Attachment 1: Product information for AusPAR Picato 0.015% and 0.05% gel Ingenol Mebutate LEO Pharma Pty Ltd PM-2011-02307-3-5 Final 6 June 2013. This Product Information was approved at the time this AusPAR was published.

PRODUCT INFORMATION

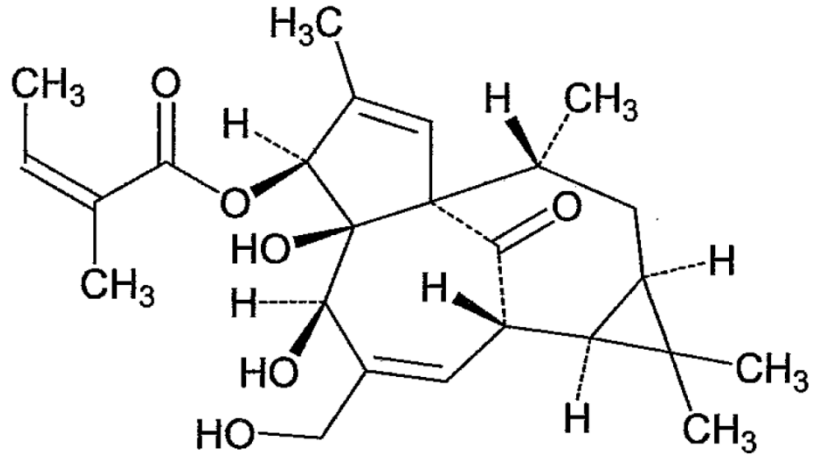
Picato® gel

Ingenol mebutate 0.015% (AUST R 190122) and ingenol mebutate 0.05% (AUST R 190113)

NAME OF THE MEDICINE

Picato® gel, 0.015% / Picato® gel, 0.05%

Picato® gel contains the active substance ingenol mebutate.



The chemical name for ingenol mebutate is:

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, (2*Z*)-

or

(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*-2,8amethanocyclopenta[*a*]cyclopropa[*e*]cyclodecen-6-yl (2Z)-2-methylbut-2-enoate.

The empirical formula is $C_{25}H_{34}O_6$. The molecular weight is 430.53 g/mol.

CAS number: 75567-37-2.

DESCRIPTION

Picato® gel is clear colourless gel intended for topical administration. It is available in two strengths:

- Picato® gel, 0.015% ingenol mebutate for treatment of solar (actinic) keratoses on the face and scalp and

- Picato® gel, 0.05% ingenol mebutate for the treatment of solar (actinic) keratoses on the body

Ingenol mebutate is a purified ingenol angelate extracted from the *E. peplus* plant and is a white to pale yellow crystalline powder.

The distribution coefficient between octanol and phosphate buffer is 4.1 at a pH of 7.4. Ingenol mebutate is practically insoluble in water.

Picato® gel contains the excipients: isopropyl alcohol, hydroxyethylcellulose, citric acid monohydrate, sodium citrate, benzyl alcohol and purified water.

PHARMACOLOGY

Mechanism of Action

The mechanism of action of Picato® in solar (actinic) keratoses is not fully understood. In vivo and in vitro models have shown a dual mechanism of action for the effects of ingenol mebutate: 1) induction of local lesion cell death and 2) promoting an inflammatory response characterised by infiltration of neutrophils and other immunocompetent cells.

Pharmacodynamics

Ingenol mebutate induces multiple mechanisms in tumour cells by exerting a direct cytotoxic effect and by modulating Protein Kinase C (PKC) isoforms.

At a high concentration (100 mcg/mL) in vitro and in vivo, ingenol mebutate induces mitochondrial swelling and loss of cell membrane integrity leading to cell death; at lower concentrations (10 to 100 ng/mL), ingenol mebutate stimulates PKC dependent activation of human endothelial cells to support neutrophil adhesion in vitro.

Exposure of isolated human keratinocytes to lower concentrations of ingenol mebutate (10 to 100 ng/mL) in vitro, was shown to induce release of cytokines IL-8 and TNF-alpha, and promote specific PKC-mediated 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 ingenol mebutate showed growth inhibitory activity against mouse squamous cell carcinoma and malignant melanoma tumour models.

Topical treatment with ingenol mebutate gel in the squamous cell carcinoma model, resulted in a localised and transient application site inflammatory reaction which peaked after a few days and resolved within 2 weeks followed by scar resolution after 2 to 3 months.

Pharmacokinetics

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

No systemic absorption was detected at or above the lower limit of detection (0.1 ng/mL) when Picato® gel, 0.05% from 4 single dose tubes was applied to an area of 100 cm^2 on the dorsal forearm in solar keratoses patients once daily for two consecutive days.

