Ingenol Mebutate Gel (Picato)

A Novel Agent for the Treatment of Actinic Keratoses

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INTRODUCTION

Actinic keratosis (AK) is a skin lesion that is often induced by sun exposure; in some cases, AKs may progress to squamous cell carcinoma (SCC).[1] Skin cancer is the most common form of cancer in the U.S., and SCC is the second most common form.[2,3] It is estimated that some form of skin cancer will develop in 20% of Americans in their lifetime (Table 1).[2,4] SCC has the potential to metastasize, and it can be fatal if it is not detected early. People with fair complexions and individuals 40 years of age and older are more likely to have AK. Long-term exposure to ultraviolet light is also considered to be a risk factor.[5]

AK presents as a scaly, flat, or elevated lesion that may range in color from red to brownish. The lesions (pustules and papules) may also vary in shape and may range from 1 mm to 1 inch in diameter. The lesions are primarily found on sun-exposed areas such as the face, ears, and hands. Most patients are asymptomatic, but some may experience burning or itching of the affected area.[6]

Both pharmacotherapy and surgical management may be used for the treatment of AK. Currently available topical therapies in the U.S. include imiquimod 5% cream (Aldara, 3M/Graceway), diclofenac sodium 3% gel (Solaraze, PharmaDerm/Fougera), 5-fluorouracil (Efudex, Valeant), and aminolevulinic acid (Levulan Kerastick, DUSA/Sun Pharma).

Imiquimod is an immunomodulator and should be used only for immunocompetent patients. Diclofenac gel, approved for AK in 2002, should be used with caution in patients with allergies to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). Because of its adverse-effect profile, 5-fluorouracil is typically considered to be associated with poor compliance rates.

Aminolevulinic acid, a photosynthesizing agent, is applied to AK lesions in combination with photodynamic therapy. Cryosurgery[7] and cosmetic resurfacing[8] procedures are the primary surgical options for patients with AK.

In January 2012, the FDA approved ingenol mebutate gel (Picato, Leo Pharma, Inc.) for the topical treatment of AK. This article summarizes available clinical data for this agent.

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PHARMACOLOGY

Ingenol mebutate is an active compound found in the sap of the *Euphorbia peplus* plant, known for its dermatological uses, including the treatment of cancerous lesions.[9] This medication treats AK lesions by rapidly inducing cell death. The exact mechanism by which this occurs is unknown. It is thought that the active ingredient has pleiotropic effects that inhibit tumor cell growth or induce tumor cell death via multiple mechanisms. This may include an immune-mediated response such as protein kinase C or neutrophil activation. These inflammatory responses may also contribute to the wound-healing properties of the drug. Application of the gel results in rapid destruction of AK lesions; therefore, treatment is necessary for only 2 or 3 days.[10–12]

Table 1 Lifelong Sun Exposure Based on a 78-Year Life Span

Age (Years)	Average Sun Exposure (%)
1–18	22.73
19–40	46.53
41–59	73.7
60–78	100

Adapted from data in Godar DE, et al. *Photochem Photobiol* 2003;77(4):453–457.[4]

PHARMACOKINETICS

Systemic absorption following topical application of ingenol mebutate is negligible. Blood levels of the drug and its two metabolites are below the lower limits, defined as less than 0.1 ng/mL, and its metabolites have been shown to have no effect on the cytochrome P450 (CYP) enzyme system. No drug interactions have been attributed to ingenol mebutate.[11]

DOSAGE AND ADMINISTRATION

Ingenol mebutate is available in two strengths, 0.015% and 0.05%. The 0.015% strength is indicated for AKs of the face and scalp. The gel is applied to the affected area once daily for 3 consecutive days. AK of the trunk and extremities (i.e., body, arms, hands, and legs) should be treated with the 0.05% gel and should be applied to the affected area once daily for 2 consecutive days. Regardless of the strength used, patients should be advised to use a new tube for each day of treatment. All tubes should be stored in the refrigerator.[11]

ADVERSE EFFECTS AND PRECAUTIONS

The most common adverse drug events (reported in 2% of patients or more) include localized application-site reactions such as skin pain, pruritus, irritation, and infection.[11] Severe skin reactions may include erythema, crusting, swelling, postulation, and ulceration. If a severe skin reaction occurs, the gel should not be used until the skin has fully healed.

Clinical trials of both gel strengths have shown that the local skin reactions typically occurred within 1 day of treatment and peaked in intensity 1 week following the completion of therapy.[13,14] Reactions generally resolved within 2 weeks for the 0.015% strength and in 4 weeks for the 0.05% strength.

