Original Effective Date: 04/01/2012
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Last P&T Approval/Version: 04/30/2025
Next Review Due By: 04/2026
Policy Number: C4194-C

Aldara/Zyclara (imiquimod)

PRODUCTS AFFECTED

Aldara (Imiquimod), Zyclara (imiquimod), imiquimod

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Actinic keratosis (AK), External genital and perianal warts/condyloma acuminate (EGW), Superficial basal cell carcinoma (sBCC)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. ACTINIC KERATOSIS (AK):
1. Documentation of a diagnosis of actinic keratosis [DOCUMENTATION REQUIRED]
AND
2. FOR NON-FORMULARY/NON-PREFERRED REQUESTS: Documentation of an inadequate response, serious side effects, or contraindication to TWO of the following topical medications:

formulary/preferred generic imiquimod, fluorouracil, or diclofenac

B. EXTERNAL GENITAL AND PERIANAL WARTS (EGW):
1. Documentation of a diagnosis of external genital and perianal warts [DOCUMENTATION REQUIRED]
AND
2. FOR NON-FORMULARY/NON-PREFERRED REQUESTS: Documentation of an inadequate response, serious side effects, or contraindication to formulary/preferred generic imiquimod

C. SUPERFICIAL BASAL CELL CARCINOMA (sBCC) [5% ONLY]:
1. Documented diagnosis of superficial basal cell carcinoma [DOCUMENTATION REQUIRED]
AND
2. Tumor (maximum diameter of 2.0 cm) is located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet)

CONTINUATION OF THERAPY:
N/A

DURATION OF APPROVAL:
Actinic Keratosis
Initial Authorization:
2.5% and 3.75% cream: 6 weeks
5% cream: 16 weeks
Continuation of therapy: NA

EGW
Initial Authorization:
3.75% cream: 8 weeks
5% cream: 16 weeks
Continuation of therapy: NA

sBCC (5% only): Initial authorization: 6 weeks, Continuation of therapy: NA

PRESCRIBER REQUIREMENTS:
None

AGE RESTRICTIONS:
EGW: 12 years of age or older
AK and sBCC: 18 years of age and older

QUANTITY:
Actinic Keratosis
2.5% and 3.75% cream: 2 pumps or packets once daily for two 2-week treatment cycles separated by a 2-week no treatment period (max 56 packets or two 7.5g pumps)
5% cream: 1 packet two times per week for 16 weeks (max 36 packets)

EGW
3.75% cream: 1 pump or packet once daily for up to 8 weeks (max 56 packets or two 7.5g pumps)
5% cream: 1 packet three times per week for a maximum of 16 weeks (max 48 packets)

sBCC (5% only): 1 packet five times per week for a full 6 weeks (max 36 packets)

PLACE OF ADMINISTRATION:
The recommendation is that topical medications in this policy will be for pharmacy benefit coverage and

patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Topical

DRUG CLASS:
Immunomodulators Imidazoquinolinamines - Topical

FDA-APPROVED USES:
ZYCLARA (imiquimod) Cream 2.5%, 3.75% is indicated for the topical treatment of clinically typical, visible, or palpable actinic keratoses (AK) of the full face or balding scalp in immunocompetent adults.
ZYCLARA (imiquimod) Cream 3.75% is indicated for the topical treatment of external genital and perianal warts/condyloma acuminata (EGW) in immunocompetent patients 12 years of age or older.
Limitations of Use: Efficacy of imiquimod cream was not demonstrated for molluscum contagiosum in children 2 to 12 years of age. Treatment with Zyclara cream has not been studied for prevention or transmission of human papillomavirus (HPV).

Aldara (imiquimod) Cream 5% is indicated for the topical treatment of:
- Clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AK) on the face or scalp in immunocompetent adults
- Biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults with a maximum tumor diameter of 2.0 cm on trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured
- External genital and perianal warts/condyloma acuminata (EGW) in immunocompetent patients 12 years of age and older

Limitations of Use: Efficacy was not demonstrated for molluscum contagiosum in children aged 2-12. The efficacy and safety of Aldara Cream have not been established for patients with Basal Cell Nevus Syndrome or Xeroderma Pigmentosum.

