Criteria for Use of Topical Imiquimod

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

These criteria were based on the best clinical evidence currently available. The recommendations in this document are dynamic, and will be revised as new clinical information becomes available. This guidance is intended to assist practitioners in providing consistent, high-quality, cost-effective drug therapy. These criteria are not intended to interfere with clinical judgment; the clinician must ultimately decide the course of therapy based on individual patient situations.

Criteria for Use	Yes	No
All of the following criteria must be met (answered YES) to use imiquimod.		
The provider documents that, after discussing treatment options with the patient, surgical methods (including cryosurgery) are deemed to be medically less appropriate treatment for the patient's lesions or are refused by the patient, OR that medical therapy is indicated as an adjunct to or instead of surgical methods.	☐	☐
Patient follow-up can be reasonably assured.	☐	☐
Patient fulfills any one of the criteria in either A, B, or C below. ***Use caution when prescribing imiquimod in immunocompromised patients.***	☐	☐
A. Patient is under the care of a dermatologist and meets any of the following conditions: ☐ Actinic Keratosis—must have clinically typical, nonhyperkeratotic, nonhypertrophic lesions AND Patient has had a documented inadequate response after at least one 4-week treatment course of topical 5-fluorouracil 0.5% to 2% (one 3-week course for 5% formulation), OR has a documented intolerance or contraindication to 5-fluorouracil formulations. ☐ Superficial Basal Cell Carcinoma—biopsy-confirmed; located on the trunk (not anogenital skin), neck, extremities (not hands and feet), or head (excluding areas within 1 cm of the eyes, nose, and mouth) *Topical 5-fluorouracil 5% is also FDA-approved for sBCC and, used with occlusion, is an alternative to consider in selected patients with small, thin, superficial tumors in whom follow-up can be reasonably assured.* ☐ Intraepithelial neoplasia / Bowen's disease / bowenoid papulosis / squamous cell carcinoma in situ—histologically confirmed AND Patient has had a documented inadequate response after at least 4 weeks of treatment with topical 5-fluorouracil 5% formulations with occlusion OR has a documented intolerance or contraindication to 5-fluorouracil formulations. ☐ Nodular basal cell carcinoma—biopsy-confirmed (excluding areas of the head within 1 cm of the eyes, nose, and mouth)		
B. Patient is under the care of a dermatologist, gynecologist, urologist, or Women's Health provider and meets the following conditions: ☐ Isolated external genital warts (< 10) on the penile shaft, glans or vulvar areas or isolated perianal warts AND Patient has had a documented inadequate response to topical 0.5% podofilox (at least 4 one-week cycles) or podophyllin (25% or higher strength for at least 4 weekly applications), or trichloroacetic acid (80% or higher strength for at least 4 weekly applications) OR has a documented contraindication or intolerance to any one of these agents. .		
☐ Extensive or severe external genital or perianal warts; e.g., more than 20 to 30 individual warts or warts involving large areas of skin in areas otherwise difficult to treat with typical destructive modalities such as cryotherapy or podophyllin.		

C. Patient is under the care of a dermatologist or primary care provider and meets any of the following conditions:

- ☐ Any type of cutaneous wart located on the face
- ☐ Nongenital, nonfacial flat warts (*verruca plana)* in patients who have a documented intolerance, contraindication, or inadequate response to 2 weeks of topical salicylic acid therapy AND either 5 weeks of topical 5-fluorouracil 1% to 5% or 3 weeks of topical tretinoin 0.025% to 0.5%, each alone or as adjunct to other therapy.
- ☐ Palmar, plantar, or nonfacial common warts in patients who have a documented intolerance, contraindication, or inadequate response to 2 weeks of topical salicylic acid alone or as adjunct to other therapy

Exclusions	**Yes**	**No**
Patient should not receive imiquimod if any one of the following criteria are met.		
For any patient:		
Hypersensitivity to imiquimod or other product components	☐	☐
Prevention of recurrence of herpes genitalis (shown to be ineffective)	☐	☐
NO beneficial response 12 weeks (for superficial basal cell carcinoma) or 16 weeks (for actinic keratosis and external genital wart) after the *start* of therapy	☐	☐

Recommended Maximal Doses	**Yes**	**No**
For patients with superficial basal cell carcinoma		
Prescribed dose is not more frequent than 5 times per week. *Although a 7-times-per-week dosing regimen of imiquimod cream 5% has been shown to be efficacious, it has been shown to be not better than 5 times per week.*	☐	☐
For patients with external genital warts		
Prescribed dose is not more frequent than 3 times per week. *Doses more frequent than the recommended 3 times weekly regimen have been shown to increase toxicity but not efficacy.*	☐	☐

Weigh Risks Versus Benefits

Some experts consider imiquimod to be a useful, albeit costly, agent for a number of off-label uses. Other medical therapies or surgical methods can usually be used, but some experts may consider imiquimod to be appropriate as a first-line agent in selected individuals. There are a number of off-label uses and doses that are supported by only small and single (unverified) randomized controlled trials, uncontrolled observational studies, or case reports/series. *Consider the appropriateness of use of topical imiquimod on a case-by-case basis. Use caution in patients who have autoimmune and other immune-mediated disorders, as imiquimod is an immune modulator*. It is not clear whether imiquimod will be effective or to what extent it will be effective in immunosuppressed patients. In patients with cancers that tend to metastasize, consider that imiquimod may limit locoregional spread but may not prevent lymphogenous / systemic metastasis.

Potential off-label uses supported by single randomized controlled trials include

- ❑ cutaneous leishmaniasis (add-on therapy)
- ❑ molluscum contagiosum
- ❑ squamous cell carcinoma in renal transplant recipients (preventive therapy)
- ❑ external genital warts in HIV-infected adults with CD4 counts ≥ 100 and Karnofsky score ≥ 70 (ineffective in complete clearance of warts but significantly reduced wart area)

Conditions for which imiquimod treatment was reported to be beneficial in uncontrolled observational studies or case reports/series include

- ❑ molluscum contagiosum
- ❑ lentigo maligna / melanoma in situ
- ❑ squamous cell carcinoma (preventive therapy).
- ❑ pyogenic granuloma

Off-label doses whose superiority over FDA-recommended doses are currently not supported by appropriately designed randomized controlled trials include

- ❑ dosing 3 times per week in actinic keratosis (lack of dose-controlled randomized trials, but safety and efficacy are supported by vehicle-controlled randomized trials). Preliminary results of a double-blind, long-term, observational follow-up study suggest there were numerically lower recurrence rates among patients who had achieved complete clearance in phase III trials evaluating imiquimod dosed 3 times per week than among patients who achieved complete clearance in trials that used the FDA-recommended twice weekly dosing. However, the long-term study was conceived after completion of phase III trials, dosage comparisons were made indirectly without statistical analyses, and results may reflect selection bias. Indirect comparisons of vehicle-corrected complete clearance rates in short-term studies do not support that there is a difference in efficacy between the two doses, although local adverse events may be more common with the higher dosage. As there are RCTs to support using a thrice-weekly dosing regimen, the higher dosing frequency may be reasonable to consider in patients who are at relatively high risk for recurrence (e.g., because of lesion location, number and extent of lesions, skin type, co-morbidities, etc.) or have had recurrence of AK after twice weekly dosing.
- ❑ cycle therapy in actinic keratosis (lack of randomized trials; preliminary data)—involves application of imiquimod cream 5% once daily 3 days per week for 4 weeks followed by a rest period of 4 weeks, and repeating the 8-week cycle if necessary for any residual lesions up to a maximum of 3 cycles (24 weeks).

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