### FDA APPROVED INDICATIONS AND DOSAGE

<table>
<thead>
<tr>
<th>Topical Diclofenac Gel Agent</th>
<th>Indication</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solaraze</td>
<td>Topical treatment of actinic keratosis</td>
<td>Apply to lesion areas twice daily. Normally 0.5 g of gel is used on each 5 cm x 5 cm lesion site. The recommended duration of therapy is from 60 days to 90 days.</td>
</tr>
</tbody>
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*a* generic available

<table>
<thead>
<tr>
<th>Topical Fluorouracil Agent</th>
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<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carac, Fluorouracil Cream 0.5%</td>
<td>Topical treatment of multiple actinic or solar keratosis of the face and anterior scalp</td>
<td>Apply once a day to the skin where actinic keratosis lesions appear, using enough to cover the entire area with a thin film. Fluorouracil agent should be applied up to 4 weeks as tolerated. Continued treatment up to 4 weeks results in greater lesion reduction</td>
</tr>
<tr>
<td>Efudex</td>
<td>Topical treatment of multiple actinic or solar keratosis.</td>
<td>Apply twice daily in an amount sufficient to cover the lesions. The usual duration of therapy is from 2 to 4 weeks. Complete healing of the lesions may not be evident for 1 to 2 months following cessation of therapy.</td>
</tr>
</tbody>
</table>

Treatment of superficial basal cell carcinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites. Apply twice daily in an amount sufficient to cover the lesions. Treatment should be continued for at least 3 to 6 weeks. Therapy may be required for as long as 10 to 12 weeks before the lesions are obliterated.
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<tr>
<td><strong>Fluoroplex</strong> <em>(fluorouracil cream 1%)</em></td>
<td>Topical treatment of multiple actinic (solar) keratosis</td>
<td>Apply sufficient medication to cover the entire face or other affected areas twice daily. Increasing the frequency of application and a longer period of administration may be required on areas other than the head and neck. A treatment period of 2-6 weeks is usually required.</td>
</tr>
</tbody>
</table>

| Tolak | Topical treatment of actinic keratosis lesions of the face, ears, and scalp | Apply once daily in an amount sufficient to cover the lesions of the face, ears, and/or scalp with a thin film, using the fingertips to gently massage the medication uniformly into the skin. Cream should be applied for a period of 4 weeks as tolerated |

<table>
<thead>
<tr>
<th>Topical Imiquimod Agent</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Aldara</strong> <em>(imiquimod 5% cream)</em></td>
<td>Clinically typical nonhyperkeratotic, nonhypertrophic actinic keratosis (AK) of face or scalp for immunocompetent adults</td>
<td>Apply 2 times per week for a full 16 weeks. Treatment area is defined as a 25cm² (5 cm x 5 cm) area on face or scalp.</td>
</tr>
</tbody>
</table>

| Biopsy confirmed primary superficial basal cell carcinoma (BCC) for immunocompetent adults | Apply 5 times per week for full 6 weeks | Tumor diameter | Diameter of cream droplet (mg imiquimod) |
| | | 0.5 to <1.0 cm | 4 mm (10 mg) |
| | | >1.0 to <1.5 cm | 5 mm (25 mg) |
| | | > 1.5 to 2.0 cm | 7 mm (40 mg) |

| External genital and perianal warts (condyloma acuminata) for patients age >12 | Apply a thin layer to wart area 3 times per week until total clearance of warts or for a maximum of 16 weeks | |