COMPENDIAL APPROVED OFF-LABELED USES:
Acyclovir-resistant Herpes simplex virus (HSV) infection; Lentigo maligna; Vulvar intraepithelial neoplasia

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Actinic Keratosis (AK) Topical therapies for AK include 5-fluorouracil [5-FU], imiquimod, ingenol mebutate, diclofenac. National Comprehensive Cancer Network [NCCN, U.S., 2017] guidelines suggest AKs should be treated aggressively at first development. Accepted modalities include cryosurgery, topical fluorouracil (5-FU), topical imiquimod, photodynamic therapy, curettage, and electrodessication. [Category 2A: based on lower level evidence, uniform NCCN consensus that the intervention is appropriate.] Other modalities that may be considered include diclofenac*, chemical peel (trichloroacetic acid), and ablative skin resurfacing (laser, dermabrasion). [*Category 2B: based on lower level evidence, NCCN consensus that the intervention is appropriate.] 10 A long-term follow-up study assessed 12-month recurrence rates associated with ingenol mebutate gel treatment in patients who previously had achieved complete clearance of AK. In total, 108 patients with complete clearance of face or scalp lesions in the original trial and 76 patients with complete clearance of trunk or extremity lesions in the original trial were enrolled in the 12-month observational follow-up study. Of these, 100 patients (face or scalp) and 71 patients (trunk or extremities)

completed all 12 months. Sustained lesion reduction rates vs. baseline were 87.2% for the face or scalp and 86.8% for the trunk or extremities. The estimated median times to recurrence were 365 days (face or scalp) and 274days (trunk or extremities)

Superficial Basal Cell Carcinoma (BCC) Overall there has been very little good quality research on treatments for BCC. Most trials have only evaluated BCCs in low risk locations. Surgery and radiotherapy appear to be the most effective treatments, with surgery showing the lowest failure rates. Other treatments might have some use, but few have been compared to surgery.12 Although surgery and radiotherapy remain the treatments of choice for most high-risk lesions, topical and nonsurgical treatments are options to treat low risk lesions.11 NCCN Guidelines (U.S., 2016) suggest in patients with low risk, superficial basal cell skin cancer, where surgery or radiation is contraindicated or impractical, topical therapies such as 5-fluorouracil, imiquimod, photodynamic therapy, or vigorous cryotherapy may be considered, even though the cure rate may be lower

Genital Warts Several guidelines state there is no definitive evidence that any of the available treatments are superior to others and no single treatment is ideal for all patients or all warts.13,14,15 For all available treatments except surgical removal, the initial response rate is 60-70% and 20- 30% will have a recurrence. The Centers for Disease Control and Prevention (CDC, U.S., 2010) suggests that treatment of genital warts should be guided by the preference of the patient, available resources, and the experience of the health care provider. Factors that might influence selection of treatment include wart size, wart number, anatomic site of wart, wart morphology, patient preference, cost of treatment, convenience, adverse effects, and provider experience. The treatment should be changed if a patient has not improved substantially. The majority of genital warts respond within 3 months of therapy.

Non-Genital Warts Off-label use of imiquimod for non-genital warts is now the most commonly used medication for warts, despite a lack of good evidence to support its use. (10)Several case reports and case series have been published.9-13 In the earliest case series (n=50), imiquimod 5% applied daily for 5 days per week resulted in complete clearance in 30% of patients, and >50% reduction in wart size in 26%.9 There was worsening or no change in 22%, and the other 22% were lost to follow-up or withdrew from the study (2 withdrew due to local side effects). In another case series (n=10), 90% of patients were successfully treated with imiquimod applied daily, under occlusion, for 4 weeks.
In one open-label study of imiquimod 5% twice daily, 13 patients had warts other than plantar warts. The reduction in the volume of the warts in these patients ranged from 42% to 100% (6 patients had complete clearing of the warts).11 However, in an unpublished controlled trial conducted by the manufacturer and briefly described in the Cochrane Review, the cure rate for imiquimod was only 9.5% to 10%, compared to 4.9% for the control.

Plantar warts: There have been a number of published case reports and one open-label trial.11,14-18In the open label trial, 24 patients had plantar warts resistant to other treatments. Imiquimod 5% twice daily resulted in a median reduction in wart volume of 59% (complete clearing in 4 patients, >75% clearing in 5, with no response in 4 patients).11 Successful treatment of plantar warts with imiquimod sometimes required use of occlusion, or treatment with other modalities such as salicylic acid, cryotherapy, or dinitrochlorobenzene. In an unpublished controlled trial of imiquimod 5% conducted by the manufacturer, using the vehicle as the control, complete clearance of plantar warts was achieved in 10% to 12.8% of patients, compared to 2.9% in the control group.3

Flat warts: Flat warts tend to appear on the neck and face where pigmentation and scarring may be a concern. A number of case reports and one case series (n=15) of imiquimod for flat warts were found.19,20 In the case series, imiquimod 5% applied nightly for up to 12 weeks resulted in complete response in 40%, excellent response (>75% clearing) in 33%, but poor response in 27%.20 No patients had pigmentation disorders or scarring. For some patients, the reduction in wart size allowed the use of ablation to complete wart removal. The onset of response was at 1 week for many patients, with a mean time for clinical response of 10.5 weeks.