In vitro study results demonstrate that ingenol mebutate does not inhibit or induce human cytochrome P450 isoforms, at clinically relevant concentrations.

CLINICAL TRIALS

Solar (Actinic) Keratoses of the Face and Scalp

The efficacy and safety of Picato® gel, 0.015%, applied to the face or scalp for 3 consecutive days, was studied in two double-blind, vehicle-controlled, clinical studies including 547 adult patients. Patients continued in the studies for an 8 week follow-up period during which they returned for clinical observations and safety monitoring. Efficacy, measured as complete and partial clearance rate, as well as median percent reduction, was assessed at day 57 (see Table 1).

Patients had 4 to 8 clinically typical, visible, non-hyperkeratotic, non-hypertrophic discrete solar keratosis lesions on the face or scalp within a contiguous 25 cm^2 treatment area. On each scheduled dosing day, the study gel was applied to the entire treatment area. The compliance rate was high, with 98% of the patients completing these studies. Study patients ranged from 34 to 89 years of age (mean 64 years) and 94% had Fitzpatrick skin type I, II, or III.

At day 57, patients treated with Picato® had higher complete and partial clearance rates than patients treated with vehicle gel ($p < 0.001$). The median percent reduction in solar keratosis lesions was higher in the group treated with Picato® compared to the vehicle group (see Table 1).

Table 1: Rates of subjects with complete and partial clearance and percent (%) reduction on face and scalp

	Picato® gel, 0.015% (n=277)	**Vehicle (n=270)**
Complete clearance rate[a]	42.2%[d]	3.7%
Partial clearance rate (≥75%)[b]	63.9%[d]	7.4%
Median % reduction[c]	83%	0%

[a] Complete clearance rate was defined as the proportion of patients with no (zero) clinically visible solar 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 solar keratosis lesions were cleared.

The safety of Picato® gel, 0.015% treatment for 3 days was assessed up to day 57. The results demonstrated that ingenol mebutate gel was well tolerated. All adverse drug reactions and local skin responses resolved without sequelae.

Statistically significant differences in patient reported outcomes were observed in favour of patients receiving Picato® compared to those receiving vehicle gel. Higher mean patient global satisfaction scores, indicating a higher level of overall satisfaction, were seen in the Picato® groups compared to the vehicle groups ($p < 0.001$) as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM).

Solar (Actinic) Keratoses of the Body

The efficacy and safety of Picato® gel, 0.05%, applied to the trunk or extremities for 2 consecutive days was studied in two double-blind, vehicle-controlled, clinical studies including 458 adult patients. Patients continued in the studies for an 8 week follow-up period during which they returned for clinical observations and safety monitoring. Efficacy, measured as complete and partial clearance rate, as well as median percent reduction, was assessed at day 57 (see Table 2).

Patients had 4 to 8 clinically typical, visible, non-hyperkeratotic, non-hypertrophic discrete solar keratosis lesions on the trunk or extremities within a contiguous 25 cm^2 treatment area. On each scheduled dosing day, the study gel was applied to the entire treatment area. The compliance rate was high, with 98% of the patients completing these studies. Study patients ranged from 34 to 89 years of age (mean 66 years) and 94% had Fitzpatrick skin type I, II, or III.

At day 57, patients treated with Picato® had higher complete and partial clearance rates than patients treated with vehicle gel ($p < 0.001$). The median percent reduction in solar keratosis lesions was higher in the group treated with Picato® compared to the vehicle group (see Table 3).

Table 2: Rates of subjects with complete and partial clearance and percent (%) reduction on the body (trunk and extremities)

	Picato® gel, 0.05% (n=226)	**Vehicle (n=232)**
Complete clearance rate[a]	34.1%[d]	4.7%
Partial clearance rate (≥75%)[b]	49.1%[d]	6.9%
Median % reduction[c]	75%	0%

[a] Complete clearance rate was defined as the proportion of patients with no (zero) clinically visible solar keratosis lesions in the treatment area.
[b] The partial clearance rate was defined as the percentage of patients in whom 75% or more of the number of baseline solar keratosis lesions were cleared.
[c] Median percent (%) reduction in number of solar keratosis lesions compared to baseline.
[d] p<0.001; compared to vehicle by logistic regression with treatment, study and anatomical location.

The safety of Picato® gel, 0.05% treatment for 2 days was assessed up to day 57. The results demonstrated that Picato® was well tolerated. All adverse drug reactions and local skin responses resolved without sequelae.

