Picato® (ingenol mebutate) Quantity Limit Criteria Program Summary

OBJECTIVE

The intent of the Picato (ingenol mebutate) Quantity Limit program is to provide automatic approval for use of Picato as listed in FDA labeling with recommended dosing, for one course per 90 days, and to require individual evaluation through the prior authorization process for patients who have increased requirements and exceed this limit. Requests for additional courses/quantities will be evaluated through the Clinical Review process when patient-specific documentation has been provided.

TARGET DRUGS

Picato® (ingenol mebutate)

PROGRAM QUANTITY AND DURATION LIMIT

Brand (generic)	GPI	Multisource Code	Total Treatment Limit	Duration of Therapy
Picato (ingenol mebutate)				
0.015% gel	90378035204020	M, N, O, Y	Actinic keratosis (face or scalp): 3 tubes (total)	3 days (1 course)/ 90 days
0.05% gel	90378035204040	M, N, O, Y	Actinic keratosis (trunk or extremities): 2 tubes (total)	2 days (1 course)/ 90 days

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Picato will be approved for increased quantity (courses of therapy) when ONE of the following are met:

1. BOTH of the following:
   a. The prescriber is treating an area of skin that has not been previously treated (requested therapy is not a re-treatment)
      AND
   b. The strength and dose is according to FDA label:
      i. For face/scalp: 0.015% gel, 3 tubes (one 3-day course)/90 days OR
      ii. For trunk/extremities: 0.05% gel, 2 tubes (one 2-day course)/90 days

   OR
2. The prescriber has submitted documentation in support of the requested quantity and duration of therapy for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

Length of Approval: up to 3 months

FDA APPROVED INDICATIONS AND DOSAGE[1]

Indications	Dosing
Picato (ingenol mebutate 0.015% gel)	
AK on the face or scalp	Apply to the affected area once daily for 3 consecutive days[ab]
Picato (ingenol mebutate 0.05% gel)	
AK on the trunk or extremities	Apply to the affected area once daily for 2 consecutive days[ab]

a - Picato gel may be applied up to one contiguous skin area of approximately 25 cm^2 using one unit dose tube. After spreading evenly, gel should be allowed to dry for 15 minutes. Patients should avoid washing and touching the treated area for a period of 6 hours after application. Following this time, patients may wash area with mild soap.
b - Safety and effectiveness of Picato for AK in patients less than 18 years of age have not been established.

CLINICAL RATIONALE

Actinic Keratoses (AK)

National Comprehensive Cancer Network [NCCN, U.S.] Guidelines (2015) suggest AK should be treated aggressively at first development. Accepted modalities include cryosurgery, topical fluorouracil (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). Diclofenac is considered Category 2B: based on lower level evidence, NCCN consensus that the intervention is appropriate. Ingenol mebutate is not yet included in current NCCN guidelines. [8]

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.[2,3]

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.[2,3]

A consensus panel suggested fluorouracil and imiquimod as the most effective topical treatments for AK involving multiple lesions or an entire area at risk. Diclofenac may be less irritating than fluorouracil. Application site adverse reactions are common with all three topical agents. Systemic adverse effects (e.g., fatigue, flu, angioedema) have also been reported with imiquimod.[2,3]

Ingenol mebutate gel (Picato)

Efficacy

Ingenol mebutate gel (Picato) was FDA approved for treatment of actinic keratosis in 2012. The mechanism of action by which it induces cell death in treating actinic keratosis lesions is unknown. Although ingenol gel requires a shorter treatment duration vs other agents (5-FU, imiquimod, diclofenac), there are no studies comparing safety/efficacy of ingenol with established topical treatments of AK in the U.S. The role of ingenol gel in treatment of AK vs other established topical treatment has not yet been defined.

