PRODUCT MONOGRAPH

PrPICATO®

ingenol mebutate

Topical Gel

0.015% and 0.05%

Chemotherapeutic for topical use (D06BX02)

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Date of Revision:
February 20, 2020

Control No.: 233545

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[Pr]PICATO®

ingenol mebutate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Topical	Gel 0.015% strength contains 70 mcg ingenol mebutate per unit dose tube 0.05% strength contains 235 mcg ingenol mebutate per unit dose tube	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

PICATO (ingenol mebutate) is indicated for:

- topical treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (AK) in adults.

Geriatrics (≥ *65 years*): No overall differences in safety or efficacy were observed between patients aged 65 years and over compared with younger patients (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations**).

Pediatrics (< *18 years*): The safety and efficacy of PICATO in patients less than 18 years of age have not been established.

CONTRAINDICATIONS

- Hypersensitivity to ingenol mebutate or to any of the excipients. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

General

The efficacy of PICATO (ingenol mebutate) in the prevention of squamous cell carcinoma (SCC) associated with actinic keratosis (AK) has not been studied. The rate of SCC reported in the treatment area was comparable in patients treated with PICATO (0.3%) and in vehicle treated patients (0.3%) in the AK clinical studies. SCC in the treatment area was reported in no patients previously treated with PICATO in three prospective, observational long term 1 year follow-up studies.

Health care professionals should advise patients to be vigilant for any lesions developing within the treatment area and to seek medical advice should any occur. Lesions clinically atypical for actinic keratosis or suspicious for malignancy should be biopsied to determine appropriate treatment.

Clinical data on re-treatment and treatment of more than one area with PICATO is not available (see **DOSAGE AND ADMINISTRATION, Dosing Considerations**).

Clinical data on treatment in immunocompromised patients is not available, but systemic risks are not expected since systemic exposure of ingenol mebutate was not detected following topical treatment with PICATO.

The PICATO 0.05% gel should not be used on the face or scalp as this could lead to severe skin reactions and a higher incidence of local skin responses. Only the PICATO 0.015% gel should be applied on the face or scalp (see **DOSAGE AND ADMINISTRATION**).

PICATO should not be used in, near, or around the eyes, mouth and lips. It should not be used on the inside of the nostrils or on the inside of the ears.

Ophthalmologic

Severe eye disorders occurred more frequently in patients treated with PICATO than vehicle, including periorbital edema, eyelid edema, eye edema, eye pain, and eyelid ptosis in the AK clinical studies. These eye disorders resolved without sequelae and may result from spreading of application site edema (see **ADVERSE REACTIONS**).

Ingenol mebutate is a known ocular irritant. Cases of chemical conjunctivitis and corneal burn following accidental exposure to eyes have been reported with PICATO treatment in the post-marketing setting. Treatment in the periocular area should be avoided. To avoid transfer of PICATO to the eyes and surrounding areas during and after application, precautions should be taken. Patients should wash their hands thoroughly with soap and water immediately after applying PICATO and should not touch the area of application for at least 6 hours (see DOSAGE AND ADMINISTRATION). If accidental exposure occurs, the eyes should be flushed immediately with large amounts of water, and the patient should seek medical care as soon as possible.

Gastrointestinal

PICATO (ingenol mebutate) must not be ingested. If accidental ingestion occurs the patient should drink plenty of water.

Hypersensitivity Reactions

Cases of hypersensitivity reactions including anaphylaxis have been reported with PICATO treatment in the post-market setting (see **ADVERSE REACTIONS**). If anaphylactic or other clinically significant hypersensitivity reactions occur, PICATO should be discontinued immediately and appropriate medical therapy should be instituted.

Skin

Severe local skin responses (LSRs) such as erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration can occur after topical application of PICATO. LSRs are common and the majority are mild to moderate. A treatment effect may not be adequately assessed until resolution of local skin responses.

Administration of PICATO is not recommended until the skin is healed from treatment with any previous medicinal product or surgical treatment.

PICATO should not be applied to areas of skin with open wounds or damaged skin where the skin barrier is compromised.

Shaving the treated area should be avoided during treatment with PICATO. Patients should be advised to wait for resolution of the local skin response as shaving may irritate the skin.

Due to the irritant properties of ingenol mebutate, contact with skin outside the treatment area should be avoided. If there is inadvertent contact with skin not in the treatment area, the area must be washed with mild soap and water.

Carcinogenesis and Mutagenesis

Long-term animal carcinogenicity studies with ingenol mebutate have not been conducted. Ingenol mebutate was not genotoxic or clastogenic in a bacterial mutation (Ames) assay, mouse lymphoma cell assay, or rat *in vivo* micronucleus assay. Ingenol mebutate was positive in the Syrian hamster embryo (SHE) cell transformation test, which detects both genotoxic and epigenetic carcinogens.

Carcinogenic and mutagenic risks to humans receiving treatment with PICATO are considered unlikely since systemic exposure of ingenol mebutate was not detected following topical treatment.

Special Populations

Pregnant Women: There are no data from the use of PICATO in pregnant women. Embryo-fetal development studies in rabbits with intravenous ingenol mebutate demonstrated an increase in embryo-fetal mortality and an increased incidence of fetal visceral and skeletal variations (see TOXICOLOGY, Reproduction). Risks to humans receiving treatment with PICATO are considered unlikely since systemic exposure of ingenol mebutate was not detected following topical treatment. However, as a precautionary measure, it is preferable to avoid the use of PICATO during pregnancy.

