

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PICATO® gel safely and effectively. See full prescribing information for PICATO® gel.

PICATO® (ingenol mebutate) gel, 0.015% for topical use
PICATO® (ingenol mebutate) gel, 0.05% for topical use
Initial U.S. Approval: 2012

RECENT MAJOR CHANGES

- Dosage and Administration (2).....10/2015
- Contraindications (4).....10/2015
- Warnings and Precautions, Ophthalmic Adverse Reactions (5.1).....10/2015
- Warnings and Precautions, Hypersensitivity Reactions (5.2).....10/2015

INDICATIONS AND USAGE

Picato® gel is an inducer of cell death indicated for the topical treatment of actinic keratosis. (1)

DOSAGE AND ADMINISTRATION

- For topical use only; not for oral, ophthalmic, or intravaginal use. (2)
- Avoid transfer of Picato to periocular area. (2)
- Avoid application near and around the mouth and lips. (2)
- For application of up to one contiguous skin area of approximately 25 cm² (5 cm x 5 cm) using one unit dose tube. (2)
- Actinic keratosis on the face or scalp: Apply Picato® gel, 0.015% to the affected area once daily for 3 consecutive days. (2)
- Actinic keratosis on the trunk or extremities: Apply Picato® gel, 0.05% to the affected area once daily for 2 consecutive days. (2)

DOSAGE FORMS AND STRENGTHS

Gel containing ingenol mebutate, 0.015% or 0.05% (3)

CONTRAINDICATIONS

Known hypersensitivity to ingenol mebutate or any component of the formulation. (4)

WARNINGS AND PRECAUTIONS

Avoid treatment in the periocular area. Eye disorders, including severe eye pain, chemical conjunctivitis, corneal burn, eyelid edema, eyelid ptosis, periorbital edema can occur after exposure. Avoid accidental transfer of the drug into the eyes and to the periocular area. If accidental exposure occurs, flush eyes with water and seek medical care. (5.1)

Local skin reactions can occur including severe reactions (e.g., vesiculation/pustulation, erosion/ulceration). Administration of Picato® gel is not recommended until skin is healed from any previous drug or surgical treatment. (5.23)

ADVERSE REACTIONS

The most common adverse reactions (≥2 %) are local skin reactions, application site pain, application site pruritus, application site irritation, application site infection, periorbital edema, nasopharyngitis and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact LEO Pharma Inc. at 1-877-494-4536 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2015

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

For topical use only; Picato[®] gel is not for oral, ophthalmic, or intravaginal use.

Avoid transfer of Picato[®] gel to periocular area [*see Warnings and Precautions (5.1)*].

Avoid application near and around the mouth and lips.

For the treatment of actinic keratosis on the face or scalp Picato[®] gel, 0.015% should be applied to the affected area once daily for 3 consecutive days.

For the treatment of actinic keratosis on the trunk or extremities Picato[®] gel, 0.05% should be applied to the affected area once daily for 2 consecutive days.

Picato[®] gel may be applied to the affected area, up to one contiguous skin area of approximately 25 cm² (e.g., 5 cm x 5 cm) using one unit dose tube. After spreading evenly over the treatment area, the gel should be allowed to dry for 15 minutes. Patients should wash their hands immediately after applying Picato[®] gel and take care not to transfer the applied drug to other areas, including the eye. Patients should avoid washing and touching the treated area for a period of 6 hours after application of Picato[®] gel. Following this time, patients may wash the area with a mild soap.

3 DOSAGE FORMS AND STRENGTHS

Gel, 0.015% or 0.05%, in a clear colorless gel base.

4 CONTRAINDICATIONS

Picato[®] gel is contraindicated in patients with known hypersensitivity to ingenol mebutate or any component of the formulation. Anaphylaxis, as well as allergic reactions leading to hospitalization have been reported in postmarketing use with Picato[®] gel [*see Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Ophthalmic Adverse Reactions

Avoid treatment in the periocular area. Eye disorders, including severe eye pain, chemical conjunctivitis, corneal burn, eyelid edema, eyelid ptosis, periorbital edema can occur after exposure [*see Adverse Reactions (6)*].

