ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Picato 150 micrograms/gram gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of gel contains 150 mcg of ingenol mebutate. Each tube contains 70 mcg of ingenol mebutate in 0.47 g of gel.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel.
Clear colourless gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Picato is indicated for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.

4.2 Posology and method of administration

Posology

Actinic keratosis on the face and scalp in adults
One tube of Picato 150 mcg/g gel (containing 70 mcg ingenol mebutate) should be applied once daily to the affected area for 3 consecutive days.

Optimal therapeutic effect can be assessed approximately 8 weeks after treatment.

A repeat treatment course of Picato can be given if an incomplete response is seen at a follow-up examination after 8 weeks or if lesions that are cleared at this examination recur in subsequent examinations.

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

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

Immunocompromised patients
Clinical data on treatment in immunocompromised patients is not available, but systemic risks are not expected since ingenol mebutate is not absorbed systemically.

Method of administration

The content of one tube covers a treatment area of 25 cm^2 (e.g. 5 cm x 5 cm). The tube is for single use only and should be discarded after use (see section 6.6).

The gel from the tube should be squeezed onto a fingertip and spread evenly over the entire treatment area, allowing it to dry for 15 minutes. The content of one tube should be used for one treatment area of 25 cm^2.
For single use only.

For treatment of the neck:
If more than half of the treatment area is located in the upper part of the neck, Picato 150 mcg/g gel should be used at the posology for face and scalp. If more than half of the treatment area is located in the lower part of the neck, Picato 500 mcg/g gel should be used at the posology for trunk and extremities.

If an area on the face or scalp and another area on the trunk or extremities are simultaneously treated, then patients should be advised to ensure they use the appropriate strengths. Care should be exercised not to apply the Picato 500 mcg/g gel on the face or scalp as this could lead to a higher incidence of local skin responses.

Patients should be instructed to wash their hands with soap and water, immediately after applying Picato and between topical applications if two different areas require different strengths. 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. After this period, the treatment area may be washed using mild soap and water.

Picato 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 is applied.

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

Eye exposure
Contact with the eyes can cause chemical conjunctivitis and corneal burns. Patients should wash their hands thoroughly after applying the gel and following any contact with the treated area, to avoid inadvertent transfer of the gel to the eyes. 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. Eye disorders such as eye pain, eyelid oedema and periorbital oedema should be expected to occur after accidental eye exposure of Picato (see section 4.8).

Ingestion
Picato must not be ingested. If accidental ingestion occurs the patient should drink plenty of water and seek medical care.

General
Administration of Picato is not recommended until the skin is healed from treatment with any previous medicinal product or surgical treatment and should not be applied to open wounds or damaged skin where the skin barrier is compromised.
Picato should not be used near the eyes, on the inside of the nostrils, on the inside of the ears or on the lips.

Local skin responses
Local skin responses such as erythema, flaking/scaling, and crusting should be expected to occur after cutaneous application of Picato (see section 4.8). 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.

Sun exposure
Studies have been conducted to assess the effects of UV irradiation of the skin following single and multiple applications of ingenol mebutate gel, 100 mcg/g. 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.

Keratoacanthoma, basal cell carcinoma, Bowen's disease, squamous cell carcinoma
Reports of keratoacanthoma, basal cell carcinoma, Bowen's disease, squamous cell carcinoma occurring within the treatment area with a time to onset ranging from weeks to months following use of ingenol mebutate gel have been received from a post-authorisation clinical trial (see section 5.1) and post-marketing. Ingenol mebutate should be used with caution in patients with a history of cutaneous malignancy. Health care professionals should advise patients to be vigilant for any lesions developing within the treatment area and to seek medical advice immediately should any occur.

Management of actinic keratosis
Lesions clinically atypical for actinic keratosis or suspicious for malignancy should be biopsied to determine appropriate treatment.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Interactions with systemically absorbed medicinal products are considered unlikely as Picato 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 showed slight embryo-fetal toxicity (see section 5.3). Risks to humans receiving cutaneous treatment with ingenol mebutate are considered unlikely as Picato is not absorbed systemically. As a precautionary measure, it is preferable to avoid the use of Picato during pregnancy.