Nursing Women: No effects on breastfed newborns/infants are anticipated since systemic exposure of ingenol mebutate was not detected following topical treatment with PICATO. The nursing mother should be instructed that physical contact between her newborn/infant and the treated area should be avoided for a period of 6 hours after application of PICATO.

Pediatrics (< *18* years): The safety and efficacy of PICATO in patients less than 18 years of age have not been established.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most frequently reported adverse drug reactions associated with PICATO (ingenol mebutate) treatment were general disorders and administration site disorders, including application site pain and application site pruritus.

Local Skin Responses (LSRs) were assessed independently in an effort to provide a better profile of the specific types of visible local skin reactions. LSRs included erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. LSRs are transient and typically occur within 1 day of treatment initiation and peak in intensity up to 1 week following completion of treatment. These effects typically resolve within 2 weeks for areas treated on the face and scalp and within 4 weeks for areas treated on the trunk and extremities.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

The adverse drug reaction profile described below reflects exposure to PICATO on a skin area of 25 cm^2 in 499 patients with actinic keratosis, including 274 patients exposed to PICATO at a concentration of 0.015% once daily for 3 consecutive days on the face or scalp, and 225 subjects exposed to PICATO at a concentration of 0.05% once daily for two consecutive days on the trunk and extremities.

Adverse Drug Reactions that occurred in ≥1% of patients treated with PICATO are presented in Table 1 and Table 2. Adverse drug reactions were generally mild to moderate in severity.

Table 1. Adverse Drug Reactions Occurring in ≥ 1 % of Patients Treated with PICATO Gel or Vehicle in Controlled Phase 3 Face/Scalp Studies

MedDRA SOC (Preferred term)	PICATO gel, 0.015% n=274 (%)	Vehicle n=271 (%)
General disorders and administration site disorders		
Application site pain‡	13.9 %	0.4 %
Application site pruritus	8.0 %	1.1 %
Application site irritation	1.8 %	0.0 %
Infections and infestations		
Application site infection	2.6 %	0.0 %
Nervous system disorders		
Headache	2.2 %	1.1 %
Eye Disorders†		
Eyelid edema	1.1 %	0.0 %
Periorbital edema	2.6 %	0.0 %

† Application site swelling on the face or scalp may gravitate to the eye area.
‡ Including application site burning

Table 2. Adverse Drug Reactions Occurring in ≥ 1 % of Patients Treated with PICATO Gel or Vehicle in Controlled Phase 3 Trunk/Extremities Studies

MedDRA SOC (Preferred term)	PICATO gel, 0.05% n=225 (%)	Vehicle n=232 (%)
General disorders and administration site disorders		
Application site pruritus	8.4 %	0.0 %
Application site irritation	3.6 %	0.4 %
Application site pain‡	2.2 %	0.0 %

‡ Including application site burning

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Other less common adverse drug reactions (less than 1% but more than 0.5%) were for scalp/face: eye pain, application site discharge, and application site parasthesia; for trunk/extremities: application site parasthesia and application site warmth.

Local Skin Responses

LSRs were evaluated within the selected treatment area and graded by the investigator on a scale of 0 to 4 (see Table 3 and Table 4).

Table 3. Investigator Assessment of Maximal Local Skin Reactions in the Treatment Area during the 57 Days Post Treatment Period (face/scalp studies)

Face and Scalp (n=545) 0.015% PICATO gel, once daily for 3 days						
Skin reactions	Any Grade* > Baseline		Mild	Moderate		Severe
			Grade 1	Grade 2	Grade 3	Grade 4
	PICATO gel (n=274)	Vehicle (n=271)	PICATO gel (n=274)	PICATO gel (n=274)	PICATO gel (n=274)	PICATO gel (n=274)
Erythema	258 (94%)	69 (25%)	25 (9%)	56 (20%)	125 (46%)	66 (24%)
Flaking / Scaling	233 (85%)	67 (25%)	52 (19%)	91 (33%)	98 (36%)	25 (9%)
Crusting	220 (80%)	46 (17%)	85 (31%)	64 (23%)	64 (23%)	16 (6%)
Swelling	217 (79%)	11 (4%)	88 (32%)	67 (24%)	48 (18%)	14 (5%)
Vesiculation / Pustulation	154 (56%)	1 (0%)	36 (13%)	53 (19%)	50 (18%)	15 (5%)
Erosion / Ulceration	87 (32%)	3 (1%)	55 (20%)	26 (9%)	5 (2%)	1 (0%)

*A grade of 0 represented no reaction present in the treated area, and a grade of 4 indicated a marked and discernible skin reaction that extended beyond the area treated.

