Ingenol Mebutate (PICATO) Gel

National Drug Monograph

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

*The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.*

# Executive Summary:

* Ingenol mebutate (PEP005; PICATO by Leo Pharma AS) is a diterpene ester extracted from the sap of a common garden plant (Euphorbia peplus) that has been used traditionally for skin cancer, warts and corns. Ingenol mebutate has a unique two-part mechanism of action involving direct cytotoxicity and neutrophil antibody stimulation. It is the fourth patient-administered, field-directed topical agent approved by the Food and Drug Administration for the treatment of actinic keratosis (AK).
* Each dose of ingenol mebutate is applied once daily to an affected contiguous skin area not more than 25 cm2, and the treatment duration with ingenol mebutate is only 2 to 3 days. A lower strength gel (0.015%) is indicated for AK lesions on the face and scalp, and a higher strength (0.05%) is indicated for the trunk and extremities. There is potential for dosing confusion because of the availability of two different strengths depending on the body area of application. As with the other available topical drug therapies for AK, it is important to avoid getting medication in the eyes. Product must be stored in a refrigerator at 2° to 8°C (36° to 46°F).
* Ingenol mebutate treatment had consistently moderate-to-large effect sizes in the treatment of AK, with NNTs for complete clearance (versus vehicle) of 3 (2 RCTs) for AK of the face or scalp, and NNTs of 3 and 5 (2 RCTs) for AK of the trunk or extremities. Durability of effects was evaluated at 12 months; recurrence rates were 54% for AK of the face or scalp and 50% for AK of the trunk or extremities.
* In meta-analytic indirect comparisons with topical diclofenac 3%, 5-fluorouracil (5FU) and imiquimod, ingenol mebutate had similar efficacy (complete clearance rates) despite a shorter course of therapy and similar, acceptable tolerability.
* CONCLUSIONS: Ingenol mebutate is a safe, well tolerated, cosmetically acceptable and efficacious short-duration treatment alternative to other topical field-based pharmacotherapies for nonhypertrophic, nonhyperkeratotic AK in immunocompetent individuals. The main advantages of ingenol mebutate relative to other topical pharmacotherapies are that it achieves similar complete clearance rates using a much shorter treatment duration, and the overall course of therapy, from start of treatment to recovery from local skin reactions, may be shorter than the actual treatment period alone (excluding recovery time) for other topical pharmacotherapies. Patient adherence to therapy may be better with ingenol mebutate than other topical drug therapies because of the simpler and shorter dosage regimen; however, this potential advantage has not been evaluated in head-to-head trials. The drug’s relative efficacy and safety in immunocompromised patients, long-term (> 1 year) durability of effects, recurrence rates and safety, and use in combination with other drug and nondrug field-based therapies have not been adequately evaluated. Its unique dual mechanism of action may justify a trial of ingenol mebutate in patients who inadequately respond to other topical therapies; however, the efficacy of ingenol mebutate in recalcitrant AK has not been evaluated.

Introduction

Ingenol mebutate gel (PEP005; PICATO by Leo Pharma AS) is the fourth patient-administered, field-directed topical product approved by the Food and Drug Administration for the treatment of actinic keratosis (AK). AK, also referred to as solar keratosis, intraepidermal SCC and SCC in situ, is an ultraviolet light-induced epidermally-confined keratinocyte dysplasia that is thought to represent an early, premalignant lesion on the continuum of progression to invasive cutaneous squamous cell carcinoma (SCC). Risk factors for AK include age, male sex, geography, fair skin (Fitzpatrick skin types I-III), immune system deficiency, human papillomavirus infection, and genetic syndromes that increase UV sensitivity.[[1]](#endnote-1) AK is considered to be the most common skin lesion with malignant potential, and its presence indicates increased risk of all skin cancers.

The clinical course of AK is variable; lesions may remain stable, spontaneously regress or progress to dermis-invading SCC, and while some lesions regress new ones may appear. Many nonvisible subclinical lesions may exist for every visible AK lesion on the skin. Patients with AK have a chronic disease, as they continue to develop AK lesions during their lifetime. Estimates of the probability that *one AK lesion* will progress to cutaneous SCC vary widely, ranging from 0.03% to 20% per year.[[2]](#endnote-2) Individuals have an average of about 8 AK lesions; therefore, the probability that a *person* will develop cutaneous SCC is estimated to be 0.15% to 80%.[[3]](#endnote-3) In the VA’s Topical Tretinoin Chemoprevention Trial, the risk of progression of AK to primary invasive or in situ SCC in the study’s high risk population was 0.60% at 1 year and 2.57% at 4 years.[[4]](#endnote-4) About 65% of all primary cutaneous SCCs and 36% of all primary basal cell carcinomas (BCCs) had originated from AK lesions.

Treatment is aimed at preventing the progression to SCC, relieving symptoms such as bleeding, and improving cosmesis. The interventions may be provider- or patient-administered, and be lesion-directed (when there are isolated lesions) or field-directed (when there are multiple lesions in a given area). Field-directed treatment is applied to a whole area of actinically damaged skin that may have multiple visible and subclinical lesions due to field cancerization. Lesion-directed therapies are liquid nitrogen, electrodessication and curettage. The physician-administered, field-directed therapies include photodynamic therapy, chemical peels, dermabrasion and laser. The patient-administered field-directed therapies are topical formulations of ingenol mebutate, 5-fluorouracil (5FU), imiquimod and diclofenac. Topical retinoids have had mixed results in clinical trials. Improved response has been shown when a topical agent (diclofenac,[[5]](#endnote-5) imiquimod[[6]](#endnote-6),[[7]](#endnote-7) or 5FU[[8]](#endnote-8)) was investigated as a pretreatment before cryotherapy. Because field-directed therapies treat subclinical lesions, they are generally preferred as they may be more appropriate than lesion-directed therapies for preventing SCC.