*generic available
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Zyclara</strong> (imiquimod 3.75% cream)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Clinically typical, visible or palpable AK of the full face or balding scalp for immunocompetent adults</td>
<td>Apply a thin film (up to two packets) to treatment area once daily before bedtime to the skin of the affected area (either the face or balding scalp) for two 2-week treatment cycles separated by a 2 week no treatment period.&lt;sup&gt;cdg&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>External genital and perianal warts (condyloma acuminata) for patients age ≥12</td>
<td>Apply a thin layer (up to one packet) once a day to the external genital/perianal warts until total clearance or for up to 8 weeks.&lt;sup&gt;cd&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Zyclara</strong> (imiquimod 2.5% cream)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Clinically typical, visible or palpable AK of the full face or balding scalp for immunocompetent adults</td>
<td>Apply a thin film (up to two packets) to treatment area once daily before bedtime to the skin of the affected area (either the face or balding scalp) for two 2-week treatment cycles separated by a 2 week no treatment period.&lt;sup&gt;cdg&lt;/sup&gt;</td>
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*generic available

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<tr>
<th><strong>Topical Ingenol</strong></th>
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<tbody>
<tr>
<td><strong>Picato</strong>® (ingenol gel 0.015%, 0.05%))</td>
<td>Topical treatment of actinic keratosis</td>
<td>Face or scalp with 0.015%: apply once daily for 3 consecutive days Trunk or extremities with 0.05%: apply once daily for 2 consecutive days For application of up to one contiguous skin area of approximately 25 cm&lt;sup&gt;2&lt;/sup&gt; (5 cm x 5 cm) using one unit dose tube</td>
</tr>
</tbody>
</table>

**CLINICAL RATIONALE**

**Actinic Keratosis (AK)**

Treatment options for AK include ablative therapies (cryosurgery, curettage, phototherapy) and topical therapies.

Ablative therapies are performed in the office setting and are usually used in patients with limited lesions. Topical therapies are used for patients with multiple lesions (>15 AK). The anatomic location of lesions impacts the response time to topical treatments. AK on the face respond the quickest (more quickly than on the scalp), whereas lesions on the arms usually take the longest to respond. After topical treatment, AK may reoccur on the treated area.<sup>16</sup>

Topical fluorouracil is an established topical treatment for AK and has been considered the standard to which other topical treatments are compared. However, imiquimod cream and diclofenac gel are also considered effective therapies. Complete clearance of lesions occurs in about 50% of patients treated with topical fluorouracil, 45% of patients on imiquimod, and about 30 to 50% of patients on topical diclofenac.<sup>16</sup>

National Comprehensive Cancer Network [NCCN, U.S., 2016] guidelines suggest AKs should be treated aggressively at first development. Accepted modalities include cryosurgery, topical 5-FU, topical imiquimod, photodynamic therapy, curettage, and electrodesiccation. [Category
A review on treatment of AK suggests imiquimod 3.75% allows for a shorter duration of treatment over a larger skin surface area (200 cm² vs. 25 cm² for 5% cream). Absolute clearance rate is higher for the 5% cream, at 45%, compared to 35% for daily use of the 3.75% preparation, and the median reduction in AK is 83%. Use of the 5% cream can give up to 57% clearance if used three times per week for 16 weeks. If inflammation is intolerable, frequency of application can be reduced to once or twice per week with preservation of efficacy. The addition of lesion-directed cryosurgery prior to application gives greater clearance than either therapy alone.

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)
The likelihood of curing superficial BCC strongly correlates with a number of risk factors: tumor size (increasing size, higher recurrence rate), tumor site (central face, higher recurrence rate), clinical margins (poorly defined, higher recurrence rate), histology (perineural or perivascular, higher risk of recurrence), history (previously recurrent, higher risk of further recurrence), and immunosuppression. The absence or presence of these factors allows clinicians to assign individual lesions as being at high or low risk of recurrence following treatment.

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. Although surgery and radiotherapy remain the treatments of choice for most high risk lesions, topical and non-surgical treatments are options to treat low risk lesions.

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. For all available treatments except surgical removal, the initial response rate is 60-70% and 20-30% will have a recurrence.

A Canadian review (2013) suggests imiquimod or podophyllotoxin (each limited to affected areas <10 cm²), and cryotherapy or trichloroacetic acid (each limited by patient pain tolerance), remain the first choice treatments for genital warts.
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.14

Guidelines classify treatments into patient applied and provider applied modalities.14,15,16
- Patient applied modalities include: podofilox 0.5% solution or gel, imiquimod 5% cream, and sinescethcichs ointment.
- Provider applied modalities include cryotherapy, podophyllin resin, trichloroacetic acid or bichloroacetic acid, and surgical removal.