Table 4. Investigator Assessment of Maximal Local Skin Reactions in the Treatment Area during the 57 Days Post Treatment Period (trunk/extremities studies)

Trunk and Extremities (n=457) 0.05% PICATO gel , once daily for 2 days						
Skin reactions	Any Grade* > Baseline		Mild	Moderate		Severe
			Grade 1	Grade 2	Grade 3	Grade 4
	PICATO gel (n=225)	Vehicle (n=232)	PICATO gel (n=225)	PICATO gel (n=225)	PICATO gel (n=225)	PICATO gel (n=225)
Erythema	207 (92%)	43 (19%)	31 (14%)	94 (42%)	61 (27%)	34 (15%)
Flaking / Scaling	203 (90%)	44 (19%)	52 (23%)	86 (38%)	66 (29%)	18 (8%)
Crusting	167 (74%)	23 (10%)	105 (47%)	39 (17%)	23 (10%)	8 (4%)
Swelling	143 (64%)	13 (6%)	65 (29%)	51 (23%)	20 (9%)	7 (3%)
Vesiculation / Pustulation	98 (44%)	2 (1%)	46 (20%)	30 (13%)	19 (8%)	3 (1%)
Erosion / Ulceration	58 (26%)	6 (3%)	37 (16%)	15 (7%)	4 (2%)	2 (1%)

*A grade of 0 represented no reaction present in the treated area, and a grade of 4 indicated a marked and discernible skin reaction that extended beyond the area treated.

For patients treated on the face or scalp for 3 consecutive days, the majority of patients treated with PICATO gel, 0.015% had a maximum LSR score on Day 4, which returned to baseline or below by Day 15.

For patients treated on the trunk or extremities for 2 consecutive days, the majority of patients treated with PICATO gel 0.05% had a maximum LSR score on Days 3 or 8, which returned to baseline or below by Day 29.

Long-term Safety Follow-up

A total of 108 patients treated with PICATO on the face/scalp and 76 patients treated on the trunk/extremities were enrolled in three prospective, observational long-term follow-up studies. There were no adverse drug reactions reported in these studies (see **CLINICAL TRIALS**).

Post-Market Adverse Drug Reactions

Eye disorders: Reports of chemical conjunctivitis and corneal burn in connection with accidental eye exposure have been reported with the use of PICATO (see **DOSAGE AND**

ADMINISTRATION and **WARNINGS AND PRECAUTIONS** for prevention of eye exposure).

Application site reactions: Reports of pigmentation changes with the use of PICATO have been reported. Cases of application site scarring have also been reported.

Hypersensitivity reactions: Reports of hypersensitivity reactions have been reported with the use of PICATO, including Stevens-Johnson syndrome.

Infections: Reports of herpes zoster have been reported with the use of PICATO

Squamous cell carcinoma (SCC): Reports of SCCs in the treatment area have been reported with the use of PICATO.

DRUG INTERACTIONS

No interaction studies have been performed. Interactions with systemically absorbed medicinal products are considered unlikely since systemic exposure of ingenol mebutate was not detected following topical treatment with PICATO *(*see **ACTION AND CLINICAL PHARMACOLOGY**).

DOSAGE AND ADMINISTRATION

Dosing Considerations

For topical use only.

PICATO (ingenol mebutate) gel is not for oral, ophthalmic or intravaginal use.

Avoid application or transfer to the eyes and surrounding areas. Avoid application in, near, and around the mouth and lips.

Clinical data on treatment for more than one treatment course of 2 or 3 consecutive days is not available. Clinical data on treatment of more than one area is not available.

The treated area should not be covered with occlusive bandages after PICATO is applied.

Recommended Dose and Dosage Adjustment

Actinic keratosis on the face or scalp:

PICATO 0.015% gel should be applied to a single treatment field area no larger than 25 cm^2 once daily for 3 consecutive days.

Actinic keratosis on the trunk or extremities:

PICATO 0.05% gel should be applied to a single treatment field area no larger than 25 cm^2 once daily for 2 consecutive days.

Geriatrics (≥ *65 years*): No dose adjustment is required (see **ACTION & CLINICAL PHARMACOLOGY, Special Populations**).

Administration

PICATO should be applied to the treatment field area as defined by the treating physician. Each tube contains enough gel to cover an area of approximately 25 cm^2 (e.g., 5 cm x 5 cm).

The gel from the unit dose tube should be squeezed onto the fingertip and spread evenly over the entire treatment area, allowing it to dry for 15 minutes. One unit dose tube should be used for the field treatment area.

Care should be taken not to apply the 0.05% PICATO gel on the face or scalp. Patients should be instructed to use the appropriate gel strength for the indicated treatment area (PICATO 0.015% should only be applied on the face or scalp and PICATO 0.05% should only be applied on the trunk or extremities).

Patients should be instructed to wash their hands immediately after applying PICATO. Care should be taken to avoid transferring PICATO to the eyes, surrounding skin, and other areas. If treating the hands, only the fingertip which is used for applying the gel should be washed.

Washing and touching the treated area should be avoided for a period of 6 hours after the application of PICATO. Following this, patients may wash the area with a mild soap.

PICATO should not be applied immediately after taking a shower or less than 2 hours before bedtime

OVERDOSAGE

There has been no experience of overdose in clinical studies with PICATO (ingenol mebutate).

For management of a suspected drug overdose or accidental ingestion, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of ingenol mebutate in actinic keratosis (AK) is not fully characterized since there is no adequate animal model of AK. *In vivo* and *in vitro* models using tumour cell lines, including squamous cell carcinoma, have shown a dual mechanism of action for the effects of ingenol mebutate: 1) direct cytotoxicity and 2) promoting an inflammatory response characterised by release of inflammatory cytokines and infiltration of immunocompetent cells.

Pharmacodynamics

At a high concentration (100 µg/ml) *in vitro* and *in vivo*, studies have shown that ingenol mebutate is cytotoxic.