Statistically significant differences in patient reported outcomes were observed in favour of patients receiving Picato® gel compared to those receiving vehicle gel. Higher mean patient global satisfaction scores, indicating a higher level of overall satisfaction, were seen in the Picato® groups compared to the vehicle groups ($p < 0.001$) as measured by the TSQM.

Long Term Efficacy

Three prospective, observational long-term 1 year follow-up studies were conducted to evaluate sustained efficacy by recurrence of solar keratosis lesions in the treatment field, and safety in patients who had received treatment with Picato® gel. One study included patients treated with Picato® gel, 0.015% on the face or scalp for 3 days and two studies included patients treated with Picato® gel, 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 3 and 4).

Table 3: Rate of recurrence of solar keratosis lesions on face and scalp

	Picato® gel, 0.015% (n=108)
Recurrence Rate 12 months KM estimate (95% CI)[a]	53.9% (44.6-63.7)
Lesion Based Recurrence Rate[b] 12 months Mean (SD)	12.8% (19.1)

[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 solar 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 SK lesions at 12 months to the number of lesions at baseline in the previous phase 3 studies.

Table 4: Rate of recurrence of solar keratosis lesions on trunk and extremities

	Picato® gel, 0.05% (n=76[c])
Recurrence Rate 12 months KM estimate (95% CI)[a]	56.0% (45.1-67.6)
Lesion Based Recurrence Rate[b] 12 months Mean (SD)	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 SK lesion in the previously treated area for patients who achieved complete clearance at day 57 in a previous phase 3 studies.

[b] The lesion-based recurrence rate for each patient defined as the ratio of the number of SK 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.

Progression to squamous cell carcinoma

At end of study (day 57), the rate of squamous cell carcinoma (SCC) reported in the treatment area was comparable in patients treated with Picato® (0.3%, 3 of 1165 patients) and in vehicle treated patients (0.3%, 2 of 632 patients), in the solar keratoses clinical studies.

SCC in the treatment area was reported in none of the 184 patients previously treated with Picato®, in three prospective, observational long-term 1 year follow-up studies.

Experience with treatment of a larger area

In a double-blind, vehicle-controlled study to evaluate systemic exposure, ingenol mebutate 0.05% gel, from 4 single dose tubes, was applied to a 100 cm^2 contiguous treatment area daily for 2 consecutive days. Results demonstrated no systemic absorption.

Picato® gel, 0.05% was well tolerated when applied to a contiguous treatment area of 100 cm^2 on trunk and extremities.

Use in the Elderly

Of the 1165 subjects treated with Picato® in the solar keratoses clinical studies, 656 subjects (56%) were 65 years and older and, 241 subjects (21%) were 75 years and older. No overall differences in safety or efficacy were observed between these subjects and younger subjects.

INDICATIONS

Picato® gel is indicated for the topical treatment of solar (actinic) keratoses in adults.

CONTRAINDICATIONS

Any known hypersensitivity to ingenol mebutate or any constituent of Picato® gel.

PRECAUTIONS

FOR EXTERNAL USE ONLY; NOT FOR ORAL, OPHTHALMIC, VAGINAL OR ANAL USE. AVOID EYE AREA.

Eye exposure: Avoid contact with eyes. If accidental exposure occurs, the eyes should be flushed immediately with large amounts of water, and the patient should seek medical assistance as soon as possible.

Ingestion: If you get Picato® in your mouth, rinse well with water right away. Contact your healthcare provider or poison information center, phone 13 11 26.

Local skin responses: Local skin responses such as erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation and erosion/ulceration can occur after topical application of Picato®. These local skin responses have been shown to be associated with the clinical efficacy. Localised skin responses are transient and typically occur within 1 day of treatment

initiation and peak in intensity up to 1 week following completion of treatment. Localised skin responses typically resolve within 2 weeks of treatment initiation when treating areas on the face and scalp and within 4 weeks of treatment initiation when treating areas on the trunk and extremities. A treatment effect may not be adequately assessed until resolution of local skin responses.

Administration of Picato® gel is not recommended until the skin is healed from any treatment with a previous drug or surgical treatment.

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 gel, 0.01%. Ingenol mebutate gel did not demonstrate any potential for photo irritation or photo allergic effects. However, due to the nature of the disease, excessive exposure to sunlight (including sunlamps and tanning beds) should be avoided or minimised.

Systemic reactions: No systemic absorption of ingenol mebutate has been detected under maximal use conditions (100 cm^2 contiguous treatment area treated with 4 unit dose tubes of Picato® gel, 0.05% once daily for 2 consecutive days) [see Clinical Pharmacology].