To avoid transfer of the drug into the eyes and to the periocular area during and after application, patients should wash hands well after applying Picato[®] gel. If accidental exposure occurs, the area should be flushed with water and the patient should seek medical care as soon as possible.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and allergic contact dermatitis, have been reported post-marketing [see *Adverse Reactions* (6.2)]. If anaphylactic or other clinically significant hypersensitivity reactions occur, discontinue Picato[®] gel immediately and institute appropriate medical therapy.

5.3 Local Skin Reactions

Severe skin reactions in the treated area, including erythema, crusting, swelling, vesiculation/postulation, and erosion/ulceration, can occur after topical application of Picato[®] gel [see *Adverse Reactions* (6)]. Administration of Picato[®] gel is not recommended until the skin is healed from any previous drug or surgical treatment.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in more detail in other sections of the labeling:

- Ophthalmic Adverse Reaction [see *Warnings and Precautions* (5.1)]
- Hypersensitivity Reactions [see *Warnings and Precautions* (5.2)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to Picato[®] gel in 499 subjects with actinic keratosis, including 274 subjects exposed to Picato[®] gel field treatment (skin area of 25 cm² in the face or scalp regions) at a concentration of 0.015% once daily for 3 consecutive days, and 225 subjects exposed to Picato[®] gel field treatment (skin area of 25 cm² in the trunk or extremities regions) at a concentration of 0.05% once daily for 2 consecutive days.

Local skin reactions, including erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration were assessed within the selected treatment area and graded by the investigator on a scale of 0 to 4. A grade of 0 represented no reaction present in the treated area, and a grade of 4 indicated a marked and severe skin reaction that extended beyond the treated area.

Table 1 Investigator Assessment of Maximal Local Skin Reactions in the Treatment Area during the 57 Days Post Treatment Period (face/scalp trials)

Face and Scalp (n=545) Picato[®] gel, 0.015% once daily for 3 days		
Skin reactions	Any Grade ^a > Baseline	Grade 4

	Picato [®] gel (n=274)	Vehicle (n=271)	Picato [®] gel (n=274)	Vehicle (n=271)
Erythema	258 (94%)	69 (25%)	66 (24%)	0 (0%)
Flaking/Scaling	233 (85%)	67 (25%)	25 (9%)	0 (0%)
Crusting	220 (80%)	46 (17%)	16 (6%)	0 (0%)
Swelling	217 (79%)	11 (4%)	14 (5%)	0 (0%)
Vesiculation/Pustulation	154 (56%)	1 (0%)	15 (5%)	0 (0%)
Erosion/Ulceration	87 (32%)	3 (1%)	1 (0%)	0 (0%)

^aMild (grade 1), Moderate (grade 2-3) or Severe (grade 4).

Table 2 Investigator Assessment of Maximal Local Skin Reactions in the Treatment Area during the 57 Days Post Treatment Period (trunk/extremities trials)

Trunk and Extremities (n=457) Picato[®] gel, 0.05% once daily for 2 days				
Skin reactions	Any Grade ^a > Baseline		Grade 4	
	Picato [®] gel (n=225)	Vehicle (n=232)	Picato [®] gel (n=225)	Vehicle (n=232)
Erythema	207 (92%)	43 (19%)	34 (15%)	0 (0%)
Flaking/Scaling	203 (90%)	44 (19%)	18 (8%)	0 (0%)
Crusting	167 (74%)	23 (10%)	8 (4%)	0 (0%)
Swelling	143 (64%)	13 (6%)	7 (3%)	0 (0%)
Vesiculation/Pustulation	98 (44%)	2 (1%)	3 (1%)	0 (0%)
Erosion/Ulceration	58 (26%)	6 (3%)	2 (1%)	0 (0%)

^aMild (grade 1), Moderate (grade 2-3) or Severe (grade 4).

Local skin reactions typically occurred within 1 day of treatment initiation, peaked in intensity up to 1 week following completion of treatment, and resolved within 2 weeks for areas treated on the face and scalp, and within 4 weeks for areas treated on the trunk and extremities.

Adverse reactions that occurred in $\geq 2\%$ of subjects treated with Picato[®] gel and at a higher frequency than the vehicle are presented in Table 3 and Table 4.