Its efficacy was shown in four double-blind, vehicle-controlled trials (two involving the face and scalp, two involving the trunk and extremities).[1,4-7] Efficacy was assessed at day 57 of clinical trials. Complete clearance rate (primary endpoint) was defined as proportion of patients without clinically visible AK lesions in the treatment area. Partial clearance rate (secondary

endpoint) was defined as proportion of with >75% reduction in the number of AK lesions at baseline in the selected treatment area.[1,4,5]

- Face/Scalp Trials:
  - Study 1: Ingenol mebutate vs placebo: complete clearance, 37.0% vs 2.0% (p<0.001); partial clearance, 60% vs 7.0% (p<0.001).
  - Study 2: Ingenol mebutate vs placebo: complete clearance, 47.0% vs 5.0% (p<0.001); partial clearance, 68.0% vs 8.0% (p<0.001).
- Trunk/Extremity Trials:
  - Study 3: Ingenol mebutate vs placebo: complete clearance, 28.0% vs 5.0% (p<0.001); partial clearance, 44.0% vs 7.0% (p<0.001).
  - Study 4: Ingenol mebutate vs placebo: complete clearance, 42.0% vs 5.0% (p<0.001); partial clearance 55.0% vs 7.0% (p<0.001).

A Canadian network meta-analysis (2013) compared eight treatments for AK [5-aminolaevulinic acid (ALA)-photodynamic therapy (PDT), cryotherapy, diclofenac 3% in 2.5% hyaluronic acid (DCF/HA), 5-fluorouracil (5-FU) 0.5% or 5.0%, imiquimod (IMI) 5%, ingenol mebutate (IMB) 0.015–0.05%, methyl aminolaevulinate (MAL)-PDT and placebo/vehicle (including placebo-PDT)] to determine their relative efficacies. The analysis included 32 publications (N=6473); inclusion criteria were parallel-group studies with nonimmunosuppressed participants: (i) reporting 'participant complete clearance' and (ii) comparing >2 of the interventions. Interventions were ranked as follows based on calculated probabilities and odd ratios: 5-FU > ALA-PDT ≈ IMI ≈ IMB ≈ MAL-PDT > cryotherapy > DCF/HA > placebo. [9]

FDA Review[6,7]

- Ingenol gel (also referred to as PEP005 Gel) applied as indicated was shown to be statistically superior to vehicle gel based on the intent to treat population at significance level of 0.05. About half of the successfully treated patients experienced 'recurrence' of ≥1 AK lesion in the treated area. Recurrence rate at month 12 was 54% for 108 face/scalp patients studied, and 58% for 38 trunk/extremities patients studied.
- The majority of adverse reactions resolved spontaneously, and reactions that required treatment were treated successfully with concomitant medications, and resulted in no serious medical outcomes or permanent side effects. Benefits appear to outweigh risks. The risks associated with use of this product are essentially limited to local adverse reactions, that is, a robust effect which is also likely to lead to the desired product performance.
- PEP005 Gel could offer an additional therapeutic option for AK with a shorter duration of treatment course than that of currently available topical products. No comparative trials have been conducted. All topical AK treatments can cause local skin reactions at the treatment area. There are no comparative data on the effect of different management strategies or different methods of removal of AKs, and on incidence, morbidity, or mortality from invasive SCC.

According to the manufacturer of Picato, no data exists on the safety and efficacy of repeated use of ingenol mebutate. Studies that will investigate this question are on-going.[8,10,11] Ingenol mebutate gel was not studied in multiple 25 cm^2 areas of the body treated simultaneously, nor has re-treatment with this drug been studied.[9]

Safety

Ingenol mebutate may cause local skin reactions. Adverse reactions in clinical trials included severe skin reactions such as erythema, application site pruritus/irritation/infection, skin flaking/crusting, and skin swelling. Severe eye pain and eye edema can occur if eye exposure occurs. Patients should wash hands after using.[1]

The FDA issued a warning about reports of severe allergic reactions and herpes zoster (shingles) associated with the use of Picato gel (ingenol mebutate). The FDA received reports of cases involving severe eye injuries and skin reactions associated with the application of Picato gel. Some cases were associated with Picato gel not being used according to the instructions for use on the label. As a result, FDA is requiring changes to the label to warn about these new safety risks and to provide additional instructions on the safe and appropriate application of the product. The allergic reaction may include throat tightness, difficulty breathing, feeling faint, or swelling of the lips or tongue.

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