A number of factors other than efficacy, safety, tolerability, size of the affected area (individual lesion versus field) and delivery of therapy (patient-applied or provider-performed) may be important considerations when specific field-directed drug therapy is selected. Other considerations include lesion characteristics (hypertrophic AKs generally require destructive therapies such as cryotherapy, surgery, or dermabrasion), distribution of lesions, duration of therapy, tolerability of treatment (e.g., in terms of pain, inflammation, hypopigmentation, and scarring), recurrence rates, treatment cost, accessibility of treatment, patient adherence with therapy, history of skin cancer, immune status, previous treatment response and cosmetic appearance.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating ingenol mebutate gel for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

Ingenol mebutate (ingenol-3-angelate) is a purified, crystallized extract from the sap of the plant Euphorbia peplus L. (E. peplus; petty spurge, radium weed, cancer weed, wart weed or milkweed). E. peplus is a common garden weed in North America, Europe, North Africa, West Asia, New Zealand and Australia, and the ‘poisonous’ milky latex sap has been used for centuries as a traditional home remedy for skin cancers, warts and corns. Ingenol mebutate, a diterpene ester, is the main active moiety in E. peplus sap. The pharmaceutical-grade compound is not considered a botanical substance because of its purity.

The mechanism of ingenol mebutate is not fully understood. Ingenol mebutate modulates protein kinase C (PKC) functions by activating PKC delta and inhibiting PKC alpha. It seems to have a two-part mechanism of action. It induces local lesional cell death (chemoablation) preferentially in transformed keratinocytes by disrupting cell plasma membranes and mitochondria. It also promotes an inflammatory response and eliminates remaining tumor cells by inducing neutrophil-mediated antibody-dependent cellular toxicity. The cytotoxic functions of neutrophils are necessary for effective ablation of lesions. Results of mice studies showed that ingenol mebutate reduced mutant p53 tumor suppressor gene patches by about 70% relative to controls. These results suggested that the drug has the potential to clear subclinical lesions since p53 mutations may be early initiating events in the formation of AK and SCC.1 Ingenol mebutate is also being considered for investigations into its chemotherapeutic potential for other types of hematologic and solid tumor cancers.

Blood concentrations of ingenol mebutate or its acyl isomer metabolites were not detectable (< 0.1 ng/ml) after application of about 1 ml of 0.05% gel to a 100-cm2 contiguous area of skin (equivalent to four times the recommended application area) on the forearm daily for 2 consecutive days.

# FDA Approved Indication(s)

Topical treatment of actinic keratosis.

# Potential Off-label Uses

*This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety’s* [*Guidance on “Off-label” Prescribing*](http://vaww.national.cmop.va.gov/PBM/Directives%20Policies%20and%20Information%20Letters/Guidance%20on%20Off%20Label%20Prescribing.pdf) *(available on the VA PBM Intranet site only).*

* Topical treatment of basal cell carcinoma (BCC),[[9]](#endnote-9) squamous cell carcinoma (SCC) and other intraepidermal carcinoma (IEC) such as Bowen’s disease. Favorable results were seen in an observational phase I/II clinical study of E. peplus sap in 36 patients with BCC, SCC or IEC, 43% of whom had failed previous treatments.[[10]](#endnote-10) Ingenol mebutate is being developed for treatment of nonmelanoma skin cancer.
* Wart and corn removal (based on traditional use of E. peplum sap)
* Use on hypertrophic, hyperkeratotic AK lesions
* Use on AK skin areas larger than the recommended 25-cm2 (5 x 5-cm or 2 x 2-in) treatment area
* Use for AK in immunosuppressed or organ transplant patients
* Use in combination or sequence with other AK therapies such as cryotherapy

# Alternative Therapies

For isolated AK lesions, liquid nitrogen cryotherapy is often used. Unlike field therapies, only visible lesions are destroyed, whereas early subclinical lesions are not eliminated. Cryotherapy may be used in combination with field therapies.

For multiple lesions, provider-administered photodynamic therapy and patient-administered topical therapies are preferable. Patient-administered, field-directed topical pharmacotherapeutic alternatives to ingenol mebutate gel on the VA National Formulary are

* 5-fluorouracil (5-FU) topical cream and topical solution and
* Imiquimod cream

The advantages and disadvantages of the patient-administered, field-directed topical drug therapies for AK are summarized in Table 1.