Table 3 Adverse reactions occurring in $\geq 2\%$ of subjects treated with Picato[®] gel and at higher frequency than vehicle (face/scalp trials)

	Face/Scalp	
Adverse Reactions	Picato[®] gel, 0.015% (N=274)	Vehicle (N=271)
Application Site Pain	42 (15%)	1 (0%)
Application Site Pruritus	22 (8%)	3 (1%)
Application Site Infection	7 (3%)	0 (0%)
Periorbital Edema	7 (3%)	0 (0%)
Headache	6 (2%)	3 (1%)

Table 4 Adverse reactions occurring in $\geq 2\%$ of subjects treated with Picato[®] gel and at higher frequency than vehicle (trunk/extremities trials)

	Trunk/Extremities	
Adverse Reactions	Picato[®] gel, 0.05% (N=225)	Vehicle (N=232)
Application Site Pruritus	18 (8%)	0 (0%)
Application Site Irritation	8 (4%)	1 (0%)
Nasopharyngitis	4 (2%)	2 (1%)
Application Site Pain	5 (2%)	0 (0%)

Less common adverse reactions in subjects treated with Picato[®] gel included: eyelid edema, eye pain, conjunctivitis.

A total of 108 subjects treated with Picato[®] gel on the face/scalp and 38 subjects treated on the trunk/extremities were followed for 12 months. Results from these studies did not change the safety profile of Picato[®] gel.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Picato (ingenol mebutate) gel, 0.015% and 0.05%: hypersensitivity, allergic contact dermatitis, herpes zoster, chemical conjunctivitis, and corneal burn.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Picato[®] gel in pregnant women. Picato[®] gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Systemic embryofetal development studies were conducted with ingenol mebutate in rats and rabbits. Intravenous doses of 1.5, 3, and 5 µg/kg/day (9, 18, and 30 µg/m²/day) ingenol mebutate were administered during the period of organogenesis (gestational days 6 – 16) to pregnant female rats. No treatment related effects on embryofetal toxicity or teratogenicity were noted at doses up to 5 µg/kg/day (30 µg/m²/day). Intravenous doses of 1, 2, and 4 µg/kg/day (12, 24, and 48 µg/m²/day) ingenol mebutate were administered during the period of organogenesis (gestational days 6 – 18) to pregnant female rabbits. An increase in embryo-fetal mortality was noted at 4 µg/kg/day (48 µg/m²/day). An increased incidence of fetal visceral and skeletal variations was noted in all three ingenol mebutate dose groups. The clinical relevance of these findings is unclear since systemic exposure of ingenol mebutate was not detected in subjects with actinic keratosis treated with Picato[®] gel, 0.05% applied to a 100 cm² treatment area [see *Clinical Pharmacology* ([12.3](#))].

8.4 Pediatric Use

Actinic keratosis is not a condition generally seen within the pediatric population.

The safety and effectiveness of Picato[®] gel for actinic keratosis in patients less than 18 years of age have not been established.

8.5 Geriatric Use

Of the 1165 subjects treated with Picato[®] gel in the clinical trials, 56% were 65 years and older and, 21% were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

10 OVERDOSAGE

Topical overdosing of Picato[®] gel could result in an increased incidence of local skin reactions.

11 DESCRIPTION

Picato[®] (ingenol mebutate) gel, 0.015% or 0.05% is a clear colorless gel for topical administration, which contains the active substance ingenol mebutate, an inducer of cell death.

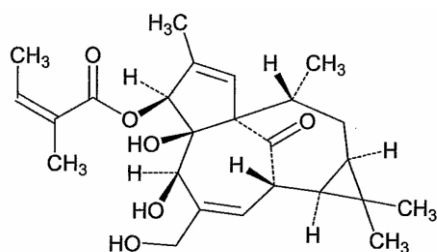
The chemical name of ingenol mebutate is:

2-Butenoic acid, 2-methyl-, (1aR,2S,5R,5aS,6S,8aS,9R,10aR)-1a,2,5,5a,6,9,10,10a-octahydro-5,5a-dihydroxy-4-(hydroxymethyl)-1,1,7,9-tetramethyl-11-oxo-1H-2,8a-methanocyclopenta[a]cyclopropa[e]cyclodecen-6-yl ester, (2Z) -

or

(1aR,2S,5R,5aS,6S,8aS,9R,10aR)-5,5a-dihydroxy-4-(hydroxymethyl)-1,1,7,9-tetramethyl-11-oxo-1a,2,5,5a,6,9,10,10a-octahydro-1H 2,8a-methanocyclopenta[a]cyclopropa[e]cyclodecen-6-yl (2Z) 2 methylbut-2-enoate.