Effects on Fertility

No fertility studies have been performed with ingenol mebutate.

Use in Pregnancy (Category B3)

There are no data from the use of ingenol mebutate in pregnant women. Animal studies are equivocal with respect to reproductive toxicity (see below). Risks to humans receiving topical treatment with Picato® are considered unlikely as ingenol mebutate is not absorbed systemically. As a precautionary measure, it is preferable to avoid the use of Picato® during pregnancy.

In rats, ingenol mebutate was not associated with foetal developmental effects at IV doses up to 5 mcg/kg/day (30 mcg/m^2/day), however, there was a possible increase in early embryonic deaths. In rabbits there were no major abnormalities at IV doses up to 4 mcg/kg/day (48 mcg/m^2/day). Minor foetal abnormalities or variants were observed in the foetuses of treated dams at doses ≥ 2 mcg/kg/day (24 µg/m^2/day). The foetal NOAEL was 1 mcg/kg/day (12 mcg/m^2/day).

Use in Lactation

No effects on the breastfed newborn/infants are anticipated as ingenol mebutate is not absorbed systemically. The nursing mother should be instructed that the newborn/infant avoid physical contact with the treated area for a period of 6 hours after application of Picato®.

Paediatric Use

Picato® is not indicated for use in the paediatric population.

Use in the Elderly

No dosage adjustment is required [see Clinical Trials].

Genotoxicity

Ingenol mebutate was not mutagenic in an *in vitro* Ames test, mouse lymphoma assay, and *in vivo* rat micronucleus test, and gave a positive response in the Syrian hamster embryo cell *in vitro* transformation assay.

Carcinogenicity

Carcinogenic evaluations of ingenol mebutate have not been conducted.

Effects on Laboratory Tests

There are no data available on the effects of Picato® on laboratory tests

INTERACTIONS WITH OTHER MEDICINES

No interaction studies have been performed. Interactions with systemically absorbed medicinal products are considered minimal as ingenol mebutate is not absorbed systemically.

ADVERSE EFFECTS

Clinical Trials

The data described below reflect exposure to ingenol mebutate or vehicle in 1002 subjects with solar keratoses treated in four vehicle controlled phase 3 studies. Subjects received field treatment (area of 25 cm^2) with Picato® at concentrations of 0.015% or 0.05% or vehicle once daily for 3 or 2 consecutive days, respectively. Adverse reactions were generally mild to moderate in intensity (Table 5).

Table 5: Adverse reactions occurring in ≥ 1% of subjects treated with Picato® and at higher frequency than vehicle

Preferred term	Picato® gel (n=499)	Vehicle (n=503)
Application site pain	8.6%	0.2%
Application site pruritus	8.2%	0.6%
Application site irritation	2.6%	0.2%
Application site infection	1.4%	0.2%
Periorbital oedema	1.4%	0.0%
Headache	1.4%	1.0%

In the four vehicle controlled phase 3 studies, local skin responses (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, 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 discernable skin reaction that extended beyond the area treated (Table 6).

For both treatment locations (face/scalp and trunk/extremities), erythema and flaking/scaling were the most common LSRs, followed by crusting and swelling in patients treated with Picato®. The local skin responses are transient and typically occur within one day of treatment initiation and peak in intensity up to one week following completion of treatment. Local skin responses typically resolve within 2 weeks for areas treated on the face and scalp and within 4 weeks for areas treated on the body (trunk and extremities).

Other less common adverse reactions (less than 1% but more than 0.5%) were, in decreasing order: application site parasthesia and eyelid oedema.

Table 6: Local skin responses in the treatment area in Picato® or vehicle - treated subjects as assessed by the investigator