Breast-feeding
No effects on the breastfed newborn/infant are anticipated as Picato 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.

Fertility
No fertility studies have been performed with ingenol mebutate.

4.7 Effects on ability to drive and use machines

Picato has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most frequently reported adverse reactions 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). Infection at the application site has been reported when treating face and scalp.

Tabulated list of adverse reactions
Table 1 reflects exposure to Picato 150 mcg/g or 500 mcg/g in 499 patients with actinic keratosis treated in four vehicle controlled phase 3 studies enrolling a total of 1,002 patients and post-marketing reports. Patients received field treatment (area of 25 cm^2) with Picato at concentrations of 150 mcg/g or 500 mcg/g or vehicle once daily for 3 or 2 consecutive days respectively.

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

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) and not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions by MedDRA System Organ Classification

	Frequency	
System Organ Class	**Face and scalp**	**Trunk and extremities**
Infections and infestations		
Application site pustules	Very common	Very common
Application site infection	Common	
Immune system disorders		
Hypersensitivity (including angioedema)	Uncommon	Uncommon
Nervous system disorders		
Headache	Common	
Eye disorders*		
Eye lid oedema	Common	
Periorbital oedema	Common	
Chemical conjunctivitis, corneal burn**	Uncommon	Uncommon
Eye pain	Uncommon	
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 pigmentation changes	Uncommon	Uncommon
Application site warmth		Uncommon
Application site scarring	Rare	Rare

*: Application site swelling on the face or scalp may gravitate to the eye area
**: Accidental eye exposure: Post-marketing reports of chemical conjunctivitis and corneal burn in connection with accidental eye exposure have been received (see sections 4.2 and 4.4 for prevention of eye exposure)
***: Including application site burning.

Description of selected adverse reactions
The incidence of local skin responses that occurred at an incidence >1% in both the 'face/scalp' and the 'trunk/extremities', respectively are: application site erythema (94% and 92%), application site exfoliation (85% and 90%), application site scab (80% and 74%), application site swelling (79% and 64%), application site vesicles (13% and 20%), application site pustules (43% and 23%) and application site erosion (31% and 25%).

Severe local skin responses occurred with an incidence of 29% on the face and scalp and with an incidence of 17% on the trunk and extremities. The incidence of severe local skin responses that occurred at an incidence >1% in both the 'face/scalp' and the 'trunk/extremities', respectively are: application site erythema (24% and 15%), application site exfoliation (9% and 8%), application site scab (6% and 4%), application site swelling (5% and 3%) and application site pustules (5% and 1%).

Long-term follow up
A total of 198 patients with complete clearance at day 57 (184 treated with Picato and 14 treated with vehicle) were followed for additionally 12 months. In another study, 329 patients who were initially treated with cryotherapy on the face/scalp were randomised after three weeks to either Picato 150 mcg/g (n=158) or vehicle (n=150) for 3 days in the same area. 149 patients in the Picato group and 140 in the vehicle group were followed for 12 months. In a later study 450 patients were initially treated with Picato 150 mcg/g, of these 134 patients were randomised to a second treatment course of Picato 150 mcg/g and the patients followed for up to 12 months after the first treatment.
These results did not change the safety profile of Picato (see section 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdosing of Picato could result in an increased incidence of local skin responses. Management of overdose should consist of treatment of clinical symptoms.

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 actinic keratosis 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 studies 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 150 mcg/g, 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 500 mcg/g, administered on the trunk and 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, actinic keratosis lesions within a contiguous 25 cm^2 treatment area on the face or scalp or on the trunk or 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 had 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 2).

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

	Face and scalp		**Trunk and extremities**	
	Picato 150 mcg/g (n=277)	**Vehicle (n=270)**	**Picato 500 mcg/g (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 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 logistic regression with treatment, study and anatomical location.