For additional clinical information see Prime Therapeutics Formulary Chapter 14.5Y: Topical Immunomodulators.

Topical Diclofenac Gel, Fluorouracil Cream, Imiquimod Cream, and Ingenol Gel Prior Authorization with Quantity Limit

OBJECTIVE
The intent of the Topical Diclofenac Gel, Fluorouracil Cream, Imiquimod Cream, and Ingenol Gel Prior Authorization with Quantity Limit program is to encourage appropriate selection of patients for treatment according to product labeling, clinical studies, and/or guidelines, and to promote the use of the cost effective generics. The PA program defines appropriate use as therapy for a Food and Drug Administration (FDA) approved label indication. In addition, the PA program will review for quantities and duration of therapy consistent with FDA labeled recommended dosing, clinical studies, and/or guidelines.

TARGET DRUGS
Diclofenac Gel
Solaraze (diclofenac gel)\(^b\)

Fluorouracil Cream
Carac (fluorouracil cream)
Fluorouracil cream
Fluoroplex (fluorouracil cream)
Efudex (fluorouracil cream)\(^a\)
Tolak (fluorouracil cream)

Imiquimod Cream
Aldara (imiquimod cream)\(^a\)
Zyclara (imiquimod cream)

Ingenol Gel
Picato (ingenol gel)

\(^a\) – generic available and not included in prior authorization program
\(^b\) – generic available and included in prior authorization program

PROGRAM PRIOR AUTHORIZATION, QUANTITY AND DURATION LIMIT

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code for Prior Authorization</th>
<th>Quantity Limit (applies to all MSC Codes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac Gel</td>
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<tr>
<td>Solaraze (diclofenac gel)(^b) 3% gel</td>
<td>90374035304020</td>
<td>M, N, O, Y</td>
<td>Actinic keratosis: one 100 gram tube per month for up to 90 days</td>
</tr>
<tr>
<td>Fluorouracil Cream</td>
<td>Carac (fluorouracil cream), Fluorouracil Cream 0.5% cream</td>
<td>90372030003705</td>
<td>M, N, O, Y</td>
</tr>
<tr>
<td>Brand (generic)</td>
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</tbody>
</table>
| Efudex (fluorouracil cream)<sup>a</sup>, 5% cream | 90372030003730 | M, N, O | Multiple actinic or solar keratosis: one 40 gram tube per month for up to 4 weeks  
Superficial basal cell carcinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites: two 40 gram tubes per month for up to 12 weeks |
| Fluoroplex (fluorouracil cream) 1% cream | 90372030003710 | M, N, O, Y | Multiple actinic or solar keratosis: one 30 gram tube per month for up to 6 weeks |
| Tolak (fluorouracil cream) 4% | 90372030003725 | M, N, O, Y | Actinic Keratosis: one 40 gram tube per month for up to 4 weeks |
| **Imiquimod Cream** | | | |
| Aldara (imiquimod cream)<sup>a</sup> 5% cream | 90773040003720 | M, N, O | External genital and perianal warts or Actinic keratosis: 12 packets per month for up to 4 months  
Superficial basal cell carcinoma: 24 packets per month for up to 2 months |
| Zyclara (imiquimod cream) 2.5% | 90773040003710 | M, N, O, Y | Actinic keratosis: 56 packets for up to 6 weeks  
two 7.5 gm pumps for up to 6 weeks  
one 15 gm pump for up to 6 weeks |
| Zyclara (imiquimod cream) 3.75% | 90773040003715 | M, N, O, Y | Actinic keratosis: 56 packets for up to 6 weeks  
two 7.5 gm pumps for up to 6 weeks  
one 15 gm pump for up to 6 weeks  
External genital or perianal warts (condyloma acuminata): 56 packets for up to 8 weeks  
two 7.5 gm pumps for up to 8 weeks  
one 15 gm pump for up to 8 weeks |