Although ocular disorders (eye irritation, pain, edema, and lid ptosis) are less common, they have also been reported

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upon accidental exposure to the gel.[13,14] Patients should avoid ocular contact with the gel. If exposure to the eyes occurs, patients should flush the eyes with large amounts of water and should also seek medical attention. For this reason, it is essential that patients wash the hands well with soap and water after they apply the product.

Additional adverse effects included headache (2%) with the 0.015% gel and nasopharyngitis (2%) with the 0.05% gel.

Ingenol mebutate is a Pregnancy Category C agent and should not be used during pregnancy unless the benefits outweigh the risks.[11] The drug's safety and efficacy have not been established in patients younger than 18 years of age, and no differences in safety have been identified in the geriatric population.

There are currently no contraindications to the use of ingenol mebutate, and no drug interactions have been identified.[11]

CLINICAL TRIALS

Although comparative trials with ingenol mebutate are scarce, two important studies indicated a role for the gel in the treatment of AK.

Anderson et al.[13]

A short-term phase 2b study enrolling 222 patients was conducted to assess the safety, tolerability, and efficacy of ingenol mebutate gel for nonfacial AK lesions on the arms, shoulders, chest, back, or scalp. This trial included four study arms in which patients were randomly assigned to either (1) the vehicle group, ingenol mebutate gel 0.025% for 3 days, vehicle on day 1, and ingenol mebutate gel 0.05% for 2 days, or (2) ingenol mebutate gel 0.05% for 3 days. Patients were assessed at day 3 for the final treatment day. They were then reassessed on days 8, 15, 29, and 57.

Efficacy was assessed according to the number of baseline AK lesions still visible in the treated area at day 57 as well as by patient satisfaction at day 57.

The primary efficacy endpoint was partial clearance, defined as a reduction of 75% or more AK lesions at day 57. Secondary endpoints were complete clearance of visible lesions at day 57 and complete clearance of all AK lesions identified at baseline.

A 7-point Likert scale questionnaire was used to evaluate patient satisfaction. Safety was assessed by evaluating the severity of any local skin reactions caused by the medication through day 8.

The investigators concluded that all three active-treatment groups were significantly more effective than the vehicle-treated group. The 0.05% dosing strength of ingenol for nonfacial AK lesions demonstrated a statistically significant resolution of lesions compared with the vehicle group. The 0.05% study arm had a 75.4% partial clearance, 54.4% complete clearance, and 57.9% complete clearance from baseline ($P < 0.0001$).

Overall, the patient satisfaction score was 7, defined as very positive for healing time, overall satisfaction, and cosmetic outcome. Patient satisfaction with ingenol was statistically significantly higher compared with patients receiving placebo. The treatment groups gave higher ratings for convenience and ease of use, but these scores were not significantly higher than the ratings in the vehicle arm. The most commonly reported local skin reactions included erythema, flaking, scaling, and crusting. These reactions were identified as being most intense between days 3 and 8, but they generally resolved within 2 to 4 weeks.

Lebwohl et al.[14]

Ingenol mebutate gel was also studied in a double-blind, vehicle-controlled, parallel-group randomized study that enrolled four arms. Two of the arms included patients with AK on the face or scalp who were treated with either ingenol mebutate gel 0.015% or vehicle gel to a 25-cm^2 area once daily for 3 consecutive days. These two groups were identified as Panel A. Patients with AK of the trunk or extremities were randomly assigned to the other two arms and received either ingenol mebutate gel 0.05% or vehicle gel once daily for 2 consecutive days. These two groups were identified as Panel B. The extremities evaluated included the arm, back of the hand, the chest, the shoulder, the back, and the legs.

For Panel A (face or scalp), 536 patients completed the study. For Panel B (trunk or extremities), 447 patients completed the study. Patients were assessed for safety of the therapy on day 3 if they had lesions on the trunk or extremities, and they were assessed on day 4 for lesions present on the face or scalp. All groups were assessed for safety on days 8, 15, 29, and 57. Safety endpoints included adverse events, local skin reactions, changes in pigmentation, and scarring. A scale from grade 0 (i.e., no reaction) to grade 4 (i.e., severe reaction) was used to record local skin reactions. Lesion size and number were assessed at baseline and on day 57.

The primary endpoint was to assess complete clearance of all visible AK lesions on day 57. The secondary endpoint was a partial clearance on day 57, which was defined as a 75% or more reduction in all visible lesions.

