# NEW ZEALAND DATA SHEET

## 1 PICATO® GEL

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

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Picato® gel 0.015%: Each tube contains 70 mcg of ingenol mebutate in 0.47 g of gel.
Picato® gel 0.05%: Each tube contains 235 mcg of ingenol mebutate in 0.47 g of gel.

Excipients: For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Clear colourless gel.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Dose and method of administration

Dose

*Solar (actinic) keratoses on face and scalp in adults*
Picato® gel 0.015% should be applied to the affected area once daily for 3 consecutive days.

*Solar (actinic) keratoses on the trunk and extremities (body) in adults*
Picato® gel 0.05% should be applied to the affected area once daily for 2 consecutive days.

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

*Elderly population*
No dose adjustment is required (see section 5.1).

Method of administration
Picato® gel should be applied to the treatment 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 single dose tube should be squeezed onto a fingertip and spread evenly over the entire treatment area, allowing it to dry for 15 minutes. One single dose tube should be used for the treatment area.

Patients should be instructed to wash their hands with soap and water immediately after applying Picato® gel. 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® gel. After this period, the treatment area may be washed using mild soap and water. Picato® gel should not be applied immediately after taking a shower or less than 2 hours before bedtime. The treated area should not be covered with occlusive bandages after Picato® gel is applied. Optimal therapeutic effect can be assessed approximately 8 weeks after treatment.

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients, listed in section 6.1.

### 4.4 Special warnings and precautions for use

Avoid contact with, or inadvertent transfer to, the eyes during treatment and for 6 hours after treatment with Picato® gel. 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.

Picato® gel must not be ingested. If accidental ingestion occurs the patient should drink plenty of water.

Local skin responses such as erythema, flaking/scaling, and crusting can occur after topical application of Picato® gel (see section 4.8). 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. 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 treatment with any previous medicinal product or surgical treatment or from any open wounds.

Clinical data on treatment for more that one treatment course of 2 to 3 consecutive days are not available.

Studies have been conducted to assess the effects of UV irradiation of 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.

Healthcare 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.

## 4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed. Interactions with systemically absorbed medicinal products are considered unlikely as Picato® gel is not absorbed systemically.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of ingenol mebutate in pregnant women. Animal studies do not indicate harmful effects with respect to reproductive toxicity (see section 5.3). Risks to humans receiving topical treatment with Picato® gel are considered unlikely as ingenol mebutate gel is not absorbed systemically. As a precautionary measure, it is preferable to avoid the use of Picato® gel during pregnancy.

Breastfeeding

No effects on the breastfed newborn/infant are anticipated as ingenol mebutate gel is not absorbed systemically. 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® gel.

Fertility

No fertility studies have been performed with ingenol mebutate.

## 4.7 Effects on ability to drive and use machines

Picato® gel has no influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions assessed by investigators are local skin responses including erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation and erosion/ulceration at the application site of ingenol mebutate gel, see Table 1 for MedDRA terms. Following the application of ingenol mebutate, most patients (>95%) experienced one or more local skin response(s). The local 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. These effects typically resolve within 2 weeks of treatment initiation for areas treated on the face and scalp and within 4 weeks of treatment initiation for areas treated on the trunk and extremities.

Tabulated summary of adverse reactions

Table 1 reflects exposure to Picato® gel (0.015% or 0.05%) in 499 patients with solar (actinic) keratoses treated in four vehicle controlled phase 3 studies enrolling a total of 1002 patients. Patients received field treatment (area of 25 $cm^2$) with Picato® gel at concentrations of 0.015% or 0.05%or vehicle once daily for 3 or 2 consecutive days respectively.

The table below presents adverse reactions by MedDRA system organ class.