At lower concentrations (10 to 100 ng/ml), ingenol mebutate activates both novel and classical protein kinase C (PKC) and is associated with immunostimulatory effects. Some classes of PKC activators, such as phorbol esters, are known to be tumour promoters. Ingenol mebutate is structurally related to phorbol esters. The clinical significance of potential proliferative effects via activation of PKC by ingenol mebutate is unknown. However, no evidence of neoplasia was noted in 6 and 9-month dermal repeat dose studies in rats and minipigs (cyclic administration).

The risk of tumour induction in humans receiving treatment with PICATO is considered very unlikely due to the short duration of treatment (2-3 days).

Exposure of isolated human keratinocytes to lower concentrations of ingenol mebutate (10 to 100 ng/ml) *in vitro*, was shown to induce release of the cytokines IL-8 and TNF-alpha and neutrophil activation. Both *in vitro* and in mice, ingenol mebutate induced IL-8 / murine IL-8 homologue MIP-2, TNF-alpha, and IL-1beta, all mediators of neutrophil recruitment and activation.

Topical treatment with ingenol mebutate gel in the squamous cell carcinoma model resulted in a localized and transient application site inflammatory reaction, which peaked after few days, and resolved within 2 weeks followed by scar resolution after 2 to 3 months. After 3 weeks of treatment with ingenol mebutate, treated mouse skin was similar to untreated skin in elasticity

Ultraviolet Light Exposure: Studies have been conducted to assess the effects of UV irradiation on the skin following single and multiple applications of ingenol mebutate, 100 mcg/g. Ingenol mebutate gel did not demonstrate any potential for photo-irritation or photo-allergic effects.

Pharmacokinetics

The systemic pharmacokinetic profile of ingenol mebutate and its metabolites has not been characterised in humans due to an absence of quantifiable whole blood levels following topical administration.

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, or 3A4, or induce CYP 1A2, 2C9, or 3A4.

Absorption: In humans, the highest concentration and treatment area evaluated was 0.05 µg/mm^2 of ingenol mebutate gel, 0.05% applied once daily to a 100 cm^2 area for two consecutive days. No systemic blood levels of ingenol mebutate or its two isomers PEP015 and PEP025 were quantifiable, i.e. concentrations were below the LLOQ (0.1 ng/mL).

Special Populations and Conditions

Pediatrics (< *18 years*): The safety and efficacy of PICATO (ingenol mebutate) in patients less than 18 years of age have not been established.

Geriatrics (≥ *65 years*): Of the 1,165 patients treated with PICATO in the actinic keratosis clinical studies, 656 patients (56%) were 65 years and older, while 241 patients (21%) were 75 years and older. No overall differences in safety or efficacy were observed between younger and older patients.

STORAGE AND STABILITY

PICATO (ingenol mebutate) gel should be stored in a refrigerator (2ºC to 8ºC).

Keep out of reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PICATO (ingenol mebutate) is a clear colourless gel.

PICATO, 0.015% Gel

Each unit dose tube contains 70 mcg of ingenol mebutate in 0.47 g gel.
Available as: 3 unit dose tubes per carton.

PICATO, 0.05% Gel

Each unit dose tube contains 235 mcg of ingenol mebutate in 0.47 g gel.
Available as: 2 unit dose tubes per carton.

Non-medicinal ingredients: Isopropyl alcohol, hydroxyethyl cellulose, benzyl alcohol, citric acid monohydrate, sodium citrate, purified water.

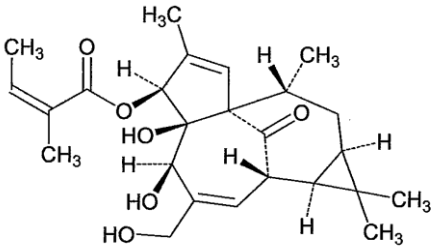
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name (I.N.N.):	ingenol mebutate
Chemical name:	2-Butenoic acid, 2-methyl-, (1a*R*,2*S*,5*R*,5a*S*,6*S*,8a*S*,9*R*,10a*R*)-1a,2,5,5a,6,9,10,10a-octahydro-5,5a-dihydroxy-4-(hydroxymethyl)-1,1,7,9-tetramethyl-11-oxo-1*H*-2,8a-methanocyclopenta [*a*]cyclopropa[*e*]cyclodecen-6-yl ester, (2Z) -
Alternative chemical name:	(1a*R*,2*S*,5*R*,5a*S*,6*S*,8a*S*,9*R*,10a*R*)-5,5a-dihydroxy-4-(hydroxymethyl)-1,1,7,9-tetramethyl-11-oxo-1a,2,5,5a,6,9,10,10a-octahydro-1*H* 2,8a-methanocyclopenta[*a*]cyclopropa[*e*]cyclodecen-6-yl (2Z) 2 methylbut-2-enoate.
Laboratory code name:	PEP005
Molecular formula:	$C_{25}H_{34}O_6$
Molecular mass:	430.53 g/mol
Chirality:	Eight chiral centres with specific optical rotation range 44° - 49°

Structural formula:



Physicochemical properties :

Physical form	White to pale yellow crystalline powder
Solubility	Freely soluble in benzyl alcohol and isopropyl alcohol, soluble in methanol, ethanol, acetonitrile and acetone, very slightly soluble in ethanol-water (1:3) and practically insoluble in n-heptane and water
Melting point	154.1 °C – 156.8 °C
pH	Weakly acidic, pKa 12.7

CLINICAL TRIALS

The efficacy and safety of PICATO (ingenol mebutate) 0.015% gel administered on the face or scalp for 3 consecutive days, and 0.05% gel administered on the trunk or extremities for 2 consecutive days was studied in four multi-centre, double-blind, randomized, parallel group, vehicle-controlled studies. For both treatment locations, eligible patients had 4 to 8 clinically typical, visible, discrete, non-hyperkeratotic, non-hypertrophic, actinic keratosis (AK) lesions within a contiguous 25 cm^2 treatment area. On each scheduled dosing day, the study gel was applied to the entire treatment area (25 cm^2). Patients continued in the studies for an 8 week follow-up period during which they returned for clinical observations and safety monitoring.

