Prior Authorization Criteria

Aldara/Zyclara (imiquimod)
Policy Number: C4194-C

CRITERIA EFFECTIVE DATES:

<table>
<thead>
<tr>
<th>ORIGINAL EFFECTIVE DATE</th>
<th>LAST REVIEWED DATE</th>
<th>NEXT REVIEW DATE</th>
</tr>
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<tbody>
<tr>
<td>4/1/2012</td>
<td>3/1/2019</td>
<td>3/1/2020</td>
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J CODE   TYPE OF CRITERIA | LAST P&T APPROVAL
---|-------------------------|------------------|
NA   RxPA                  | Q2                |

PRODUCTS AFFECTED:
Aldara (Imiquimod, Zyclara (imiquimod)

DRUG CLASS:
Immunomodulators Imidazoquinolinamines - Topical

ROUTE OF ADMINISTRATION:
External

PLACE OF SERVICE:
Retail Pharmacy

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

FDA-APPROVED USES: indicated for the topical treatment of Clinically typical, visible or palpable actinic keratosis (AK) of the full face or balding scalp in immunocompetent adults., External genital and perianal warts/condyloma acuminata (EGW) in patients 12 years or older.

Aldara Cream is indicated for the topical treatment of biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the 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.

COMPENDIAL APPROVED OFF-LABEL USES: None

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS: actinic keratosis (AK), external genital and perianal warts/condyloma acuminata (EGW)

REQUIRED MEDICAL INFORMATION:
A. ACTINIC KERATOSIS (AK):
1. Documentation of a diagnosis of actinic keratosis AND
2. Documentation patient is NOT immunocompromised AND
3. FOR ZYCLARA ONLY: Documentation of an inadequate response, intolerance or contraindication to TWO of the following: generic imiquimod, fluorouracil, or diclofenac
Prior Authorization Criteria

B. EXTERNAL GENITAL AND PERIANAL WARTS:
   1. Documentation of a diagnosis of external genital and perianal warts (EGW)
      AND
   2. Documentation of an inadequate response, intolerance or contraindication to ONE of the
      following: podofilox, fluorouracil, or trichloroacetic acid

C. SUPERFICIAL BASAL CELL CARCINOMA:
   1. Documented diagnosis of superficial basal cell carcinoma
      AND
   2. Tumor is located on the trunk (excluding anogenital skin) neck, or extremities (excluding
      hands and feet)

DURATION OF APPROVAL: Initial authorization: AK- 14 days, EGW: 8 weeks, SBCC: 6 weeks
Continuation of therapy: NA

QUANTITY: Imiquimod 5% CREAM: Superficial Basal Cell Carcinoma: 20 packets/28 days, Actinic
Keratosis: 8 packets/28 days, External Genital or Perianal Warts: 12 packets/28 days. ZYCLARA
CREAM: 2 bottles

PRESCRIBER REQUIREMENTS: None

AGE RESTRICTIONS: 12 years of age or older

GENDER: Male and female

CONTINUATION OF THERAPY: NA

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION: All other uses of Aldara/Zyclara
(imiquimod) are considered experimental/investigational and therefore, will follow Molina’s Off-Label
policy. 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.11,14-18 In 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%
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.

OTHER SPECIAL CONSIDERATIONS:
Treatments for cutaneous warts

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<tr>
<th>Mechanism</th>
<th>Examples</th>
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<tr>
<td>Ablative therapies*</td>
<td>Salicylic, lactic and other acids; cantharadin; silver nitrate; cryotherapy; laser therapy and photodynamic therapy; hyfrecation; curettage</td>
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<tr>
<td>Antimitotic and antiviral therapy</td>
<td>5-fluorouracil, bleomycin, topical cidofovir, podophyllin/podophyllotoxin</td>
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<td>Stimulate host immune responses against the virus</td>
<td>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</td>
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<tr>
<td>Miscellaneous</td>
<td>Duct tape*, retinoids</td>
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BACKGROUND:
Actinic Keratosis (AK) Topical therapies for AK include 5-fluorouracil [5-FU], imiquimod, ingenol mebutate, diclofenac9. 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 274 days (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 rigorous 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.

**APPENDIX:** None

**REFERENCES:**