Table 1 Summary of Patient-administered, Field-directed Topical Drug Therapies for AK

| Treatment and Dosage | Mechanism | Advantages | Disadvantages | Other Considerations |
| --- | --- | --- | --- | --- |
| **Adapalene**  0.1% or 0.3% gel (DIFFERIN by Galderma Labs and generic by Taro) daily for 4 wks then twice daily | Activates intranuclear retinoic acid receptors (RAR) with selectivity for RARβ and RARγ, independent of p53 | May improve appearance of photodamaged skin | Insufficient, inconsistent data on efficacy/safety of retinoids in AK. | Off-label use.  Only 1 RCT to support efficacy of gel. Cream formulation (0.1%) was not studied.  Results were not supported by a larger trial which showed that topical tretinoin 0.1% cream was ineffective. |
| **Diclofenac Sodium**  3% gel (SOLARAZE by PharmaDerm) twice daily for 60–90 d | Cyclooxygenase inhibitor | Well tolerated; limited inflammation, irritation and erythema  Seems to be better tolerated than 5FU | Long treatment duration, delayed time to complete / optimal healing (up to 30 d after end of tx)  May be less effective than 5FU  Recommended for face; shown to be ineffective on non-facial areas (e.g., scalp, arms, forearms, hands)  Dry skin, pruritus, erythema, rash at application site; potential allergic reaction | No recurrence data  Shorter courses are less effective.  Transdermal systemic absorption is low (Cp ≤ 20 ng/ml). However, there are warnings for use in pts with active gastrointestinal ulceration or bleeding and severe renal or hepatic impairments. |
| **5-Fluorouracil (5FU)**   * 0.5% cream (CARAC by Valeant) once daily for 4 wk * 1% cream (generic by Aqua) on entire face or other affected areas twice daily for 2–6 wk * 5% cream (EFUDEX by Valeant; generics by Mylan and Taro) or 2% or 5% solution (generics by Solco and Taro) on nonfacial areas twice daily until superficial erosion occurs, usually 2–4 wk | Thymidine depletion, decreased DNA synthesis, cell death | >50 y of experience; 90% effective in pts who can tolerate it; 50% responder rate for complete clearance of AK  0.5%: Better tolerated than higher strengths.  Suggested topical tx alternative for AK in solid organ transplant recipients | Inflammation lasts about 2 wk  Temporarily disfiguring with long healing time; erythema, blistering, necrosis, erosion then reepithelialization takes about 4–6 wk (including 2–4 wks of tx) | Topical corticosteroids may be used following 5FU course to reduce inflammation.  More frequent doses and longer tx duration with 1% cream may be needed for tx of areas other than face and neck. |
| **Imiquimod**   * 2.5% or 3.75% cream (ZYCLARA by Valeant): once daily to either the entire face or balding scalp for two 2-week treatment cycles separated by a 2-week no-treatment period * 5% cream (ALDARA by Valeant; generics by Taro, Perrigo, Sandoz and Global Pharma Corp.): apply to contiguous 25 cm2 area (forehead, scalp or one cheek) 2–3 times per wk for 12–16 wk | Toll-like receptor agonist (TLR-7, TLR-8); induction of proinflammatory cytokins; Th-1 antitumor response; upregulation of apoptosis | Milder erythema than 5FU  Relatively short duration of therapy with 3.75% cream  Lower incidence of treatment-emergent adverse events with 3.75% cream than 5% cream applied for 16 wk  Low 1-y recurrence rates  Suggested topical tx alternative for AK in solid organ transplant recipients | Recommended use is limited to AK on the head  Erythema, edema, erosion/ulceration, exudate, scabbing/crusting, pain, pruritus  Severe erosion/ulceration in 9%–11% of pts using 2.5% or 3.75% cream  Flu-like symptoms  Lymphadenopathy was seen in 2%–3% of patients; resolves by 4 wk after end of tx | Less frequent dosing (1–2 times per wk) of 5% cream may improve tolerability  Shorter courses of 5% cream treatment with a treatment-free interval may also be effective for nonhypertrophic AK.  5% cream application is limited to a contiguous 25 cm2 area (whereas the lower strengths have no limitation on size of application area). |
| **Ingenol Mebutate**  Apply gel (PICATO) once daily to a 25 cm2 area   * 0.015%: on the face or scalp for 3 days * 0.05%: on the trunk or extremities for 2 days |  | Short duration of therapy  Durable effects at 1 y: 54%–55% recurrence rate; 87% reduction in lesion count  The only alternative to 5FU that is approved for AK on trunk or extremities | Erythema, scaling, crusting, swelling, edema, vesiculation, pustulation, ulceration, dyspigmentation, pain, pruritus, irritation |  |

Sources: UpToDate Online (2013)[[11]](#endnote-11); Uhlenhake (2013)[[12]](#endnote-12)

# Dosage and Administration

The lower strength of ingenol mebutate gel (0.015%) is indicated for AK lesions on the face and scalp, and the higher strength gel (0.05%) is indicated for AK lesions on the trunk and extremities (Table 2). There is potential for dosing confusion because of the availability of two different strengths depending on the body area of application.

Table 2 Dosage Regimen

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Therapy** | **Formulation** | **Treatment Location(s)** | **Max. Single Contiguous Application Area or Max. Dose** | **No. of Doses Per Day** | **Duration of Therapy (d)** |
| Ingenol Mebutate Gel | 0.015% Gel in unit-dose tubes (PICATO, Leo Pharma) | Face and scalp | 25 cm2 (3.9 in2) | One, leave for 6 hours then may wash with soap and water | 3 consecutive days |
| 0.05% Gel in unit-dose tubes (PICATO, Leo Pharma) | Trunk and extremities | 25 cm2  (3.9 in2) | One, leave for 6 hours then may wash with soap and water | 2 consecutive days |

One unit-dose tube of ingenol mebutate should be used for up to one contiguous 25-cm2 skin area. Transfer of gel to other areas of skin or the eyes should be avoided. After application, the gel should be allowed to dry for 15 minutes. The application area should not be washed or touched for 6 hours. Thereafter, patients may wash the area with mild soap.