The investigators also evaluated the percentage change from baseline in the total number of AK lesions. The mean age of enrolled patients was 65.1 years, and approximately half the patients in all study groups had a history of skin cancer. More than 75% of patients in both panels had previously been treated for AK lesions with cryotherapy, imiquimod, or fluorouracil.

In Panel A studies (face and scalp), lesions completely cleared at day 57 in 42.2% of subjects in the ingenol gel group compared with 3.7% of patients in the placebo group ($P < 0.0001$). Partial clearance for facial or scalp lesions was identified in 63.9% in the treatment groups and in 7.4% of placebo patients ($P < 0.001$). An 83% reduction in AK lesions from baseline was noted for ingenol gel compared with a 0% reduction for placebo.

In Panel B studies (trunk and extremity), a complete clearance rate of 34.1% was observed for the ingenol gel group compared with 4.7% for the placebo group ($P < 0.001$). There was a partial clearance rate of 49.1% in the treated patients compared with a rate of 6.9% in the placebo patients ($P < 0.001$). There was a 75% reduction of lesions from baseline in the treated group compared with a reduction of 0% for those receiving placebo.

In Panel A, erythema was the most common local skin reaction reported in the treated group (69.7%) compared with the placebo group (2.2%). For all study groups, the most common application-site adverse skin reactions were pain, pruritus, and irritation of the treated area. Scarring and pigmentation changes were minimal. Skin reactions peaked at day 4 for the face/scalp treatment group and on day 3 for the trunk/extremity treatment group. Local reactions resolved by the day 15 assessment for both groups.

Table 2 Picato Gel and Other FDA-Approved Topical Therapies for Actinic Keratoses (AKs)

Active Ingredient	Brand Name	Indications	Directions	Cost per Treatment
Imiquimod cream	Aldara 5% cream	AKs of face and scalp	Apply two times per week for 16 weeks on face or scalp	$1,023.18
Diclofenac sodium gel	Solaraze 3% gel	AKs	Apply to lesions twice daily for 60 to 90 days	$1,863.84–$2,795.76
5-Fluorouracil	Efudex 5% cream	Multiple AKs	Apply twice daily for 2 to 4 weeks	$287.50
	Fluoroplex 1% cream and solution	Multiple AKs	Apply daily for 2 to 6 weeks	Cream: $462.00 Solution: $75.61
	Carac 0.5% cream	Multiple AKs of face and anterior scalp	Apply daily for 4 weeks	$466.66
Aminolevulinic acid	Levulan Kerastick 20% solution	AKs of face and scalp	Apply on lesions 14 to 18 hours before blue light exposure	$1,285.46
Ingenol mebutate	Picato 0.015% and 0.05% gel	0.015% gel: AKs of face and scalp 0.05% gel: AKs of trunk and extremities	Apply daily to lesions for 3 days Apply daily to lesions for 2 days	$765.76 $765.76

Cost data from *Red Book Online*.[15]

P&T COMMITTEE CONSIDERATIONS

Ingenol mebutate (Picato) is available in two different therapy packs; each contains either two 0.47-g tubes of 0.015% gel or three 0.47-g tubes of 0.05% gel. The 2-day therapy pack containing 0.015% gel is intended for facial and scalp AK lesions; the 3-day pack of 0.05% gel is indicated for AK lesions on the neck or extremities.

The average wholesale price (AWP) of $765.76 is the same for either a 2-day supply of the 0.015% gel or the 3-day supply of the 0.05% gel.[15]

No head-to-head trials have been conducted to compare the gel's efficacy with that of other therapies approved for AK (Table 2). With an expected duration of treatment of 2 to 3 days, ingenol mebutate may carry less financial burden on patients and institutions. Other AK therapies, such as imiquimod cream, are used for 16 weeks[16] and may be more costly and inconvenient to apply. Diclofenac sodium gel is applied to AK lesions for 60 to 90 days (see Table 2). The maximum benefit of diclofenac gel is sometimes seen 30 days after completion of therapy.[17] The cost is between $1,863.84 and $2,795.76.[17]

Because ingenol mebutate resolves the lesions in a short time, we recommend adding this agent to outpatient formularies. There are no published pharmacoeconomic analyses that confirm the value of using ingenol mebutate as a cost-effective treatment option. Such analyses would be valuable in guiding P&T committees in their decisions about formulary additions.

CONCLUSION

Ingenol mebutate may offer several advantages over other AK treatments currently on the market, including a shorter duration of use, faster resolution of lesions, and a favorable side-effect profile. Two pivotal placebo-controlled trials have shown that this new agent has a place in the treatment of patients with AK lesions.

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