Drug Monograph

Drug/Drug Class: **Picato® (ingenol mebutate) Gel/ Inducer of Cell Death**

Prepared for: MO HealthNet
Prepared by: ACS, A Xerox Company

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use. Picato® is available as a 0.015% or 0.05% topical gel.
Dosage Forms & Manufacturer:	LEO Laboratories Ltd. (LEO Pharma) 285 Cashel Road, Dublin 12 Ireland or DPT Laboratories, Ltd. 307 E. Josephine Street San Antonio, TX 78215, USA
Summary of Findings:	Picato® topical gel is an inducer of cell death that has demonstrated efficacy for the topical treatment of actinic keratosis (AK). Ingenol mebutate gel is the first field-directed topical therapy for AK that can be used for two or three days, and it provides a new treatment option for patients with this condition.
Status Recommendation:	☐ Prior Authorization (PA) Required ☒ Open Access ☐ Clinical Edit ☐ PDL Product
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ No Prior Authorization Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

Actinic keratosis is a precancerous condition that is caused by cumulative sun exposure. It has the potential to progress to squamous cell carcinoma, which is the second most common type of skin cancer.

Dosage Form(s)[1]

Picato® is available as a 0.015% or 0.05% topical gel. The 0.015% is indicated for use on the face and scalp and the 0.05% is for use on the trunk and extremities.

Manufacturer

LEO Laboratories Ltd. (LEO Pharma) 285 Cashel Road, Dublin 12 Ireland
or
DPT Laboratories, Ltd. 307 E. Josephine Street San Antonio, TX 78215, USA

Indication(s)[1]

Picato® topical gel is indicated for the treatment of actinic keratosis.

Clinical Efficacy[1-6] (mechanism of action/pharmacology, comparative efficacy)

Ingenol mebutate topical gel is derived from the Euphorbia peplus plant. The exact method by which Picato® induces cell death in treating AK legions is unknown but it appears to have a dual mechanism of action: (1) rapid lesion necrosis, and (2) specific neutrophil-mediated, antibody-dependent cellular cytotoxicity. Because of the rapid destruction of actinic keratosis lesions after application, treatment is necessary for only 2 or 3 days. The subsequent immune-mediated response targets any residual dysplastic epidermal cells.

The estimated expected systemic exposure (< 0.1 nanogram/mL) following topical application of ingenol mebutate gel 0.05% to AK subjects is negligible.

The approval of ingenol mebutate gel was primarily based upon 4 randomized, double-blind, vehicle-controlled clinical trials involving 547 adults with AK of the face and scalp and 458 adults with AK of the trunk and extremities. Results from these trials showed that Picato gel is effective in treating actinic keratosis of the face, scalp, trunk and extremities. Clinical comparisons between ingenol mebutate gel and other topical agents used for AK are not available.

Actinic Keratosis – Face and Scalp

STUDY DESIGN	Two randomized, double-blind, vehicle-controlled clinical trials (n=547).
INCLUSION CRITERIA	Adult patients with AK of the face and scalp.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients were randomized to treatment with either ingenol mebutate gel 0.015% or vehicle gel for 3 consecutive days, followed by an 8-week follow-up period. The studies enrolled subjects with 4 to 8 clinically typical, visible, discrete AK lesions within a 25 cm(2) contiguous treatment area. Hypertrophic and hyperkeratotic lesions were excluded from treatment. On each scheduled dosing day, the study gel was applied to the entire treatment area. A total of 536 subjects (98%) completed these studies. Study subjects ranged from 34 to 89 years of age (mean 64 years) and 94% had Fitzpatrick skin type I, II, or III. Approximately 85% of subjects were male, and all ingenol mebutate gel subjects were Caucasian. Efficacy was assessed at Day 57. Complete clearance rate was defined as the proportion of subjects with no (zero) clinically visible AK lesions in the treatment area. Partial clearance rate was defined as the proportion of subjects with 75% or greater reduction in the number of AK lesions at baseline in the selected treatment area.
RESULTS	In Study 1, 37% and 60% of patients treated with ingenol mebutate gel had a complete or partial clearance rate, respectively, compared with 2% and 7%, respectively, in the vehicle group. In Study 2, 47% and 68% of patients treated with ingenol mebutate gel had a complete or partial clearance rate, respectively, compared with 5% and 8%, respectively, in the vehicle group. Subjects who achieved complete clearance at Day 57 in Study 1 and Study 2 entered a 12-month follow-up period. Based on 108 ingenol mebutate gel subjects who achieved complete clearance in Study 1 and Study 2, the recurrence rate at 12 months was 54%, where recurrence was defined as the percentage of subjects with any identified AK lesion in the previously treated area who achieved complete clearance at Day 57.
SAFETY	The most common adverse effects (>= 2%) were application site pain, pruritus, or infection, periorbital edema, and headache.