There are differences among the field-based topical therapies for actinic keratosis in dosage regimens (Table 3).

Table 3 Dosage Regimen for Other Topical Field-based Therapies for Actinic Keratosis

| Therapy | **Formulation** | Treatment Location(s) | **Max. Single Contiguous Application Area or Max. Dose** | **No. of Doses Per Day** | **Duration of Therapy (d)** |
| --- | --- | --- | --- | --- | --- |
| Diclofenac Gel | 3% Gel (SOLARAZE, Pharmaderm / Fougera Pharmaceuticals) | Scalp, forehead, face, forearm and hand | Studied up to 5 major body areas each measuring 5 x 5 cm2. Max. dose not established. | Two | 60–90  (Maximal effect may not be evident for up to 30 d after completion of therapy) |
| 5-Fluorouracil | 0.5% Cream (CARAC, Valeant Pharmaceuticals International) | Entire affected area of face or anterior bald scalp | Not established | One | Up to 28 |
| 1% Cream (FLUOROPLEX, Aqua Pharmaceuticals) | Entire face, other areas | Not established | Two | Usually 14–42 d |
| 5% Cream (EFUDEX, Valeant Pharmaceuticals International)  and  2% and 5% Solutions (Solco and Taro [generics]) | Lesions; body area not specified | Not established | Two | 14–28; stop when lesion reaches erosion stage  (Complete healing may not be evidence for 30–60 d after completion of therapy) |
| Imiquimod | 5% Cream (ALDARA by Valeant; various generic mfrs\*) | Face or scalp (not both concurrently) | 25 cm2 (one packet) on the face or scalp | Twice per week at bedtime, leave on for 8 h then remove with soap and water | 112 (i.e., 16 wk); do not extend tx duration |
| 3.75% Cream (ZYCLARA and ZYCLARA PUMP by Valeant)  and  2.5% Cream (ZYCLARA PUMP by Valeant) | Face or balding scalp | 0.5 g (2 packets or 2 full actuations of the pump) | One, at bedtime, leave on for 8 h then remove with soap and water | Two 14-d cycles separated by 14-d treatment-free period; do not extend tx duration |

Excludes adapalene, for which there is only one RCT in AK.

\*Manufacturers of AB-rated imiquimod cream 5%: Apotex, Fougera, Glenmark, Global, Perrigo, Sandoz, Taro

One potential advantage with ingenol mebutate is the short (2- or 3-day) treatment duration.

Like other topical drug therapies, ingenol mebutate is approved for treating an area up to only 25 cm2 (5 x 5 cm or about 2 x 2 in), and each unit-dose tube of ingenol mebutate contains only enough medication to cover an area of that size. Other affected areas may be treated simultaneously on an off-label basis (and patients will likely misuse ingenol mebutate by treating areas larger than prescribed) but multiple tubes will need to be used and local application reactions may be more severe when treating a larger total area.

## Storage and stability

Store in a refrigerator at 2° to 8°C (36° to 46°F); excursions are permitted between 0° and 15°C (32° and 59°F). Protect from freezing.

# Efficacy

Efficacy measures of interest include cosmetic acceptability, relief of associated symptoms, clearance of subclinical lesions and prevention of skin cancer.

## Efficacy Measures Used in Clinical Trials

* Complete Clearance: no (zero) clinically visible AK lesions in the treatment area.
* Partial Clearance: 75% or greater reduction in number of AK lesions from baseline in the treatment area
* Recurrence Rate: percentage of subjects with any identified AK lesion in the previously treated area who achieved complete clearance at Day 57.

## Summary of efficacy findings

Two small Phase II studies that supported further investigation of ingenol mebutate for AK are not included in this review.[[13]](#endnote-13),[[14]](#endnote-14) Four 8-week, Phase III, multicenter, double-blind, vehicle-controlled randomized clinical trials (RCTs)[[15]](#endnote-15),[[16]](#endnote-16),[[17]](#endnote-17),17 were performed, and results were reported in one publication.14 Two studies evaluated ingenol mebutate (at the subsequently approved recommended doses) for AK of the face or scalp (N=547), and two studies for AK of the trunk or extremities (N=458). Methodologies were similar for the four trials: each subject had 4 to 8 clinically typical, visible, discrete AK lesions within a 24-cm2 contiguous treatment area, excluding hypertrophic and hyperkeratotic lesions. Completion rates for the trials were high (98% for the two studies for AK of face or scalp, and for the two studies for AK of the trunk or extremities). About 85% of subjects were male in the face/scalp studies and 62% were male in the trunk/extremities studies. All subjects treated with ingenol mebutate were Caucasian. Mean ages were 64 years and 66 years for the face/scalp and trunk/extremities studies, respectively (overall age range, 34–89 years), and 94% of subjects had Fitzpatrick skin type I, II or III.

* Results reflect a Caucasian study population of mostly men with mean ages of 64–66 years.
* There were no studies directly comparing ingenol mebutate with other active treatment alternatives.
* Ingenol mebutate treatment had consistently moderate-to-large effect sizes in the treatment of AK, with NNTs for complete clearance (versus vehicle) of 3 (2 RCTs) for AK of the face or scalp, and NNTs of 3 and 5 (2 RCTs) for AK of the trunk or extremities. See Table 4 to Table 6.