Frequencies have been defined according to the following convention:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1 Adverse reactions by MedDRA System Organ Class**

| | Frequency | |
|---|---|---|
| **System Organ Class** | **Face and Scalp** | **Trunk and extremities** |
| **Infections and Infestations** | | |
| Application site pustules | Very common | Very common |
| Application site infection | Common | |
| **Nervous system disorders** | | |
| Headache | Common | |
| **Eye Disorders*** | | |
| Eye lid oedema | Common | |
| Eye pain | Uncommon | |
| Periorbital oedema | Common | |
| **General disorders and administration site conditions** | | |
| Application site erosion | Very common | Very common |
| Application site vesicles | Very common | Very common |
| Application site swelling | Very common | Very common |
| Application site exfoliation | Very common | Very common |
| Application site scab | Very common | Very common |
| Application site erythema | Very common | Very common |
| Application site pain** | Very common | Common |
| Application site pruritus | Common | Common |
| Application site irritation | Common | Common |
| Application site discharge | Uncommon | |
| Application site paraesthesia | Uncommon | Uncommon |
| Application site ulcer | Uncommon | Uncommon |
| Application site warmth | | Uncommon |
| * Application site swelling on the face or scalp may gravitate to the eye area<br>** Including application site burning | | |

Long-term follow up

A total of 198 patients (184 treated with Picato® gel and 14 treated with vehicle) were enrolled in long-term efficacy follow-up studies. Results from these studies did not change the safety profile of Picato® gel (see section 5.1).

Post-marketing Experience

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been identified from post-marketing experience. It is not always possible to estimate their incidence. The adverse reactions in the below paragraph are presented in order of decreasing frequency.

Application site pigmentation changes are uncommon but have been reported. Rare cases of application site scarring have been reported. Stevens-Johnson syndrome has been reported.

Accidental eye exposure: Post-marketing reports of chemical conjunctivitis and corneal burn in connection with accidental eye exposure have been received (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

### 4.9 Overdose

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

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 (actinic) 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibiotics and chemotherapeutics for dermatological use, other chemotherapeutics, ATC code: D06BX02.

Mechanism of action

The mechanism of action of ingenol mebutate for use in solar (actinic) keratoses remains to be fully characterised. 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 local production of proinflammatory cytokines and chemokines and infiltration of immunocompetent cells.

Pharmacodynamic effects

Results from two clinical trials on biological effects of ingenol mebutate have shown that topical administration induced epidermal necrosis and a profound inflammatory response in both epidermis and the upper dermis of the treated skin, dominated by infiltrating T cells, neutrophils and macrophages. Necrosis in the dermis was rarely observed.

Gene expression profiles of skin biopsies from the treated areas is suggestive of inflammatory responses and response to wounding, which is consistent with the histology assessments.

Non-invasive examination of the treated skin by reflectance confocal microscopy have shown that the skin changes induced by ingenol mebutate were reversible, with almost complete normalisation of all measured parameters on day 57 after treatment, which is supported also by clinical findings and studies in animals.

Clinical efficacy and safety

The efficacy and safety of Picato® gel 0.015%, administered on the face or scalp for 3 consecutive days was studied in two double-blind, vehicle-controlled, clinical studies including 547 adult patients. Likewise the efficacy and safety of Picato® gel 0.05%, administered on 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, discrete, non-hyperkeratotic, non-hypertrophic, solar (actinic) keratoses lesions on the face or scalp within a contiguous 25 $cm^2$ treatment area on the face or scalp or on the trunk and extremities. 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 and 66 years, respectively, for the two strengths) and 94% had Fitzpatrick skin type I, II, or III.

At day 57, patients treated with Picato® gel had higher complete and partial clearance rates than patients treated with vehicle gel ($p<0.001$). The median percent reduction in solar (actinic) keratoses lesions was higher in the group treated with ingenol mebutate compared to the vehicle group (see Table 2).

**Table 2 Rates of subjects with complete and partial clearance and median percent (%) lesion reduction in actinic keratoses**

| | Face and scalp | | Trunk and Extremities | |
|---|---|---|---|---|
| | **Picato® gel 0.015% (n=277)** | **Vehicle (n=270)** | **Picato® gel 0.05% (n=226)** | **Vehicle (n=232)** |
| Complete Clearance Rate[a] | 42.2%[d] | 3.7% | 34.1%[d] | 4.7% |
| Partial Clearance Rate[b] (≥75%) | 63.9% [d] | 7.4% | 49.1%[d] | 6.9% |
| Median % Reduction[c] | 83% | 0% | 75% | 0% |

[a] Complete clearance rate was defined as the proportion of patients with no (zero) clinically visible solar (actinic) keratoses 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 (actinic) keratoses lesions were cleared.
[c] Median percent (%) reduction in solar (actinic) keratoses lesions compared to baseline.
[d] p<0.001; compared to vehicle by logistic regression with treatment, study and anatomical location.