Local skin responses maximum score past baseline	Grade	Face/Scalp		Trunk/Extremities	
		Picato® gel 0.015% (n=274)	Vehicle (n=271)	Picato® gel 0.05% (n=225)	Vehicle (n=232)
Erythema	1 2 3 4	25 (9%) 56 (20%) 125 (46%) 66 (24%)	127 (47%) 33 (12%) 6 (2%) 0 (0%)	31 (14%) 94 (42%) 61 (27%) 34 (15%)	102 (44%) 16 (7%) 2 (1%) 0 (0%)
Flaking/scaling	1 2 3 4	52 (19%) 91 (33%) 98 (36%) 25 (9%)	142 (52%) 36 (13%) 4 (1%) 0 (0%)	52 (23%) 86 (38%) 66 (29%) 18 (8%)	131 (56%) 15 (6%) 3 (1%) 0 (0%)
Crusting	1 2 3 4	85 (31%) 64 (23%) 64 (24%) 16 (6%)	47 (17%) 5 (2%) 0 (0%) 0 (0%)	105 (47%) 39 (17%) 23 (10%) 8 (4%)	38 (16%) 4 (2%) 2 (1%) 0 (0%)
Swelling	1 2 3 4	88 (32%) 67 (24%) 48 (18%) 14 (5%)	12 (4%) 2 (1%) 0 (0%) 0 (0%)	65 (29%) 51 (23%) 20 (9%) 7 (3%)	13 (6%) 0 (0%) 0 (0%) 0 (0%)
Vesiculation/ pustulation	1 2 3 4	36 (13%) 53 (19%) 50 (18%) 15 (5%)	1 (0%) 0 (0%) 0 (0%) 0 (0%)	46 (20%) 30 (13%) 19 (8%) 3 (1%)	1 (0%) 1 (0%) 0 (0%) 0 (0%)
Erosion/ Ulceration	1 2 3 4	55 (20%) 26 (10%) 5 (2%) 1 (0%)	4 (1%) 0 (0%) 0 (0%) 0 (0%)	37 (16%) 15 (7%) 4 (2%) 2 (1%)	6 (3%) 0 (0%) 0 (0%) 0 (0%)

Clinical Trial Experience – Long-term Safety Follow-up

Three prospective, observational long-term follow-up studies were conducted to evaluate recurrence of solar keratosis lesions and safety in subjects receiving treatment with Picato® on the face, scalp or body (trunk or extremities). Only those subjects 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. Subjects were followed every 3 months for up to 12 months.

A total of 198 subjects (184 treated with Picato® and 14 treated with vehicle), enrolled in the long-term follow-up studies. Results from these studies did not change the safety profile for Picato® [*see* Clinical Trials].

DOSAGE AND ADMINISTRATION

Picato® gel is indicated for TOPICAL USE ONLY**.** Picato® gel is NOT for oral, ophthalmic, intravaginal or anal use.

Adults

For the Treatment of Solar (Actinic) Keratoses on the Face and Scalp

Picato® gel, 0.015% should be applied to the affected area once daily for 3 consecutive days.

For the Treatment of Solar (Actinic) Keratoses on the Body

Picato® gel, 0.05% should be applied to the affected area once daily for 2 consecutive days.

Application Instructions for the Face and Scalp and Body

Picato® should be applied to a defined treatment area. A treatment area is defined as one contiguous area of approximately 25 cm^2 (e.g., 5 cm x 5 cm). Each tube contains enough gel to treat a 25 cm^2 treatment area.

- Patients should be instructed to squeeze the gel from the single use tube onto the fingertip and then spread it evenly over the area to be treated, avoiding touching the treatment area and allowing it to dry for 15 minutes.

- Picato® should not be applied immediately before or after taking a shower or less than 2 hours before bedtime.

- Patients should be instructed to wash their hands after applying Picato®.

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 application of Picato®.

Children

There is no relevant use of Picato® gel in the paediatric population.

OVERDOSAGE

There has been no experience of overdose in clinical studies with Picato®.

In a clinical study 4 single dose tubes of Picato® gel, 0.05% was applied daily for 2 consecutive days to a 100 cm^2 area of skin for the treatment of solar keratoses. The result demonstrated no change in the safety profile compared to the safety profile of Picato® gel, 0.05% when 1 tube is applied to a 25 cm^2 area for 2 consecutive days.

PRESENTATION AND STORAGE CONDITIONS

Picato® is a topical gel available in 2 dosage strengths: 0.015% and 0.05%.

The 0.015% dosage strength is indicated for the face and scalp and is available in 3 single use tubes per carton. Each tube contains 70 mcg of ingenol mebutate in 0.47 g of gel.

The 0.05% dosage strength is indicated for the body and is available in 2 single use tubes per carton. Each tube contains 235 mcg of ingenol mebutate in 0.47 g of gel.

Picato® should be stored in a refrigerator (2ºC – 8ºC).

NAME AND ADDRESS OF SPONSOR:

In Australia:

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AUST R

Picato® (ingenol mebutate) gel, 0.015%: AUST R 190122

Picato® (ingenol mebutate) gel, 0.05%: AUST R 190113

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POISONS SCHEDULE OF MEDICINE:

S4

DATE OF ENTRY INTO ARTG: 9 NOVEMBER 2012

Attachment 1: Product information for AusPAR Picato 0.015% and 0.05% gel Ingenol Mebutate LEO Pharma Pty Ltd PM-2011-02307-3-5 Final 6 June 2013. This Product Information was approved at the time this AusPAR was published.

Picato is a registered trademark of LEO Pharma A/S, Denmark

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