Table 4 Results of Clinical Trials, AK of Face or Scalp

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | STUDY 1 | |  | STUDY 2 | |
| Outcome, Day 57 | IMG 0.015%  N=135 | VEH  N=134 |  | IMG 0.015%  N=142 | VEH  N=136 |
| Complete Clearance Rate, n (%) | 50 (37) | 3 (2) |  | 67 (47) | 7 (5) |
| Scalp | 4/26 (15) | 0/25 (0) |  | 9/31 (29) | 1/25 (4) |
| Face | 46/109 (42) | 3/109 (2) |  | 58/111 (52) | 6/111 (5) |
| Partial Clearance Rate, n (%) | 81 (60) | 9 (7) |  | 96 (68) | 11 (8) |

IMG, Ingenol mebutate gel. VEH, Vehicle

Table 5 Results of Clinical Trials, AK of Trunk or Extremities

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | STUDY 3 | |  | STUDY 4 | |
| Outcome, Day 57 | IMG 0.05%  N=126 | VEH  N=129 |  | IMG 0.05%  N=100 | VEH  N=103 |
| Complete Clearance Rate, n (%) | 35 (28) | 6 (5) |  | 42 (42) | 5 (5) |
| Arm | 22/84 (26) | 4/82 (5) |  | 27/59 (46) | 3/67 (5) |
| Back of Hand | 4/25 (16) | 0/29 (0) |  | 6/28 (21) | 0/27 (0) |
| Chest | 8/9 (89) | 1/8 (13) |  | 3/5 (60) | 1/3 (33) |
| Other (inc. Shoulder, Back, Leg) | 1/8 (13) | 1/10 (10) |  | 6/8 (75) | 1/6 (17) |
| Partial Clearance Rate, n (%) | 56 (44) | 9 (7) |  | 55 (55) | 7 (7) |

IMG, Ingenol mebutate gel. VEH, Vehicle

Table 6 Complete Clearance, Effect Size

|  |  |  |
| --- | --- | --- |
| Outcome Measure, Day 57 |  |  |
| AK of Face or Scalp | Study 1 | Study 2 |
| NNT (95% CI) | 3 (3–4) | 3 (2–4) |
| AK of Trunk or Extremities | Study 3 | Study 4 |
| NNT (95% CI) | 5 (4–7) | 3 (3–4) |

## Long-term Durability / Recurrence

The Product Information reported that, in an observational follow-up study based on 108 subjects with AK of the face or scalp who achieved complete clearance on ingenol mebutate gel 0.015% in studies 1 and 2, the recurrence rate at 12-months was 54%.[[18]](#endnote-18) The recurrence rate at 12 months was 50% in 38 subjects with AK of the trunk or extremities who had achieved complete clearance on ingenol mebutate gel 0.05% in Study 4 then entered a follow-up study.

In the published long-term study, the sustained clearance rate after 12 months was reported as 46.1% for patients with AK on the face or scalp, and 44.0% for patients with AK on the trunk or extremities.[[19]](#endnote-19) The estimated median times to new or recurrent lesions in the treatment area were 365 days for face or scalp and 274 days for the trunk or extremities.

Recurrence was also reported in terms of a post hoc end point, the percentage reduction in the total number of AK (new or recurrent lesions) at 12 months relative to the number of lesions at baseline in the previous study for patients who had achieved complete clearance at day 57. The overall percentage reduction was referred to as sustained lesion reduction. The sustained lesion reduction rates compared with baseline were 87.2% in 100 study completers (of 108 study entrants) with AK of the face or scalp, and 86.8% in 71 study completers (of 76 entrants) with AK of the trunk or extremities.

There was no evaluation of potential treatment effects on the incidence of squamous cell carcinoma. Data on this outcome are also lacking in studies of other treatments for AK.19

## Indirect Comparisons from Meta-analysis

A Cochrane meta-analysis of placebo- and active-controlled trials evaluating different therapies for actinic keratosis included 83 randomized clinical trials (total N=10,036).[[20]](#endnote-20) The trials included 18 topical treatments, among other oral, mechanical and chemical interventions. Two ingenol mebutate studies[[21]](#endnote-21),[[22]](#endnote-22) were included for the primary outcome measure, “participant complete clearance” for all lesions (target and subclinical lesions); a third study[[23]](#endnote-23) evaluated only target lesions and results are not discussed here. Results for the efficacious field-directed topical treatments for which indirect comparative data were available are shown in Table 7.

Table 7 Results of Meta-analysis: “Participant Complete Clearance” of Target and New Lesions