Safety of Picato® gel 0.015% treatment for 3 days or Picato® gel 0.05% 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.

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 ingenol mebutate groups compared to the vehicle groups (p<0.001) as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM).

*Long term efficacy*

Three prospective, observational long term 1 year follow-up studies were conducted to evaluate sustained efficacy by recurrence of solar (actinic) keratoses 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 truck or extremities (body) 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 Table 3 and 4).

**Table 3 Rate of recurrence of solar (actinic) keratoses lesions on face and scalp**

| | **Picato® gel 0.015% (n=108)** |
|---|---|
| Recurrence Rate 12 months<br>KM estimate (95% CI)[a] | 53.9% (44.6-63.7) |
| Lesion Based Recurrence Rate[b] 12 months<br>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 (actinic) keratoses 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 solar (actinic) keratoses lesions at 12 months to the number of lesions at baseline in the previous phase 3 studies.

**Table 4 Rate of recurrence of solar (actinic) keratoses lesions on trunk and extremities (body)**

| | **Picato® gel 0.05% (n=76[c])** |
|---|---|
| Recurrence Rate 12 months<br>KM estimate (95% CI)[a] | 56.0% (45.1-67.6) |
| Lesion Based Recurrence Rate[b] 12 months<br>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 solar (actinic) keratoses 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 solar (actinic) keratoses 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.

*Risk of 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 ingenol mebutate gel (0.3%, 3 of 1165 patients) and in vehicle treated patients (0.3%, 2 of 632 patients) in the solar (actinic) keratoses clinical studies conducted with ingenol mebutate.

SCC in the treatment area was reported in no patients (0 of 184 patients previously treated with ingenol mebutate gel) in the 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 the trunk and extremities (body).

*Elderly population*

Of the 1165 patients treated with Picato® gel in the solar (actinic) keratoses clinical studies conducted with ingenol mebutate gel, 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.

### 5.2 Pharmacokinetic properties

The systemic pharmacokinetic profile of ingenol mebutate and its metabolites has not been characterised in humans due to the absence of quantifiable whole 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 (actinic) keratoses patients once daily for 2 consecutive days.

In vitro study results demonstrate that ingenol mebutate does not inhibit or induce human cytochrome P450 isoforms.

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

The non-clinical safety studies demonstrate that topical administration of ingenol mebutate gel is well tolerated with skin irritation potential and negligible risk of systemic toxicity under the recommended conditions of use.

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). In rabbits there were no major abnormalities. Minor foetal abnormalities or variants were observed in the foetuses of treated dams; however, the findings did not suggest a clear association with IV ingenol mebutate administration. The foetal NOAEL was 1 mcg/kg/day (12 mcg/$m^2$/day).

## 6 PHARMACEUTICAL PROPERTIES

### 6.1 List of excipients

Isopropyl alcohol

Hydroxyethylcellulose

Citric acid monohydrate

Sodium citrate

Benzyl alcohol
Purified water

### 6.2 Incompatibilities
Not applicable

### 6.3 Shelf life
2 years. Tubes should not be re-used once opened.

### 6.4 Special precautions for storage
Store in refrigerator (2ºC – 8ºC).

### 6.5 Nature and contents of container
Single dose laminate tubes with inner layer of High Density Polyethylene (HDPE) and aluminium as the barrier layer. Caps of HDPE.

Picato® gel 0.015% for application to the face and scalp is available in a carton containing 3 single-dose tubes with 0.47 g of gel each.

Picato® gel 0.05% for application to the body is available in a carton containing 2 single-dose tubes with 0.47 g of gel each.

### 6.6 Special precautions for disposal and other handling
Nil.

## 7 MEDICINE SCHEDULE
Prescription medicine

## 8 SPONSOR
LEO Pharma Ltd
Auckland
New Zealand
Ph: 0800 497 456



## 9 DATE OF FIRST APPROVAL
23 May 2012

## 10 DATE OF REVISION OF THE TEXT
06 November 2019

## SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information |
|---|---|
| 4.8 | Addition of Stevens-Johnson syndrome to post-marketing experience. |