Actinic Keratosis – Trunk and Extremities

STUDY DESIGN	Two randomized, vehicle-controlled clinical trials (n=458).
INCLUSION CRITERIA	Adult patients with AK of the trunk and extremities.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients were randomized to treatment with either ingenol mebutate gel 0.05% or vehicle gel for 2 consecutive days, followed by an 8-week follow-up period. The studies enrolled subjects with 4 to 8 clinically typical, visible, discrete AK lesions within a 25 cm(2) contiguous treatment area. Hypertrophic and hyperkeratotic lesions were excluded from treatment. On each scheduled dosing day, the study gel was

	applied to the entire treatment area. A total of 447 subjects (98%) completed these studies. Study subjects ranged from 34 to 89 years of age (mean 66 years) and 94% had Fitzpatrick skin type I, II, or III. Approximately 62% of subjects were male, and all ingenol mebutate gel subjects were Caucasian. Efficacy was assessed at Day 57. Complete clearance rate was defined as the proportion of subjects with no (zero) clinically visible AK lesions in the treatment area.
RESULTS	In Study 1, 28% and 44% of patients treated with ingenol mebutate gel had a complete or partial clearance rate, respectively, compared with 5% and 7%, respectively, in the vehicle group. In Study 2, 42% and 55% of patients treated with ingenol mebutate gel had a complete or partial clearance rate, respectively, compared with 5% and 7%, respectively, in the vehicle group. Subjects who achieved complete clearance at Day 57 in Study 2 entered a 12-month follow-up period. Based on 38 ingenol mebutate gel subjects who achieved complete clearance in Study 2, the recurrence rate at 12 months was 50%, where recurrence was defined as the percentage of subjects with any identified AK lesion in the previously treated area who achieved complete clearance at Day 57.
SAFETY	The most common adverse effects (>= 2%) were application site pain, pruritus, or irritation, and nasopharyngitis.

Contraindications[1]

- None

Warnings and Precautions[1]

- Eye disorders, including severe eye pain, eyelid edema, eyelid ptosis, and periorbital edema can occur after exposure; avoid contact with periocular area; flush eyes with water and seek medical care with accidental exposure.
- Local skin reactions can occur, including vesiculation, pustulation, erosion, and ulceration; use not recommended until skin is healed from previous drug or surgical treatment.

Adverse Effects[1]

Face/scalp trials	**Any Grade**		**Grade 4**	
	Ingenol mebutate (n=274)	**Placebo (n=271)**	**Ingenol mebutate (n=274)**	**Placebo (n=271)**
▪ Erythema	94%	25%	24%	0%
▪ Flaking/scaling	85%	25%	9%	0%
▪ Crusting	80%	17%	6%	0%
▪ Swelling	79%	4%	5%	0%
▪ Vesiculation/postulation	56%	0%	5%	0%
▪ Erosion/ulceration	32%	1%	0%	0%

Trunk/extremities trials	Any Grade		Grade 4	
	Ingenol mebutate (n=225)	**Placebo (n=232)**	**Ingenol mebutate (n=225)**	**Placebo (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%

Drug Interactions[1]

- Lithium
- NSAIDs

Dosage and Administration[1]

Actinic keratosis on the face and scalp: Apply 0.015% gel to the affected area once daily for 3 consecutive days.

Actinic keratosis on the trunk and extremities: Apply 0.05% gel to the affected area once daily for 2 consecutive days.

Cost Comparisons (at commonly used dosages)

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/ PACKAGE*
Ingenol mebutate topical	Picato	Leo Pharma	0.015% gel, 3 unit dose tubes/carton	Apply once daily for 3 days	$ 196.69
			0.05% gel, 2 unit dose tubes/carton	Apply once daily for 2 days	$ 295.00
Diclofenac topical	Solaraze	Doak	3% gel, 100 g	Apply twice daily for 60 to 90 days	$ 544.98

Fluorouracil topical	Carac	Valeant	0.5% cream, 30 g	Apply twice daily for 2 to 6 weeks	$ 314.29
Fluorouracil topical	Fluoroplex	Aqua	1% cream, 30 g	Apply twice daily for 2 to 6 weeks	$ 325.00
Imiquimod topical	Zyclara	Medicis	3.75% cream, 28 unit dose packets/carton	Apply once daily for 4 weeks	$ 468.08

***Wholesale Acquisition Cost**

Conclusion

Picato® topical gel is an inducer of cell death that has demonstrated efficacy for the topical treatment of actinic keratosis (AK). Ingenol mebutate gel is the first field-directed topical therapy for AK that can be used for two or three days, and it provides a new treatment option for patients with this condition.

Recommendation

MO HealthNet Division recommends Open Access status for this product.

References

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3. Li L, Shukla S, Lee A et al: The skin cancer chemotherapeutic agent ingenol-3- angelate (PEP005) is a substrate for the epidermal multidrug transporter (ABCB1) and targets tumor vasculature. Cancer Res 2010; 70(11):4509-4519.
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6. Siller G, Gebauer K, Welburn P et al: PEP005 (ingenol mebutate) gel, a novel agent for the treatment of actinic keratosis: results of a randomized, double-blind, vehicle-controlled, multicentre, phase IIa study. Australas J Dermatol 2009; 50(1):16-22.

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