| Topical Treatment  Agent / Comparator | K | N | RR (95% CI) | GRADE Quality | Comments |
| --- | --- | --- | --- | --- | --- |
| Active-controlled Trials, Immunocompetent | | | | | |
| 5-Fluorouracil 5% (high strength) vs. Imiquimod 5% | 2 | 89 | 1.85 (0.41–8.33) | Very low | High heterogeneity between studies; 5-FU tx was for 2–4 wks; imiquimod tx was for 4–16 wks across studies. Possible advantage of 5FU over imiquimod in complete clearance needs confirmation. Imiquimod 5% had better cosmetic outcomes than 5FU. |
| Diclofenac 3% vs. Imiquimod 5% x 12 wk | 1 | 49 | — | — | Diclofenac and imiquimod were “equivalent.” |
| Placebo- or Vehicle-controlled Trials, Immunocompetent | | | | | |
| Diclofenac 3% in 2.5% Hyaluronic Acid / Vehicle | 3 | 420 | 2.46 (1.66–3.66) | Moderate | NNT = 5.4  Pooled results from 30-, 60- and 90-d txs; assessment taken 30 d after tx. |
| 5-Fluorouracil 0.5% (low strength) / Vehicle x 1, 2 and 4 wk | 3 | 522 | 8.86 (3.67–21.44) | High | NNT = 8.5. Pooled results from 1-, 2- and 4-wk txs. The review did not include 1% 5FU cream. |
| Imiquimod 5% / Placebo x 3x/wk for 4–16 wk | 9 | 1871 | 7.70 (4.63–12.79) | High | NNT = 8  Tx was given for 3–24 wks; assessments taken at 0–20 wks post-tx. Imiquimod 5% had better cosmetic outcomes than 5-fluorouracil. Total number of doses did not seem to affect efficacy. |
| Imiquimod 3.75% / Placebo 1x/d for 2 wk on, 2 wk off, 2 wk on (assessed at 8–20 wk post-tx) | 3 | 730 | 6.45 (3.87–10.73) | High | 3.75% imiquimod given once daily may be more efficient than 5% imiquimod given twice weekly. |
| Ingenol mebutate 0.01%–0.05% / Vehicle 1x/d for 2–3 d | 2 | 456 | 4.50 (2.61–7.74) | [High]\* | NNT = 3.4 (Calc. 95% CI 3–5).  For changes in pigmentation (cosmetic outcomes), 95% CIs overlapped (0.01% and 0.05% gels). |
| Placebo- or Vehicle-controlled Trials, Immunocompromised | | | | | |
| Imiquimod 5% / Placebo | 1 | 43 | 18.5 (1.2 to 286.4) | Not reported | NNT not calculable. No placebo patient achieved complete clearance. |

K, Number of RCTs

\* The quality of the four ingenol mebutate trials (Lebwohl, et al., 2012) was not reported by Gupta, et al. (2012). Author of this monograph assessed the quality as high.

Based on point estimates of relative risks for participant complete clearance, the order of topical drug efficacy from highest to lowest seems to be 5-fluorouracil 0.5%, imiquimod, ingenol mebutate, followed by diclofenac. Based on 95% CIs, 5-fluorouracil and imiquimod each seems to be better than diclofenac (CIs do not overlap). Preliminary data from direct comparisons between 5-fluorouracil and imiquimod (2 RCTs with no or assessor-only blinding) suggest that 5-fluorouracil may produce a higher rate of complete clearance; however, these results need to be confirmed with additional studies.

The 95% CIs for 3-day treatment with ingenol mebutate overlap with those for longer treatment courses with each of the other agents; therefore, one cannot conclude that there are differences between ingenol mebutate and the other therapies. Similar benefits were obtained despite a shorter course of therapy with ingenol mebutate.

# Adverse Events (Safety Data)

Safety data from clinical trials reflect the experience of 499 subjects treated with ingenol mebutate gel at the recommended dosing regimen for AK (0.015% gel in 274 subjects with face or scalp lesions; 0.05% gel in 225 subjects with trunk or extremity lesions).

Long-term (12-month) data were available on 108 subjects with AK of the face or scalp, and 38 subjects with AK of the trunk or extremities.

## Deaths and Other Serious Adverse Events

None reported.

## Withdrawals Due to Adverse Events

There were no differences between ingenol mebutate and vehicle groups in the rates of withdrawals due to adverse events in both the face and scalp trial (0.4% in each treatment group) and the trunk and extremity trial (0.9% in each treatment group).15

According to the Cochrane review by Gupta (2012),19 no withdrawals due to adverse events were reported in two studies (total N=285),20,22 and 1 of 255 (0.4%) study patients withdrew due to an adverse event (pain) in a third study; however, the assigned treatment group was not identified.21 Findings are summarized in Table 8.

Table 8 Results of Meta-analysis: Withdrawals Due to Adverse Events

| Topical Agent / Comparator | K | N | RR (95% CI) | GRADE Quality | Comments |
| --- | --- | --- | --- | --- | --- |
| Active-controlled Trials |  |  |  |  |  |
| 5-Fluorouracil 5% (high strength) vs. Imiquimod 5% | 1 | 50 | Not estimable | Moderate | No WDAEs in either tx group |
| Diclofenac 3% in 2.5% Hyaluronic Acid vs. Imiquimod 5% | 1 | 49 | Not estimable | Moderate | No WDAEs in either tx group |
| Placebo- or Vehicle-controlled Trials | | | | | |
| Diclofenac in 2.5% Hyaluronic Acid / Vehicle | 4 | 592 | 3.59 (1.92 to 6.70) | High | NNT = 9.4 |
| 5-Fluorouracil 0.5% (low strength) / Vehicle | 1 | 177 | 5.41 (0.3to 96.2) | Very low | Incidence of WDAEs tended to increase with longer tx duration (NSD). The 5% and 0.5% 5FU creams are associated with similar WDAEs. |
| Imiquimod 5% / Placebo | 8 | 2290 | 2.59 (1.59 to 4.23) | Moderate | NNT = 27 |
| Imiquimod 3.75% / Placebo | 2 | 483 | 0.92 (0.22 to 3.93) | Moderate | NSD |
| Ingenol mebutate 0.01%–0.05% / Vehicle | 3 | 540 | — | — | No WDAEs in 2 RCTs; 1 WDAE in third RCT but tx group was not reported. |

K, Number of RCTs

## Common Adverse Events

Pooled adverse event data from the product information are shown in Table 9 and Table 10.