The molecular formula is C₂₅H₃₄O₆ and molecular weight is 430.5. Ingenol mebutate is represented by the following structural formula:



Ingenol mebutate is a white to pale yellow crystalline powder.

Picato[®] gel, 0.015% and 0.05% contains 150 mcg and 500 mcg of ingenol mebutate, respectively in each gram of gel consisting of isopropyl alcohol, hydroxyethyl cellulose, citric acid monohydrate, sodium citrate, benzyl alcohol and purified water.

Picato[®] gel is clear colorless gel and supplied in unit dose laminate tubes, for single use, containing a nominal fill weight of 0.47 g, with a deliverable weight of 0.25 g. The tubes should be discarded after single use.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action by which Picato[®] gel induces cell death in treating AK lesions is unknown.

12.2 Pharmacodynamics

The pharmacodynamics of Picato[®] gel is unknown.

12.3 Pharmacokinetics

Absorption

The systemic exposure to Picato[®] gel, 0.05% was assessed in two studies in a total of 16 subjects with AK, following application of approximately 1 g of Picato[®] gel, 0.05% to an area of 100 cm² of the dorsal forearm once daily for two consecutive days. In these studies, the blood levels of ingenol mebutate and two of its metabolites (acyl isomers of ingenol mebutate) were measured. Blood levels of ingenol mebutate and the two metabolites were below the lower limit of quantification (0.1 ng/mL) in all the blood samples of the subjects evaluated.

Drug Interactions

In vitro studies demonstrated that [³H]-ingenol mebutate undergoes extensive metabolism in human hepatocytes.

In vitro studies to assess the potential of ingenol mebutate to inhibit or induce human cytochrome P450 (CYP) enzymes demonstrated that ingenol mebutate does not inhibit CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 or induce CYP 1A2, 2C9, and 3A4. The estimated expected systemic exposure (< 0.1 ng/mL) following topical application of Picato[®] gel, 0.05% to AK subjects in the pharmacokinetic studies described above is negligible compared to the concentrations of ingenol mebutate evaluated in the in vitro studies.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of Picato[®] gel or ingenol mebutate. The effects of ingenol mebutate on fertility have not been evaluated.

Ingenol mebutate was negative in the Ames test, in vitro mouse lymphoma assay, and in vivo rat micronucleus test, but positive in the Syrian hamster embryo (SHE) cell transformation assay.

14 CLINICAL STUDIES

14.1 Actinic Keratosis of the Face and Scalp

In two double-blind, vehicle-controlled, clinical trials, 547 adult subjects with AK on the face or scalp were randomized to treatment with either Picato[®] 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 cm² 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 Picato[®] gel-treated 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. Table 5 presents the efficacy results for each trial.

Table 5 Number and Percent of Subjects Achieving Complete and Partial Clearance at Day 57 in Each Trial				
	Study 1		Study 2	
	Picato[®] gel, 0.015% (N=135)	Vehicle (N=134)	Picato[®] gel, 0.015% (N=142)	Vehicle (N=136)
Complete Clearance Rate	50 (37%)	3 (2%)	67 (47%)	7 (5%)
Partial Clearance Rate (≥ 75%)	81 (60%)	9 (7%)	96 (68%)	11 (8%)

Table 6 presents the response rates by anatomical location for each trial.

Table 6 Number and Percent of Subjects Achieving Complete Clearance at Day 57 by Anatomical Location and by Trial				
	Study 1		Study 2	
	Picato[®] gel, 0.015% (N=135)	Vehicle (N=134)	Picato[®] gel, 0.015% (N=142)	Vehicle (N=136)

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%)

Subjects who achieved complete clearance at Day 57 in Study 1 and Study 2 entered a 12-month follow-up period. Based on 108 Picato[®] gel-treated 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.