The efficacy of PICATO in AK is based on clinical clearance; histological assessment of clearance was not performed. The primary efficacy endpoint was complete clearance rate, defined as the proportion of patients at Day 57 with no clinically visible AK lesions in the selected treatment area. The secondary endpoint was partial clearance rate, defined as the proportion of patients at Day 57 with a 75% or greater reduction in the number of clinically visible AK lesions identified at baseline in the selected treatment area. The median percent reduction from baseline in the total number of AK lesions at Day 57 was also determined.

Face and Scalp

Study patients (n=547) 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 subjects were Caucasian. A total of 536 subjects (98%) completed these studies (see Table 5).

Table 5. Clinical Efficacy Studies of Actinic Keratosis on the Face and Scalp

Study #	Trial design	Dosage, route of administration and duration	Study patients by dose group	Mean age (Range) years	Gender by dose group M/F
PEP005-016	Multi-centre, double-blind, randomized, parallel group, vehicle-controlled	PICATO 0.015% or vehicle, once a day topical, for 3 consecutive days	135 134	63.5 (37–88) 63.0 (40–85)	116/19 120/14
PEP005-025	Multi-centre, double-blind, randomized parallel group, vehicle-controlled	PICATO 0.015% or vehicle, once a day topical, for 3 consecutive days	142 136	64.8 (34–88) 65.0 (46-89)	117/25 112/24

At Day 57, patients treated with PICATO gel had statistically significantly higher complete and partial clearance rates than patients treated with vehicle gel ($p < 0.001$). The median percent reduction in actinic keratosis lesions was higher in the group treated with ingenol mebutate compared to the vehicle group (see Table 6). Efficacy varied between anatomical locations (Table 7). Within each group, the complete and partial clearance rates were higher in patients treated with PICATO gel than patients treated with vehicle.

Table 6. Rates of Patients with Complete and Partial Clearance and Percent (%) Reduction on the Face and Scalp

	Study PEP005-016		Study PEP005-025	
	PICATO 0.015% gel (n=135)	Vehicle (n=134)	PICATO 0.015% gel (n=142)	Vehicle (n=136)
Complete Clearance Rate[a]	50 (37%)[d]	3 (2%)	67 (47%)[d]	7 (5%)
Partial Clearance Rate (≥ 75%)[b]	81 (60%)[d]	9 (7%)	96 (68%)[d]	11 (8%)
Median % Reduction[c]	83%	0%	87%	0%

[a] Complete clearance rate was defined as the proportion of patients with no (zero) clinically visible actinic keratosis lesions in the treatment area.
[b] Partial clearance rate was defined as the percentage of patients in whom 75% or more of the number of baseline actinic keratosis lesions were cleared.
[c] Median percent (%) reduction in actinic keratosis lesions compared to baseline.
[d] $p<0.001$; compared to vehicle by Cochran-Mantel-Haenszel test stratified by study site.

Table 7. Number and Rate of Patients with Complete and Partial Clearance at Day 57 by Anatomical Location (Face and Scalp Studies PEP005-016 and PEP005-025 Combined)

	Complete Clearance		Partial Clearance (≥ 75%)	
	PICATO 0.015 % gel (n=277)	Vehicle (n=270)	PICATO 0.015 % gel (n=277)	Vehicle (n=270)
Face	104/220 47%	9/220 4%	157/220 71%	18/220 8%
Scalp	13/57 23%	1/50 2%	20/57 35%	2/50 4%

The safety of PICATO 0.015% gel treatment was assessed up to day 57 and ingenol mebutate gel was found to be well tolerated. All adverse drug reactions and local skin responses resolved without sequelae.

Trunk and Extremities

Study patients (n=458) 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 subjects were Caucasian. A total of 447 subjects (98%) completed these studies (see Table 8).

Table 8. Clinical Efficacy Studies of Actinic Keratosis on the Trunk and Extremities

Study #	Trial design	Dosage, route of administration and duration	Study patients by dose group	Mean age (Range) years	Gender by dose group M/F
PEP005-014	Multi-centre, double-blind, randomized, parallel group, vehicle-controlled	PICATO 0.05% or vehicle, once a day topical, for 2 consecutive days	126 129	67.2 (43–88) 66.9 (36–87)	86/40 73/56
PEP005-028	Multi-centre, double-blind, randomized, parallel group, vehicle-controlled	PICATO 0.05% or vehicle, once a day topical, for 2 consecutive days	100 103	65.3 (43–87) 64.9 (34–89)	59/41 68/35

At Day 57, patients treated with PICATO gel had statistically significantly higher complete and partial clearance rates than patients treated with vehicle gel ($p < 0.001$). The median percent reduction in actinic keratosis lesions was higher in the group treated with ingenol mebutate

compared to the vehicle group (see Table 9). Efficacy varied between anatomical locations (Table 10). Within each group, the complete and partial clearance rates were higher in patients treated with PICATO gel than patients treated with vehicle.