**Ingenol Gel**
**Brand (generic)** | **GPI** | **Multisource Code for Prior Authorization** | **Quantity Limit (applies to all MSC Codes)**
---|---|---|---
Picato (ingenol gel) 0.015% | 90378035204020 | M, N, O, Y | Actinic keratosis (face or scalp): 3 tubes for up to 90 days
Picato (ingenol gel) 0.05% | 90378035204040 | M, N, O, Y | Actinic keratosis (trunk or extremities): 2 tubes for up to 90 days

**PRIOR AUTHORIZATION CRITERIA FOR APPROVAL**

**Solaraze, diclofenac gel** will be approved when BOTH of the following are met:
1. ONE of the following:
   a. The patient’s medication history includes at least one generic fluorouracil cream or generic imiquimod cream in the past 90 days OR
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to an available generic fluorouracil cream or generic imiquimod cream

   AND

   2. The patient has a diagnosis of actinic keratosis AND ONE of the following:
      a. The quantity prescribed does not exceed one 100 gram tube per month for up to 90 days.
      OR
      b. The quantity exceeds the set quantity and the prescriber has submitted documentation in support of the requested quantities and/or duration of therapy for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

**Carac, Fluorouracil Cream** will be approved when BOTH of the following are met:
1. ONE of the following:
   a. The patient’s medication history includes generic fluorouracil cream in the past 90 days OR
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to an available generic fluorouracil cream

   AND

   2. The patient has diagnosis of multiple actinic or solar keratosis AND ONE of the following:
      a. The quantity prescribed does not exceed one 30 gram tube over 4 weeks OR
      b. The quantity exceeds the set quantity and the prescriber has submitted documentation in support of the requested quantities and/or duration of therapy for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

**Efudex** will be approved when ALL of the following is met:
1. ONE of the following:
   a. The patient’s medication history includes generic fluorouracil cream in the past 90 days OR
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to an available generic fluorouracil cream
AND
2. ONE of the following:
   a. The patient has a diagnosis of multiple actinic or solar keratosis AND ONE of the following:
      i. The quantity prescribed does not exceed one 40 gram tube over 4 weeks
         OR
      ii. The quantity exceeds the set quantity and the prescriber has submitted documentation in support of the requested quantities and/or duration of therapy for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist
   OR
   b. The patient has a diagnosis of superficial basal cell carcinoma AND ONE of the following:
      i. The quantity prescribed does not exceed two 40 gram tubes per month over 12 weeks
      OR
      ii. The quantity exceeds the set quantity and the prescriber has submitted documentation in support of the requested quantities and/or duration of therapy for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

Fluoroplex will be approved when BOTH of the following are met:
1. ONE of the following:
   a. The patient’s medication history includes generic fluorouracil cream in the past 90 days
   OR
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to an available generic fluorouracil cream

AND
2. The patient has a diagnosis of multiple actinic or solar keratosis AND ONE of the following:
   a. The quantity prescribed does not exceed one 30 gram tube over 6 weeks
   OR
   b. The quantity exceeds the set quantity and the prescriber has submitted documentation in support of the requested quantities and/or duration of therapy for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

Tolak will be approved when BOTH of the following are met:
1. ONE of the following:
   a. The patient’s medication history includes generic fluorouracil cream in the past 90 days
   OR
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to an available generic fluorouracil cream

AND
2. The patient has a diagnosis of actinic keratosis AND ONE of the following:
   a. The quantity prescribed does not exceed one 40 gram tube over 4 weeks
   OR
   b. The quantity exceeds the set quantity and the prescriber has submitted documentation in support of the requested quantities and/or duration of therapy for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist
**Aldara** will be approved when BOTH of the following are met:

1. **ONE of the following:**
   a. The patient’s medication history includes generic imiquimod cream in the past 90 days
   **OR**
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to an available generic imiquimod cream