14.2 Actinic Keratosis of the Trunk and Extremities

In two double-blind, vehicle-controlled clinical trials, 458 adult subjects with AK on the trunk or extremities were randomized to treatment with either Picato[®] 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 cm² 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 Picato[®] gel-treated 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. The 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. Table 7 presents the efficacy results for each study.

Table 7 Number and Percent of Subjects Achieving Complete and Partial Clearance at Day 57 in Each Trial				
	Study 3		Study 4	
	Picato[®] gel, 0.05% (N=126)	Vehicle (N=129)	Picato[®] gel, 0.05% (N=100)	Vehicle (N=103)
Complete Clearance Rate	35 (28%)	6 (5%)	42 (42%)	5 (5%)
Partial Clearance Rate (≥ 75%)	56 (44 %)	9 (7 %)	55 (55 %)	7 (7 %)

Table 8 presents the response rates by anatomical location for each study.

Table 8 Number and Percent of Subjects Achieving Complete Clearance at Day 57 by Anatomical Location and by Trial				
	Study 3		Study 4	
	Picato[®] gel, 0.05% (N=126)	Vehicle (N=129)	Picato[®] gel, 0.05% (N=100)	Vehicle (N=103)
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 ^a	1/8 (13 %)	1/10 (10 %)	6/8 (75 %)	1/6 (17 %)

^aOther includes shoulder, back, leg.

Subjects who achieved complete clearance at Day 57 in Study 4 entered a 12-month follow-up period. Based on 38 Picato[®] gel-treated subjects who achieved complete clearance in Study 4, 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.

In a separate trial, in an open-label treatment period, subjects were treated for AK lesions on their face or scalp. Those subjects who did not achieve clearance at Day 57 or experienced recurrence after achieving clearance at Day 57 were randomized to receive a second treatment course of Picato[®] or its vehicle gel. Some subjects had a treatment benefit with the second treatment course of Picato[®] gel when evaluated 8 weeks after the retreatment.

16 HOW SUPPLIED/STORAGE AND HANDLING

Picato[®] gel is a clear colorless gel and is supplied in unit dose laminate tubes containing a nominal fill weight of 0.47 g, with a deliverable weight of 0.25 g. The tubes should be discarded after single use.

Picato[®] gel is available in 2 dosage strengths: 0.015% and 0.05%.

Dosage Strength	Number of unit dose tubes per carton	NDC#
0.015 %	3	50222-502-47
0.05 %	2	50222-503-47

Store Picato[®] gel in a refrigerator at 36°F – 46°F (2°C – 8°C); excursions permitted between 32°F – 59°F (0°C – 15°C) (see USP for controlled cold temperature). Protect from freezing.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use)

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions can occur with Picato[®] gel. Advise patients of the symptoms of allergic reactions and anaphylaxis, and instruct patients to seek immediate medical attention if these symptoms occur [*see Warnings and Precautions (5.2)*].

Ophthalmic Adverse Reactions

Inform patients that severe eye injury can occur with Picato[®] gel. Advise patients that Picato[®] gel is not for ophthalmic use. Advise patients to avoid application around the eyes. If severe eye

pain or other symptoms of accidental exposure occur, advise patients to flush eyes with water and seek medical care [*see Warnings and Precautions (5.1)*].

Local Skin Reactions

Inform patients that treatment with Picato[®] gel may lead to local skin reactions [*see Warnings and Precautions (5.3)*].

Important Administration Instructions

Advise patients that Picato[®] gel is for external use only. Advise patients to avoid application near and around the eyes, mouth and lips.

Patients should avoid inadvertent transfer of Picato[®] gel to other areas, or to another person. Instruct patients to:

- allow the treated area to dry for 15 minutes after application.
- avoid washing and touching the treated area, or participating in activities that cause excessive sweating, for 6 hours after treatment. Following this time, patients may wash the area with a mild soap and water.
- keep out of the reach of children.