The level of efficacy varied between the individual anatomical locations. Within each location the complete and partial clearance rates were higher in the group treated with ingenol mebutate compared to the vehicle group (see table 3 and 4).

Table 3 Number and percent (95% CI) of subjects achieving complete and partial clearance at day 57 by anatomical location face and scalp				
	Complete Clearance		**Partial Clearance(≥ 75%)**	
	Picato 150 mcg/g (n=277)	**Vehicle (n=270)**	**Picato 150 mcg/g (n=277)**	**Vehicle (n=270)**
Face	104/220 47% (41-54%)	9/220 4% (2-8%)	157/220 71% (65-77%)	18/220 8% (5-13%)
Scalp	13/57 23% (13-36%)	1/50 2% (0-11%)	20/57 35% (23-49%)	2/50 4% (1-14%)

Table 4 Number and percent (95% CI) of subjects achieving complete and partial clearance at day 57 by anatomical location trunk and extremities				
	Complete clearance		**Partial clearance (≥ 75%)**	
	Picato 500 mcg/g (n=226)	**Vehicle (n=232)**	**Picato 500 mcg/g (n=226)**	**Vehicle (n=232)**
Arm	49/142 35% (27-43%)	7/149 5% (2-9%)	75/142 53% (44-61%)	11/149 7% (4-13%)
Back of Hand	10/54 19% (9-31%)	0/56 0% (0-6%)	16/54 30% (18-44%)	1/56 2% (0-10%)
Chest	11/14 79% (49-95%)	2/11 18% (2-52%)	12/14 86% (57-98%)	2/11 18% (2-52%)
Other[a]	7/16 44% (20-70%)	2/16 13% (2-38%)	8/16 50% (25-75%)	2/16 13% (2-38%)
[a]Other includes shoulder, back, leg.				

Safety of Picato 150 mcg/g treatment for 3 days or Picato 500 mcg/g treatment for 2 days was assessed up to day 57, the majority of the reported adverse reactions and local skin responses were mild to moderate in intensity and all 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 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 actinic keratosis lesions in the treatment field, and safety in patients who had received treatment with Picato. One study included patients treated with Picato 150 mcg/g on the face or scalp for 3 days and two studies included patients treated with Picato 500 mcg/g 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 table 5).

Table 5 Rate of recurrence of actinic keratosis lesions		
	Picato 150 mcg/g gel Face and scalp	**Picato 500 mcg/g gel Trunk and extremities**

	(n=108)	(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.

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 1,165 patients) and in vehicle treated patients (0.3%, 2 of 632 patients) in the actinic keratosis clinical studies conducted with ingenol mebutate gel.

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 more than one treatment course
In a double blind, vehicle-controlled study, up to two treatment courses of Picato 150 mcg/g were administered to 450 patients with 4-8 AKs in a 25 cm^2 treatment area on the face or scalp. Patients, in whom a first treatment course did not lead to complete clearance of all AKs in the treatment area after 8 weeks, were randomised to another treatment course with Picato or vehicle. Patients in whom the first treatment course led to complete clearance were seen at 26 and 44 weeks and randomised to a second treatment course if they had a recurrence in the field. In all patients, assessment of efficacy was 8 weeks after the randomisation. The first treatment course, given open label, resulted in a complete clearance rate of 62% (277/450). The results of the randomised and blinded second treatment course are presented in table 6.

Table 6 Complete clearance[a] of the field 8 weeks after randomisation and Month 12

	Field recalcitrant[c]		Field recurrent[d]	
	Picato 150 mcg/g gel (n= 92)	**Vehicle (n=49)**	**Picato 150 mcg/g gel (n=42)**	**Vehicle (n=20)**
8 weeks after randomisation	47% (43) (p=0.001[b])	18% (9)	60% (25) (p=0.013[b])	25% (5)
Month 12	18% (17) (p=0.016[b])	4% (2)	31% (13) (p=0.10[b])	15% (3)

[a] Complete clearance rate is defined as the proportion of patients with no (zero) clinically visible actinic keratosis lesions in the treatment area.
[b] Cochran-Mantel-Haenszel test of Picato® gel 150 mcg/g compared to vehicle adjusted for anatomical location (face/scalp) and country.
[c] Patients, in whom the first treatment course did not lead to complete clearance of all AKs in the treatment area.
[d] Patients in whom the first treatment course did lead to complete clearance and who had a recurrence in the treatment area at either week 26 or 44.