2. **ONE of the following:**
   a. The patient has a diagnosis of external genital and/or perianal warts/condyloma acuminata **AND** ONE of the following:
      i. The quantity prescribed does not exceed 12 packets/month over 4 months
      **OR**
      ii. The quantity exceeds the set quantity and the prescriber has submitted documentation in support of the requested quantities and/or duration of therapy for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist
   **OR**
   b. The patient has a diagnosis of actinic keratosis **AND** ONE of the following:
      i. The quantity prescribed does not exceed 12 packets/month over 4 months
      **OR**
      ii. The quantity exceeds the set quantity and the prescriber has submitted documentation in support of the requested quantities and/or duration of therapy for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist
   **OR**
   c. The patient has a diagnosis of superficial basal cell carcinoma **AND** ONE of the following:
      i. The quantity prescribed does not exceed 24 packets/month over 2 months
      **OR**
      ii. The quantity exceeds the set quantity and the prescriber has submitted documentation in support of the requested quantities and/or duration of therapy for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

**Zyclara 2.5%** will be approved when BOTH of the following are met:

1. **ONE of the following:**
   a. The patient’s medication history includes generic imiquimod cream in the past 90 days
   **OR**
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to an available generic imiquimod cream

2. The patient has a diagnosis of actinic keratosis **AND** ONE of the following:
   a. The quantity prescribed does not exceed 56 packets, two 7.5 gm pumps, or one 15 gm pump over 6 weeks
   **OR**
   b. The quantity exceeds the set quantity and the prescriber has submitted documentation in support of the requested quantities and/or duration of therapy for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist
Zyclara 3.75% will be approved when ALL of the following are met:
1. ONE of the following:
   a. The patient’s medication history includes generic imiquimod cream in the past 90 days
   **OR**
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to an available generic imiquimod cream

   **AND**
2. ONE of the following:
   a. The patient has a diagnosis of actinic keratosis **AND** ONE of the following:
      i. The quantity prescribed does not exceed 56 packets, two 7.5 gm pumps, or one 15 gm pump over 6 weeks
      **OR**
      ii. The quantity exceeds the set quantity and the prescriber has submitted documentation in support of the requested quantities and/or duration of therapy for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist
   **OR**
   b. The patient has a diagnosis of external genital or perianal warts/condyloma acuminata **AND** ONE of the following:
      i. The quantity prescribed does not exceed 56 packets, two 7.5 gm pumps, or one 15 gm pump over 8 weeks
      **OR**
      ii. The quantity exceeds the set quantity and the prescriber has submitted documentation in support of the requested quantities and/or duration of therapy for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

Picato 0.015% will be approved when BOTH of the following are met:
1. ONE of the following:
   a. The patient’s medication history includes generic fluorouracil cream or generic imiquimod cream in the past 90 days
   **OR**
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to an available generic fluorouracil cream or generic imiquimod cream

   **AND**
2. ONE of the following:
   a. The patient has a diagnosis of actinic keratosis of the face or scalp **AND** ONE of the following:
      i. The quantity prescribed does not exceed 3 tubes over 90 days
      **OR**
      ii. The quantity exceeds the set quantity and the prescriber has submitted documentation in support of the requested quantities and/or duration of therapy for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

Picato 0.05% will be approved when BOTH of the following are met:
1. ONE of the following:
   a. The patient’s medication history includes generic fluorouracil cream or generic imiquimod cream in the past 90 days
   **OR**
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to an available generic fluorouracil cream or generic imiquimod cream
2. ONE of the following:
   a. The patient has a diagnosis of actinic keratosis of the trunk or extremities AND ONE of the following:
      i. The quantity prescribed does not exceed 2 tubes over 90 days 
      OR
      ii. The quantity exceeds the set quantity and the prescriber has submitted documentation in support of the requested quantities and/or duration of therapy for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

   **Length of Approval:** up to 12 months