Table 9. Rates of Patients with Complete and Partial Clearance and Percent (%) Reduction on the Trunk and Extremities

	Study PEP005-014		Study PEP005-028	
	PICATO 0.05% gel (n=126)	Vehicle (n=129)	PICATO 0.05% gel (n=100)	Vehicle (n=103)
Complete Clearance Rate[a]	35 (28%)[d]	6 (5%)	42 (42%)[d]	5 (5%)
Partial Clearance Rate (≥ 75%)[b]	56 (44%)[d]	9 (7%)	55 (55%)[d]	7 (7%)
Median % Reduction[c]	69 %	0 %	75%	0%

[a] Complete clearance rate was defined as the proportion of patients with no (zero) clinically visible actinic keratosis lesions in the treatment area.
[b] Partial clearance rate was defined as the percentage of patients in whom 75% or more of the number of baseline actinic keratosis lesions were cleared.
[c] Median percent (%) reduction in actinic keratosis lesions compared to baseline.
[d] $p<0.001$; compared to vehicle by Cochran-Mantel-Haenszel test stratified by study site.

Table 10. Number and Rate of Patients with Complete and Partial Clearance at Day 57 by Anatomical Location (Trunk and Extremities Studies PEP005-014 and PEP005-028 Combined)

	Complete Clearance		Partial Clearance (≥ 75%)	
	PICATO 0.05 % gel (n=226)	Vehicle (n=232)	PICATO 0.05 % gel (n=226)	Vehicle (n=232)
Arm	49/142 35%	7/149 5%	75/142 53%	11/149 7%
Back of Hand	10/54 19%	0/56 0%	16/54 30%	1/56 2%
Chest	11/14 79%	2/11 18%	12/14 86%	2/11 18%
Other[a]	7/16 44%	2/16 13%	8/16 50%	2/16 13%

[a]Other includes shoulder, back and leg.

The safety of PICATO 0.05% gel treatment for 2 days was assessed up to day 57 and ingenol mebutate gel was found to be well-tolerated. All adverse drug reactions and local skin responses resolved without sequelae.

Long-term Efficacy

Three prospective, observational long-term 1 year follow-up studies were conducted to evaluate sustained efficacy by recurrence of actinic keratosis lesions in the treatment field, and safety in patients who had received treatment with PICATO. One study included patients treated with PICATO 0.015% on the face or scalp for 3 days and two studies included patients treated with PICATO 0.05% on the trunk or extremities for 2 days. Only those patients who achieved complete clearance in the treated area at the end of the phase 3 studies (Day 57) were eligible for long term follow-up. Patients were followed every 3 months for 12 months (see Tables 11).

Table 11. Rate of Recurrence of Actinic Keratosis Lesions

	PICATO 0.015% gel Face and Scalp (n=108)	**PICATO 0.05% gel Trunk and Extremities (n=76[c])**
Recurrence Rate 12 months KM estimate (95% CI)[a]	53.9% (44.6-63.7%)	56.0% (45.1-67.6%)
Lesion Based Recurrence Rate[b] 12 months Mean (SD)	12.8% (19.1%)	13.2% (23.0%)

[a] The recurrence rate is the Kaplan-Meier (KM) estimate at the target study date of the visit expressed as a percentage (95% CI). Recurrence was defined as any identified actinic keratosis lesion in the previously treated area for patients who achieved complete clearance at day 57 in the previous phase 3 studies.
[b] The lesion-based recurrence rate for each patient defined as the ratio of the number of actinic keratosis lesions at 12 months to the number of lesions at baseline in the previous phase 3 studies.
[c] Of these, 38 subjects were previously treated in a vehicle controlled phase 3 study and 38 subjects were previously treated in an uncontrolled phase 3 study.

Local Tolerability

Results of 3 topical safety studies in healthy volunteers showed that PICATO gel did not produce a sensitization response and results indicated no potential for dermal phototoxicity, or dermal photosensitization.

DETAILED PHARMACOLOGY

There is no adequate disease model for AK. Therefore, i*n vivo* and *in vitro* models using tumour cell lines, including squamous cell carcinoma, were used to investigate the mechanism of action of ingenol mebutate (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics**).

In safety pharmacology studies, ingenol mebutate did not inhibit I_{Kr} ion channel activity in vitro or adversely affect QT intervals or electrocardiogram waveform morphology *in vivo* in dogs at the highest doses evaluated (5 µg/mL and 15 µg/kg, respectively). Mild haemodynamic effects (≥5 µg/kg) and increased respiration and minute volume ventilation (≥7.5 µg/kg) were observed in dogs following a single IV administration. No significant effects on central nervous system parameters were noted in rats following IV administration of ≤10 µg/kg ingenol mebutate.

TOXICOLOGY

In all topical administration studies, dose limiting toxicity was associated with the severity of the irritant response to ingenol mebutate gel administration. Dose- and frequency-dependent skin responses in rats and minipigs, characterised by erythema and oedema, and microscopic observations of acanthosis, dermal inflammation/fibrosis, epidermal hyperplasia, erosion/ulceration, and scab formation, were similar between species and were consistent across studies.

Gross and histological observations of dermal irritation were reversible at all tested dose levels in both rats and minipigs.

In topical administration studies, single or three daily repeat doses of 0.1% ingenol mebutate up to 500 µg on 150-600 mm^2 in rats or minipigs did not produce mortality or systemic toxicity.