Actinic Keratosis of the Face and Scalp, sequential use after cryotherapy
In a two-arm study, 329 adult patients with AK on the face or scalp were randomised to treatment with Picato gel, 150 mcg/g or vehicle 3 weeks after cryotherapy of all visible lesions in the treatment area. The study enrolled patients with 4 to 8 clinically typical, visible, discrete non-hypertrophic and non-hyperkeratotic AK lesions within a 25 cm^2 contiguous treatment area.

Eleven weeks after baseline which is 8 weeks after Picato gel or vehicle, the complete clearance rate was 61% among patients randomised to Picato gel, and 49% among patients randomised to vehicle. At 12 months, the complete clearance rates in these groups were 31% and 19% respectively. The percent reduction of the AK count in the Picato group was 83% at 11 weeks and 57% at 12 months, where in the vehicle group it was 78% at 11 weeks and 42% at 12 months. The mean number of AKs in the Picato group was 5.7 at baseline, 0.8 at week 11, and 0.9 at month 12 as opposed to 5.8, 1.0 and 1.2 in the vehicle group at these time points.
Safety results from the study were comparable to the safety profile of Picato gel, 150 mcg/g as monotherapy

Experience with treatment of a larger area
In a double-blind, vehicle-controlled study to evaluate systemic exposure, Picato 500 mcg/g, from 4 tubes, was applied to a 100 cm^2 contiguous treatment area daily for 2 consecutive days. Results demonstrated no systemic absorption.
Picato 500 mcg/g was well tolerated when applied to a contiguous treatment area of 100 cm^2 on the trunk and extremities.

In a double-blind, vehicle-controlled study in patients with AK on trunk and extremities, an investigational product with ingenol mebutate gel 600 mcg/g was applied once daily for 2, 3, or 4 days to a skin area of 250 cm^2. The trial included a large group of severely sun-damaged patients. 12/163 subjects treated with an investigational product of ingenol mebutate reported 16 skin tumour events inside the treatment area (1 SCC, 1 Bowen's disease and 14 keratoacanthoma following centralised pathology review) compared to 0/61 in the vehicle group.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Picato in all subsets of the paediatric population in actinic keratosis (see section 4.2 for information on paediatric use).

Elderly population
Of the 1,165 patients treated with Picato in the actinic keratosis 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 cutaneous administration.

Absorption
No systemic absorption was detected at or above the lower limit of detection (0.1 ng/mL) when Picato 500 mcg/g from 4 tubes was applied to an area of 100 cm^2 on the dorsal forearm in actinic keratosis 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 cutaneous administration of ingenol mebutate gel is well tolerated with any skin irritation being reversible and a negligible risk of systemic toxicity under the recommended conditions of use.

In rats, ingenol mebutate was not associated with fetal developmental effects at IV doses up to 5 mcg/kg/day (30 mcg/m^2/day). In rabbits there were no major abnormalities. Minor fetal abnormalities or variants were observed in the fetuses of treated dams at doses of 1 mcg/kg/day (12 mcg/m^2/day).

6. PHARMACEUTICAL PARTICULARS

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

6.4 Special precautions for storage

Store in a refrigerator (2ºC-8ºC).
Tubes should be discarded after first opening.

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 150 mcg/g gel is available in a carton containing 3 tubes with 0.47 g of gel each.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

LEO Laboratories Ltd.
285 Cashel Road
Crumlin, Dublin 12
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/796/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 November 2012
Date of latest renewal: 13 July 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Picato 500 micrograms/gram gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of gel contains 500 mcg of ingenol mebutate. Each tube contains 235 mcg of ingenol mebutate in 0.47 g of gel.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel.
Clear colourless gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Picato is indicated for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.