Ungual and periungual warts: Warts growing under and around nail beds can be difficult to treat due to

difficulty accessing the wart, and pain caused by treatment. In one case series (n=15), imiquimod 5% applied 5 nights per week under occlusion (following pre-treatment with salicylic acid) resulted in complete resolution of recalcitrant ungual and periungual warts in 80% of patients within 1-6 weeks. Two patients also had clearing of other untreated warts. The remaining 20% of patients were non- responders.21

Special populations: immunocompromised patients and children
Topical imiquimod has been used successfully to treat cutaneous warts in immunocompromised patients (HIV positive patients, immunosuppressive therapy),22-27 However, in one series of organ transplant patients the clearance rates were relatively low.26 Imiquimod 5% has also been used in children as young as 5 years of age with good success and safety.9,21,28

Safety: In all of the case reports, case series and trials we reviewed, side effects were mainly mild and local, such as erythema, burning, itching, erosion, and scabbing. In one series involving children, imiquimod was applied sparingly with a toothpick twice daily, with no redness or itching observed. Systemic side effects (fever, lymphadenopathy, muscle aches) were rarely reported9,19 This may be due to the limited transdermal absorption of imiquimod (estimated to be <1%)8.

Limitations: The main limitation to stronger recommendations for the use of imiquimod is the lack of evidence from controlled trials. All of the published evidence for using imiquimod for cutaneous warts is case reports, case series, or uncontrolled trials. Imiquimod has not been directly compared to other treatments such as topical salicylic acid, preventing firm conclusions about its place in therapy from being made.

Many of the patients in the case reports and uncontrolled trials had warts that were recalcitrant to other treatments. Various regimens that may add ancillary measures (occlusion, pre-treatment, or co- treatment with keratolytics and other therapies) were reported. The optimal dose and duration of therapy are unknown. The lower strength imiquimod creams may be better tolerated, but they have not been studied for cutaneous warts.
Imiquimod has some theoretical advantages over other therapies in that it is easy to apply, well- tolerated and cosmetically acceptable, may also clear distant lesions. However, the cost of imiquimod is a disadvantage.

Conclusions
The use of imiquimod for non-genital cutaneous warts remains off-label, and the lack of well- designed controlled trials and comparative studies prevents firm conclusions about its place in therapy from being made.

Mechanism	Examples
Ablative therapies*	Salicylic, lactic, and other acids; cantharadin; silver nitrate; cryotherapy; laser therapy and photodynamic therapy; hyfrecation; curettage
Antimitotic and antiviral therapy	5-fluorouracil, bleomycin, topical cidofovir, podophyllin/podophyllotoxin
Stimulate host immune responses against the virus	Oral cimetidine; topical and oral zinc; intralesional candida, mumps, or *Trichophyton* antigen; intralesional interferon; contact sensitizers such as dinitrochlorobenzene, diphencyprone, and squaric acid dibutyl ester
Miscellaneous	Duct tape*, retinoids

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Aldara/Zyclara (imiquimod) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications to imiquimod include: No labeled contraindications.

Exclusions/Discontinuation:
Per FDA labeled indication, patient must be immunocompetent.

OTHER SPECIAL CONSIDERATIONS:
None

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Aldara CREA 5%
Imiquimod CREA 3.75%
Imiquimod CREA 5%
Imiquimod Pump CREA 3.75%
Zyclara CREA 3.75%
Zyclara Pump CREA 2.5%
Zyclara Pump CREA 3.75%

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION-Notable revisions: Required Medical Information FDA-Approved Uses Contraindications/Exclusions/Discontinuation References	Q2 2025
REVISION-Notable revisions: Required Medical Information Background References	Q2 2024
REVISION-Notable revisions: Diagnosis Required Medical Information Duration of Approval Quantity Route of Administration FDA Approved Uses Compendial Approved Off-Labeled Uses Background Contraindications/Exclusions/Discontinuation Available Dosage Forms References	Q2 2023
REVISION-Notable revisions: Diagnosis Duration of Approval Place of Administration References	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file