpable, actinic keratoses (AK) of the full face or baling scalp in immunocompetent adults and the treatment of external genital and perianal warts (EGW)/condyloma acuminata in patients 12 years or older.

Imiquimod is a Toll-like receptor 7 agonist. The mechanism of action of Zyclara**™** in treating AK and EGW lesions is unknown.

Policy:

Actinic Keratosis

INITIAL CRITERIA Ingenol mebutate (Picato®), diclofenac 3% (Solaraze®) gel, imiquimod (Zyclara®) 3.75%, 2.5%, or tirbanibulin (Klisyri®) is approved when BOTH of the following are met:

1. Diagnosis of actinic keratosis; and

2. ONE of the following:
    a. For imiquimod (Zyclara®) 3.75%, 2.5% only, inadequate response or inability to tolerate imiquimod 5%; or
    b. For Tirbanibulin (Klisyri®) only, inadequate response or inability to tolerate BOTH of the following generics:
        i. Fluorouracil; and
        ii. Imiquimod

Initial authorization duration:

- 30 days for tirbanibulin (Klisyri®), ingenol mebutate (Picato®) imiquimod (Zyclara®) 3.75%, 2.5%.
- 3 months for diclofenac 3% (Solaraze®)

REAUTHORIZATION CRITERIA Ingenol mebutate (Picato®), diclofenac 3% (Solaraze®) gel, imiquimod (Zyclara®) 3.75%, 2.5%, or tirbanibulin (Klisyri®) is re-approved when there is documentation of a diagnosis of actinic keratosis at a different site.

Reauthorization duration:

- 30 days for tirbanibulin (Klisyri®), ingenol mebutate (Picato®) imiquimod (Zyclara®) 3.75%, 2.5%.
- 3 months for diclofenac 3% (Solaraze®)

Genital warts

INITIAL CRITERIA Imiquimod (Zyclara®) 3.75% is approved when BOTH of the following are met:

1. Diagnosis of genital warts; and
2. Inadequate response or inability to tolerate imiquimod 5%

Initial authorization duration: 30 days

REAUTHORIZATION CRITERIA Imiquimod (Zyclara®) 3.75% is re-approved when there is documentation of positive clinical response to therapy.

Reauthorization duration: 30 days

Black Box Warning as shown in the drug Prescribing Information:

Solaraze® (diclofenac 3%):

Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial and stroke, which can be fatal. This risk may occur in treatment and may increase with duration of use.

Solaraze® is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.

Guidelines:

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the prescription drug benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

References:

Jorizzo J. Treatment of actinic keratosis. UpToDate. April 2018. Available at: https://www.uptodate.com/contents/treatment-of-actinic-keratosis?source=search_result&search=actinic%20keratosis&selectedTitle=1~46. Accessed September 30, 2021.

Picato® (ingenol mebutate) [package insert]. Parsippany, NJ. Leo Pharma Inc. June 2017. Available at: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=5accc7a5-8209-4680-b0ae-2a6963500419&type=display. Accessed September 30, 2021.

Solaraze® (diclofenac 3%) [package insert]. Melville, NY. PharmaDerm. April 2016. Available at: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=89a7bfbd-051f-4d87-a642-96b0df81b8e2&type=display. Accessed September 30, 2021.

Willemze R. Classification of primary cutaneous lymphomas. UpToDate. August 2018. Available at: https://www.uptodate.com/contents/classification-of-primary-cutaneous-lymphomas?source=machineLearning&search=CTCL&selectedTitle=7~106&sectionRank=1&anchor=H474649238#H474649238. Accessed September 30, 2020.

Klisyri™ (tirbanibulin) [package insert]. Exton, PA: Almirall; December 2020. Available from: https://klisyrihcp.com/assets/klisyri-prescribing-information.pdf. Accessed September 30, 2021.

Zyclara™ **(imiquimod) [package insert]. Bridgewater, NJ: Bausch Health US, LLC; Revised 2020 Jun. Available at:** https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=28cd9b5b-680b-480f-b33d-9c5b52bbf03d. Accessed September 9, 2021

Applicable Drugs:

Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

Brand Name	Generic Name
Picato®	ingenol mebutate
Solaraze®	diclofenac 3%
Klisyri™	Tirbanibulin
Zyclara™	Imiquimod

Cross References:

Off-Label Use policy Rx.01.33

Policy Version Number:	11.00
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Policy Effective Date:	January 01, 2022
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