4.2 Posology and method of administration

Posology

Actinic keratosis on the trunk and extremities in adults
One tube of Picato 500 mcg/g gel (containing 235 mcg ingenol mebutate) should be applied once daily to the affected area for 2 consecutive days.

Optimal therapeutic effect can be assessed approximately 8 weeks after treatment.

A repeat treatment course of Picato can be given if an incomplete response is seen at a follow-up examination after 8 weeks or if lesions that are cleared at this examination recur in subsequent examinations.

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

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

Immunocompromised patients
Clinical data on treatment in immunocompromised patients is not available, but systemic risks are not expected since ingenol mebutate is not absorbed systemically.

Method of administration

The content of one tube covers a treatment area of 25 cm^2 (e.g. 5 cm x 5 cm). The tube is for single use only and should be discarded after use (see section 6.6).

The gel from the tube should be squeezed onto a fingertip and spread evenly over the entire treatment area, allowing it to dry for 15 minutes. The content of one tube should be used for one treatment area of 25 cm^2.
For single use only.

For treatment of the neck:
If more than half of the treatment area is located in the upper part of the neck, Picato 150 mcg/g gel should be used at the posology for face and scalp. If more than half of the treatment area is located in the lower part of the neck, Picato 500 mcg/g gel should be used at the posology for trunk and extremities.

If an area on the face or scalp and another area on the trunk or extremities are simultaneously treated, then patients should be advised to ensure they use the appropriate strengths. Care should be exercised not to apply the Picato 500 mcg/g gel on the face or scalp as this could lead to a higher incidence of local skin responses.

Patients should be instructed to wash their hands with soap and water, immediately after applying Picato, and between topical applications if two different areas require different strengths. 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. After this period, the treatment area may be washed using mild soap and water.

Picato 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 is applied.

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

Eye exposure
Contact with the eyes can cause chemical conjunctivitis and corneal burns. Patients should wash their hands thoroughly after applying the gel and following any contact with the treated area, to avoid inadvertent transfer of the gel to the eyes. 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. Eye disorders such as eye pain, eyelid oedema and periorbital oedema should be expected to occur after accidental eye exposure of Picato (see section 4.8).

Ingestion
Picato must not be ingested. If accidental ingestion occurs the patient should drink plenty of water and seek medical care.

General
Administration of Picato is not recommended until the skin is healed from treatment with any previous medicinal product or surgical treatment and should not be applied to open wounds or damaged skin where the skin barrier is compromised.
Picato should not be used near the eyes, on the inside of the nostrils, on the inside of the ears or on the lips.

Local skin responses
Local skin responses such as erythema, flaking/scaling, and crusting should be expected to occur after cutaneous application of Picato (see section 4.8). 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.

Sun exposure
Studies have been conducted to assess the effects of UV irradiation of the skin following single and multiple applications of ingenol mebutate gel, 100 mcg/g. 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.

Keratoacanthoma, basal cell carcinoma, Bowen's disease, squamous cell carcinoma
Reports of keratoacanthoma, basal cell carcinoma, Bowen's disease, squamous cell carcinoma occurring within the treatment area with a time to onset ranging from weeks to months following use of ingenol mebutate gel have been received from a post-authorisation clinical trial (see section 5.1) and post-marketing. Ingenol mebutate should be used with caution in patients with a history of cutaneous malignancy. Health care professionals should advise patients to be vigilant for any lesions developing within the treatment area and to seek medical advice immediately should any occur.

Management of actinic keratosis
Lesions clinically atypical for actinic keratosis or suspicious for malignancy should be biopsied to determine appropriate treatment.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Interactions with systemically absorbed medicinal products are considered unlikely as Picato 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 showed slight embryo-fetal toxicity (see section 5.3). Risks to humans receiving cutaneous treatment with ingenol mebutate are considered unlikely as Picato is not absorbed systemically. As a precautionary measure, it is preferable to avoid the use of Picato during pregnancy.