Chronic topical application of 0.02% ingenol mebutate gel up to 30 µg on 600 mm^2 for 3 consecutive days repeated monthly for 6 months in rats and 0.03% ingenol mebutate gel up to 180 µg on 2400 mm^2 for 3 consecutive days repeated monthly for 41 weeks in minipigs also demonstrated no systemic toxicity.

Clinical pathology findings were limited to occasional increases in circulating neutrophils and/or monocytes in rats which were associated with acute/chronic dermal inflammation.

Reproduction

In rats, ingenol mebutate was not associated with fetal developmental effects at IV doses up to 5 µg/kg/day (30 µg/m^2/day). In rabbits, dams receiving 4 µg/kg/day showed an increased incidence of early embryonic deaths compared with the controls (13% vs. 7%). Minor foetal abnormalities were also observed at an increased incidence in the foetuses of ingenol mebutate treated dams (at doses of 1-4µg/kg/day), including variation in the origin of arteries arising directly from the aortic arch, unilateral/bilateral rib costal cartilage not attached to sternum, incompletely ossified cervical vertebral arches and jugal connected/fused to the zygomatic process of the maxilla.

No fertility studies have been performed with ingenol mebutate.

Carcinogenesis and Mutagenesis

Carcinogenicity studies with ingenol mebutate have not been conducted.

Ingenol mebutate was not mutagenic in an *in vitro* Ames test, mouse lymphoma assay, and *in vivo* rat micronucleus test. An *in vitro* Syrian hamster embryonic (SHE) cell transformation assay was positive. The SHE transformation assay gave a positive result after the 24 h and 7 day exposure periods. There was an increase in toxicity (decrease in relative plating efficiency) and increase in morphologically transformed colonies (MTC). Toxicity noted at ≥ 0.05 µg/mL at 24 h and after 7 days. A statistical increase in MTC was seen from 0.1 µg/mL at 24 h and 0.025 µg/mL at 7 days.

A 6-month repeat dose IV rat study in 154 rats found that one male and one female dosed twice weekly with 15 µg/kg had a kidney tubular adenoma and tubular hyperplasia of the kidney. A pituitary adenoma was also present in the female with the renal adenoma. At the 1-month recovery kill, one male had a thyroid follicular cell carcinoma. There was no evidence of neoplasia at lower IV doses or in the 6 month dermal rat and 41 week dermal minipig repeat dose studies.

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25. A multi-center, Randomized, parallel group, double-blind, vehicle-controlled study to evaluate the Efficacy and safety of PEP005 (ingenol mebutate) Gel, 0.05% In patients with actinic keratoses on non-head locations (REGION-Ib; PEP005-028) 2010 Sep 8 (data on file)

26. A multi-center, randomized, parallel group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of PEP005 (ingenol mebutate) Gel, 0.015% in patients with actinic keratoses on the head (face or scalp). (REGION-IIa; PEP005-016) 2010 Sep 8 (data on file)

27. A multi-center, randomized, parallel group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of PEP005 (ingenol mebutate) Gel, 0.015% in patients with actinic keratoses on the head (face or scalp). (REGION-IIb; PEP005-025) 2010 Sep 8 (data on file)

PART III: CONSUMER INFORMATION

PrPICATO®
Ingenol mebutate gel

This leaflet is part III of a three-part "Product Monograph" published when Picato® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Picato®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Picato® is used for the topical treatment of Actinic Keratosis.

Actinic Keratosis (AK) lesions are thick, hard, scaly patches on skin that has been damaged by too much sun (UV) exposure.

What it does:
Picato® gel contains ingenol mebutate which is thought to be toxic to cells and promote a local inflammatory response.

When it should not be used:
Do not use Picato® gel if you are allergic (hypersensitive) to ingenol mebutate or any of the ingredients in the gel.

What the medicinal ingredient is:
Picato® gel contains ingenol mebutate.

What the important nonmedicinal ingredients are:
Picato® gel contains isopropyl alcohol, hydroxyethyl cellulose, citric acid monohydrate, sodium citrate, benzyl alcohol and purified water.

What dosage forms it comes in:
Picato® is a clear, colourless gel available in 2 strengths.
Picato® gel 0.015 %: Each carton contains 3 unit dose tubes
Picato® gel 0.05 %: Each carton contains 2 unit dose tubes

WARNINGS AND PRECAUTIONS

- Do not apply the gel in, near, or around the eyes. Picato® gel is irritating to the eyes. If accidental application to the eye occurs, flush the area with plenty of water and seek medical care immediately
- Do not apply the gel on the inside of the nostrils, on the inside of the ears, on or near the mouth and lips, or on skin outside the treatment area as defined by your doctor.
- Do not apply Picato® 0.05% on the face or scalp, only use Picato® 0.015% on the face or scalp.
- Make sure that the skin has healed from the other treatments or surgery before applying Picato® gel.
- Do not use Picato® on open wounds or areas of damaged skin.
- If Picato® gel is accidentally swallowed drink plenty of water and seek medical care immediately.
- Look out for any new scaly red patches, open sores, elevated or warty growths within the treatment area. If any of these occur, talk to your doctor.
- Picato® gel has not been studied in patients under 18 years of age.

BEFORE you use Picato® gel talk to your doctor or pharmacist if you:
- Are pregnant or planning to become pregnant.
- Are breastfeeding.
- Have had other treatments for AK.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including non-prescription medicines (such as vitamins, herbal remedies, etc.). It is not known if Picato® gel and other medicines can affect each other.