Table 9 Local Skin Reactions

|  | **Any Grade > Baseline** | |  | **Grade 4** | |
| --- | --- | --- | --- | --- | --- |
| **Reaction** | **IMG** | **VEH** |  | **IMG** | **VEH** |
| Face and Scalp | N=274 | N=271 |  | N=274 | N=271 |
| Erythema | 94% | 25% |  | 24% | 0% |
| Flaking / Scaling | 85% | 25% |  | 9% | 0% |
| Crusting | 80% | 17% |  | 6% | 0% |
| Swelling | 79% | 4% |  | 5% | 0% |
| Vesiculation / Pustulation | 56% | 0% |  | 5% | 0% |
| Erosion / Ulceration | 32% | 1% |  | 0% | 0% |
| Trunk and Extremities | N=225 | N=232 |  | N=225 | N=232 |
| Erythema | 92% | 19% |  | 15% | 0% |
| Flaking / Scaling | 90% | 19% |  | 8% | 0% |
| Crusting | 74% | 10% |  | 4% | 0% |
| Swelling | 64% | 6% |  | 3% | 0% |
| Vesiculation / Pustulation | 44% | 1% |  | 1% | 0% |
| Erosion / Ulceration | 26% | 3% |  | 1% | 0% |

Grades: 1 Mild; 2–3 Moderate; 4 Severe. IMG, Ingenol mebutate gel. VEH, Vehicle

Table 10 Rates of Adverse Events

|  |  |  |
| --- | --- | --- |
| **Reaction** | **IMG** | **VEH** |
| Face and Scalp | N=274 | N=271 |
| Pain, application site | 15% | 0% |
| Pruritus, application site | 8% | 1% |
| Infection, application site | 3% | 0% |
| Periorbital edema | 3% | 0% |
| Headache | 2% | 1% |
| Trunk and Extremities | N=225 | N=232 |
| Pruritus, application site | 8% | 0% |
| Irritation, application site | 4% | 0% |
| Nasopharyngitis | 2% | 1% |
| Pain, application site | 2% | 0% |
|  | | |

According to the Cochrane review by Gupta (2012),19 data on skin irritation per se was not available from the three studies20,21,22 included in the review.

Like the other topical treatments for AK, application site reactions are substantial; in particular, erythema with ingenol mebutate may often be severe (Grade 4 in 24% of patients). The local reactions generally resolved spontaneously in 2 to 4 weeks. Ingenol mebutate has been associated with headache and nasopharyngitis but seems to lack the systemic flu-like symptoms seen with imiquimod and the scarring that is possible with 5FU.

## Most Common Local Skin Reactions with Alternative Topical Drug Therapies

Patients may be able to distinguish and may prefer one agent over the others because of potential differences in the nature and quality of the application site reactions among the topical agents. The most frequent local skin reactions for each of the other topical agents are as follows:

**Diclofenac Gel**: Dry skin (32%), contact dermatitis with erythema / induration (9%), pruritus (4%), and contact dermatitis with vesicles (2%).

**5FU 0.5% Cream** (vs. vehicle): Erythema (93.4% vs. 59.8%), dryness (83.3% vs. 47.2%), burning (74.7% vs. 22%), erosion (44% vs. 13.4%), pain (43.6% vs. 5.5%), edema (35.4% vs. 4.7%).

**5FU 1% Cream:**Allergic contact dermatitis, burning, inflammation, irritation, pain, pruritus, and telangiectasia have been reported. Occasionally, hyperpigmentation and scarring have also been reported. No incidence rates were available.

**5FU 5% Cream and 2% and 5% Solutions:** Allergic contact dermatitis, burning, crusting, erosions, erythema, hyperpigmentation, irritation, pain, photosensitivity, pruritus, rash, scarring, soreness, and ulceration. No incidence rates were available.

**Imiquimod 2.5% and 3.75% Cream** (vs. vehicle): Erythema (96% and 96% vs. 78%), flaking/scaling/dryness (88% and 91% vs. 77%), scabbing/crusting (84% and 93% vs. 45%), edema (63% and 75% vs. 19%), erosion/ulceration (52% and 62% vs. 9%), exudate (39% and 51% vs. 4%).

## Cosmetic Outcomes

Ingenol mebutate therapy was associated with minimal dyspigmentation and minimal scarring.15

According to the Cochrane review by Gupta (2012; 3 RCTs,20,21,22 N=540), ingenol mebutate was not associated with scarring, but 17 (5.2%) of 325 ingenol mebutate–treated patients versus 1 (0.5%) of 189 vehicle-treated patients experienced pigmentation changes (RR 3.36; 95% CI 0.63–17.80; NSD). The RR point estimate for the 0.05% gel versus vehicle (RR 4.86; 95% CI 0.48–49.39) was higher than that for the 0.01% gel (RR 1.47; 0.08–25.88), with both strengths applied for 2 days; however, the 95% CIs overlapped and there was no statistically significant difference between the different strengths.

Of the topical therapies, imiquimod seemed to produce better cosmetic outcomes than 5-fluorouracil. No conclusions about comparative cosmetic outcomes were made with ingenol mebutate.