Breast-feeding
No effects on the breastfed newborn/infant are anticipated as Picato 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.

Fertility
No fertility studies have been performed with ingenol mebutate.

4.7 Effects on ability to drive and use machines

Picato has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most frequently reported adverse reactions 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). Infection at the application site has been reported when treating face and scalp.

Tabulated list of adverse reactions
Table 1 reflects exposure to Picato 150 mcg/g or 500 mcg/g in 499 patients with actinic keratosis treated in four vehicle controlled phase 3 studies enrolling a total of 1,002 patients and post-marketing reports. Patients received field treatment (area of 25 cm^2) with Picato at concentrations of 150 mcg/g or 500 mcg/g or vehicle once daily for 3 or 2 consecutive days respectively.

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

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) and not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions by MedDRA System Organ Classification

	Frequency	
System Organ Class	**Face and scalp**	**Trunk and extremities**
Infections and infestations		
Application site pustules	Very common	Very common
Application site infection	Common	
Immune system disorders		
Hypersensitivity (including angioedema)	Uncommon	Uncommon
Nervous system disorders		
Headache	Common	
Eye disorders*		
Eye lid oedema	Common	
Periorbital oedema	Common	
Chemical conjunctivitis, corneal burn**	Uncommon	Uncommon
Eye pain	Uncommon	
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 pigmentation changes	Uncommon	Uncommon
Application site warmth		Uncommon
Application site scarring	Rare	Rare

*: Application site swelling on the face or scalp may gravitate to the eye area
**: Accidental eye exposure: Post-marketing reports of chemical conjunctivitis and corneal burn in connection with accidental eye exposure have been received (see sections 4.2 and 4.4 for prevention of eye exposure)
***: Including application site burning.

Description of selected adverse reactions
The incidence of local skin responses that occurred at an incidence >1% in both the 'face/scalp' and the 'trunk/extremities', respectively are: application site erythema (94% and 92%), application site exfoliation (85% and 90%), application site scab (80% and 74%), application site swelling (79% and 64%), application site vesicles (13% and 20%), application site pustules (43% and 23%) and application site erosion (31% and 25%).

Severe local skin responses occurred with an incidence of 29% on the face and scalp and with an incidence of 17% on the trunk and extremities. The incidence of severe local skin responses that occurred at an incidence >1% in both the 'face/scalp' and the 'trunk/extremities', respectively are: application site erythema (24% and 15%), application site exfoliation (9% and 8%), application site scab (6% and 4%), application site swelling (5% and 3%) and application site pustules (5% and 1%).

Long-term follow up
A total of 198 patients with complete clearance at day 57 (184 treated with Picato and 14 treated with vehicle) were followed for additionally 12 months. In another study, 329 patients who were initially treated with cryotherapy on the face/scalp were randomised after three weeks to either Picato 150 mcg/g (n=158) or vehicle (n=150) for 3 days in the same area. 149 patients in the Picato group and 140 in the vehicle group were followed for 12 months. In a later study 450 patients were initially treated with Picato 150 mcg/g, of these 134 patients were randomised to a second treatment course of Picato 150 mcg/g and the patients followed for up to 12 months after the first treatment.
These results did not change the safety profile of Picato (see section 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdosing of Picato could result in an increased incidence of local skin responses. Management of overdose should consist of treatment of clinical symptoms.

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 actinic keratosis 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 studies 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 150 mcg/g, 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 500 mcg/g, administered on the trunk and 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, actinic keratosis lesions within a contiguous 25 cm^2 treatment area on the face or scalp or on the trunk or 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 had 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 2).

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

	Face and scalp		**Trunk and extremities**	
	Picato 150 mcg/g (n=277)	**Vehicle (n=270)**	**Picato 500 mcg/g (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 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 logistic regression with treatment, study and anatomical location.