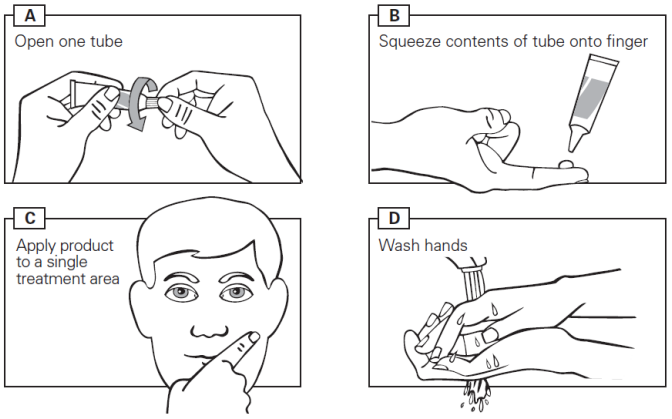
PROPER USE OF THIS MEDICATION

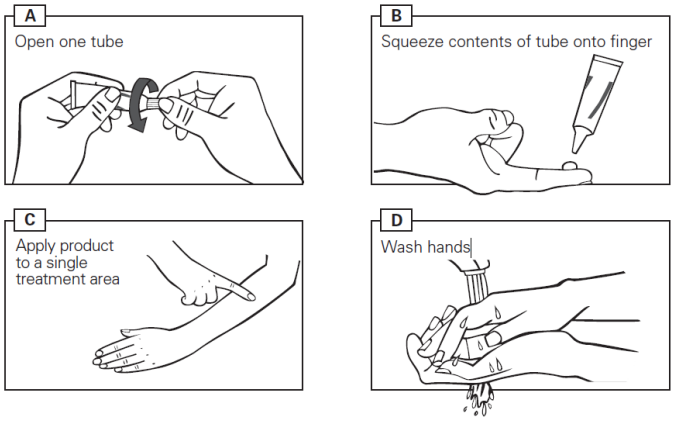
Always use Picato® gel exactly as prescribed by your doctor and only on the area(s) of skin to be treated. Use the correct Picato® gel on the correct skin area. Do not use Picato® gel 0.05% on the face or scalp.

Usual dose:
- For treatment of AK on the face or scalp, use one unit dose tube of 0.015% gel once daily for 3 days in a row.
- For treatment of AK on the body, arms, hands or legs, use one unit dose tube of 0.05% gel once daily for 2 days in a row.

Instructions for use:
- Open a new tube each time you use Picato® gel. Remove the cap from the tube just before using.
- Squeeze the contents from one tube onto your fingertip.
- One tube has enough gel to cover about a 25 cm2 (5 cm x 5 cm) area of skin.
- Gently rub the gel over the affected skin area.
- To help prevent accidental transfer of Picato® gel to your eyes or other areas of your body:
  - Wash your hands immediately after applying Picato® gel. If you are treating your hands, you should wash only the fingertip you used for applying the gel.
  - Allow the area to dry for 15 minutes.
  - Do not wash or touch the treated area yourself or allow anyone to touch the treated skin for a period of 6 hours after applying Picato® gel.
  - Do not apply Picato® gel immediately after taking a shower or less than 2 hours before bedtime.
- After 6 hours you may wash the area with a mild soap and water.
- Do not cover the treated skin area with a bandage or other type of dressing after you have applied Picato® gel.
- Avoid shaving the treated skin area during treatment with

Picato®.





Overdose:

In case of drug overdose or accidental ingestion, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, contact your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects with Picato® include:

The most common side effects:
Local skin reactions at the treatment site. These include redness, flaking, scabbing and crusting, swelling, blister or ulcer, skin that becomes hard or thickened, and peeling skin. These reactions can start within one day of treatment and may get worse for up to one week after you have stopped using Picato®. These will usually get better within 2 weeks from when you started treatment on the face or scalp, and within 4 weeks from when you started treatment on body, arms, hands or legs. If these reactions do not improve, see your doctor.

Common side effects:
Pain, itching, skin irritation or infection at the treatment area, swelling around the eyes, and headache.

Side effects need immediate medical attention and help:
- Serious allergic reaction (swelling of the lips or tongue, trouble breathing or wheezing, chest tightness, dizziness or passing out)
- Stevens-Johnson syndrome (unexplained widespread skin pain, red or purple skin rash that spreads, blisters on skin and the mucous membrane of mouth, nose, eyes and genitals, shedding of skin within days after blisters form)
- Serious chemical pinkeye and serious burn injuries to the eyes

It is possible that you may experience lightening or darkening of your skin with the use of Picato® gel. In addition, there can be scarring of the skin.

Talk to your Health Care Provider if you have questions about your treatment or side effects.

HOW TO STORE IT

Store Picato® gel in a refrigerator (2°C to 8°C).

Keep Picato® gel out of the reach of children and pets.

Do not use Picato® gel after the expiry date (EXP). Tubes should not be re-used once opened.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at** www.healthcanada.gc.ca/medeffect
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at
www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.leo-pharma.com/canada or by contacting the sponsor, LEO Pharma Inc., at: 1-800-668-7234. Additional information can also be found at www.picatosupport.ca.

This leaflet was prepared by LEO Pharma Inc.

Last revised: February 20, 2020