## Other Adverse Events

Eyelid edema, eye pain, conjunctivitis

## Long-term Safety

No new safety concerns were identified during a 12-month follow-up.

# Contraindications

None

# Warnings and Precautions

Eye disorders, including severe eye pain, eyelid edema, eyelid ptosis, and periorbital edema, can occur if ingenol mebutate gel is transferred to the periocular area. If accidental exposure to the eye occurs, the patient should flush the area with water and seek medical attention as soon as possible.

Severe local skin reactions, including erythema, crusting, swelling, vesiculation / postulation and erosion / ulceration, can occur after topical application of ingenol mebutate gel. Application of ingenol mebutate gel should be withheld until the skin is healed from any previous drug or surgical treatment.

# Special Populations

## Pregnancy

Category C. There was no evidence of adverse embryofetal effects in studies conducted in pregnant rats. There was an increase in embryofetal mortality (highest dose only) and fetal visceral and skeletal variations (all doses) when pregnant rabbits received 12, 24, or 48 mcg/m2/day of ingenol mebutate intravenously. However, the clinical relevance of these findings is unclear, as human systemic exposure to ingenol mebutate was below the limit of detection in subjects with actinic keratosis applied ingenol mebutate gel, 0.05% over a 100-cm2 treatment area.

## Geriatric Use

Of 1165 treated subjects in clinical trials, 56% were 65 years or older and 21% were 75 years or older. No overall differences in safety or efficacy were observed between older (≥ 65 years of age) and younger subjects.

## Immunocompromised / Organ Transplant

No data.

# Postmarketing Safety Experience

Data not available.

# Sentinel Events

None

# Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| NME Drug Name | Lexi-Comp | First DataBank | ISMP | Clinical Judgment |
| Ingenol mebutate 0.015%, 0.05% topical gel | None | None | None | Inderal  Istalol 0.5% ophth soln |
| PICATO | None | None | None | Pilocar |

# Drug Interactions

## Drug-Drug Interactions

In vitro pharmacokinetic studies using blood concentrations of ingenol mebutate higher than those achieved with topical administration (< 0.1 ng/ml) revealed no CYP inhibition or induction effects.

# Pharmacoeconomic Analysis

No pharmacoeconomic analyses relevant to VA were found.

# Practice Guideline Recommendations

Practice guidelines for the treatment of actinic keratosis that were published from January 2008 to January 2014 are summarized in Table 11.

Table 11 Practice Guidelines: Role of Patient-administered, Field-based Drug Therapies

| Topic |  | Diclofenac | 5FU | Imiquimod | Retinoids |
| --- | --- | --- | --- | --- | --- |
| **European Skin Academy (2008)[[24]](#endnote-24)**. Consensus opinion, best practices | | | | | |
| Complete Clinical Clearance Rate (Tx Duration, d) |  | 50% (90) | 50% | 84% | Conflicting; some studies show no efficacy |
| Recurrence Rates |  | — | Up to 55% (very high) | 10% in 1 y  20% in 2 y |  |
| Local Adverse Events |  | Most mild–moderate; severe inflammation possible | Severe inflammation, pruritus, pain, erosions, ulceration, infections, scarring (rare) | Pain, erythema, itching, pruritus |  |
| Precautions |  |  | Sunlight exposure can intensify AEs |  |  |
| Place in Therapy |  | First-line alternative | First-line alternative in tx algorithm; however, in the text, the authors noted that 5FU is often used as palliative therapy when no other tx is possible b/o AEs | First-line alternative | Second-line, after diclofenac 3% gel, imiquimod, PDT, 5FU (all + sun protection) |
| Other Considerations |  |  | Intermittent “pulse” tx can reduce severe AEs | Clearance of AK is more common in pts who experience severe local reactions. | Counteracts vitamin A deficiency induced by UV.  May decrease photodamaged cells. |
| **Swiss Clinical Practice Guidelines for Skin Cancer in Organ Transplant Recipients[[25]](#endnote-25)** | | | | | |
| Treat in-situ SCC (actinic keratosis, Bowen’s disease) and field cancerisation |  | — | Effective; none of these 3 topical treatments  (5FU, imiquimod, retinoids) is distinguished as being best | | |

# Conclusions

Ingenol mebutate is a safe, well tolerated, cosmetically acceptable and efficacious short-duration treatment alternative to other topical field-based pharmacotherapies for nonhypertrophic, nonhyperkeratotic AK in immunocompetent individuals. The main advantages of ingenol mebutate relative to other topical pharmacotherapies are that it achieves similar complete clearance rates using a much shorter treatment duration, and the overall course of therapy, from start of treatment to recovery from local skin reactions, may be shorter than the actual treatment period alone (excluding recovery time) for other topical pharmacotherapies. Patient adherence to therapy may be better with ingenol mebutate than other topical drug therapies because of the simpler and shorter dosage regimen; however, this potential advantage has not been evaluated in head-to-head trials. The drug’s relative efficacy and safety in immunocompromised patients, long-term (> 1 year) durability of effects, recurrence rates and safety, and use in combination with other drug and nondrug field-based therapies have not been adequately evaluated. Its unique dual mechanism of action may justify a trial of ingenol mebutate in patients who inadequately respond to other topical therapies; however, the efficacy of ingenol mebutate in recalcitrant AK has not been evaluated.

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