The level of efficacy varied between the individual anatomical locations. Within each location the complete and partial clearance rates were higher in the group treated with ingenol mebutate compared to the vehicle group (see table 3 and 4).

Table 3 Number and percent (95% CI) of subjects achieving complete and partial clearance at day 57 by anatomical location face and scalp				
	Complete Clearance		**Partial Clearance(≥ 75%)**	
	Picato 150 mcg/g (n=277)	**Vehicle (n=270)**	**Picato 150 mcg/g (n=277)**	**Vehicle (n=270)**
Face	104/220 47% (41-54%)	9/220 4% (2-8%)	157/220 71% (65-77%)	18/220 8% (5-13%)
Scalp	13/57 23% (13-36%)	1/50 2% (0-11%)	20/57 35% (23-49%)	2/50 4% (1-14%)

Table 4 Number and percent (95% CI) of subjects achieving complete and partial clearance at day 57 by anatomical location trunk and extremities				
	Complete clearance		**Partial clearance (≥ 75%)**	
	Picato 500 mcg/g (n=226)	**Vehicle (n=232)**	**Picato 500 mcg/g (n=226)**	**Vehicle (n=232)**
Arm	49/142 35% (27-43%)	7/149 5% (2-9%)	75/142 53% (44-61%)	11/149 7% (4-13%)
Back of Hand	10/54 19% (9-31%)	0/56 0% (0-6%)	16/54 30% (18-44%)	1/56 2% (0-10%)
Chest	11/14 79% (49-95%)	2/11 18% (2-52%)	12/14 86% (57-98%)	2/11 18% (2-52%)
Other[a]	7/16 44% (20-70%)	2/16 13% (2-38%)	8/16 50% (25-75%)	2/16 13% (2-38%)
[a]Other includes shoulder, back, leg.				

Safety of Picato 150 mcg/g treatment for 3 days or Picato 500 mcg/g treatment for 2 days was assessed up to day 57, the majority of the reported adverse reactions and local skin responses were mild to moderate in intensity and all 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 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 actinic keratosis lesions in the treatment field, and safety in patients who had received treatment with Picato. One study included patients treated with Picato 150 mcg/g on the face or scalp for 3 days and two studies included patients treated with Picato 500 mcg/g 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 table 5).

Table 5 Rate of recurrence of actinic keratosis lesions		
	Picato 150 mcg/g gel Face and scalp	**Picato 500 mcg/g gel Trunk and extremities**

	(n=108)	(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.

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 1,165 patients) and in vehicle treated patients (0.3%, 2 of 632 patients) in the actinic keratosis clinical studies conducted with ingenol mebutate gel.

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 more than one treatment course
In a double blind, vehicle-controlled study, up to two treatment courses of Picato 150 mcg/g were administered to 450 patients with 4-8 AKs in a 25 cm^2 treatment area on the face or scalp. Patients, in whom a first treatment course did not lead to complete clearance of all AKs in the treatment area after 8 weeks, were randomised to another treatment course with Picato or vehicle. Patients in whom the first treatment course led to complete clearance were seen at 26 and 44 weeks and randomised to a second treatment course if they had a recurrence in the field. In all patients, assessment of efficacy was 8 weeks after the randomisation. The first treatment course, given open label, resulted in a complete clearance rate of 62% (277/450). The results of the randomised and blinded second treatment course are presented in table 6.

Table 6 Complete clearance[a] of the field 8 weeks after randomisation and Month 12

	Field recalcitrant[c]		**Field recurrent[d]**	
	Picato 150 mcg/g gel (n= 92)	**Vehicle (n=49)**	**Picato 150 mcg/g gel (n=42)**	**Vehicle (n=20)**
8 weeks after randomisation	47% (43) (p=0.001[b])	18% (9)	60% (25) (p=0.013[b])	25% (5)
Month 12	18% (17) (p=0.016[b])	4% (2)	31% (13) (p=0.10[b])	15% (3)

[a] Complete clearance rate is defined as the proportion of patients with no (zero) clinically visible actinic keratosis lesions in the treatment area.
[b] Cochran-Mantel-Haenszel test of Picato® gel 150 mcg/g compared to vehicle adjusted for anatomical location (face/scalp) and country.
[c] Patients, in whom the first treatment course did not lead to complete clearance of all AKs in the treatment area.
[d] Patients in whom the first treatment course did lead to complete clearance and who had a recurrence in the treatment area at either week 26 or 44.

Actinic Keratosis of the Face and Scalp, sequential use after cryotherapy
In a two-arm study, 329 adult patients with AK on the face or scalp were randomised to treatment with Picato gel, 150 mcg/g or vehicle 3 weeks after cryotherapy of all visible lesions in the treatment area. The study enrolled patients with 4 to 8 clinically typical, visible, discrete non-hypertrophic and non-hyperkeratotic AK lesions within a 25 cm^2 contiguous treatment area.

Eleven weeks after baseline which is 8 weeks after Picato gel or vehicle, the complete clearance rate was 61% among patients randomised to Picato gel, and 49% among patients randomised to vehicle. At 12 months, the complete clearance rates in these groups were 31% and 19% respectively. The percent reduction of the AK count in the Picato group was 83% at 11 weeks and 57% at 12 months, where in the vehicle group it was 78% at 11 weeks and 42% at 12 months. The mean number of AKs in the Picato group was 5.7 at baseline, 0.8 at week 11, and 0.9 at month 12 as opposed to 5.8, 1.0 and 1.2 in the vehicle group at these time points.
Safety results from the study were comparable to the safety profile of Picato gel, 150 mcg/g as monotherapy

Experience with treatment of a larger area
In a double-blind, vehicle-controlled study to evaluate systemic exposure, Picato 500 mcg/g, from 4 tubes, was applied to a 100 cm^2 contiguous treatment area daily for 2 consecutive days. Results demonstrated no systemic absorption.
Picato 500 mcg/g was well tolerated when applied to a contiguous treatment area of 100 cm^2 on the trunk and extremities.

In a double-blind, vehicle-controlled study in patients with AK on trunk and extremities, an investigational product with ingenol mebutate gel 600 mcg/g was applied once daily for 2, 3, or 4 days to a skin area of 250 cm^2. The trial included a large group of severely sun-damaged patients. 12/163 subjects treated with an investigational product of ingenol mebutate reported 16 skin tumour events inside the treatment area (1 SCC, 1 Bowen's disease and 14 keratoacanthoma following centralised pathology review) compared to 0/61 in the vehicle group.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Picato in all subsets of the paediatric population in actinic keratosis (see section 4.2 for information on paediatric use).

Elderly population
Of the 1,165 patients treated with Picato in the actinic keratosis 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 cutaneous administration.

Absorption
No systemic absorption was detected at or above the lower limit of detection (0.1 ng/mL) when Picato 500 mcg/g from 4 tubes was applied to an area of 100 cm^2 on the dorsal forearm in actinic keratosis 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 cutaneous administration of ingenol mebutate gel is well tolerated with any skin irritation being reversible and a negligible risk of systemic toxicity under the recommended conditions of use.

In rats, ingenol mebutate was not associated with fetal developmental effects at IV doses up to 5 mcg/kg/day (30 mcg/m^2/day). In rabbits there were no major abnormalities. Minor fetal abnormalities or variants were observed in the fetuses of treated dams at doses of 1 mcg/kg/day (12 mcg/m^2/day).

6. PHARMACEUTICAL PARTICULARS

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

6.4 Special precautions for storage

Store in a refrigerator (2ºC-8ºC).
Tubes should be discarded after first opening.

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 500 mcg/g gel is available in a carton containing 2 tubes with 0.47 g of gel each.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

LEO Laboratories Ltd.
285 Cashel Road
Crumlin, Dublin 12
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/796/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 November 2012
Date of latest renewal: 13 July 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
LEO Laboratories Ltd.
285 Cashel Road
Crumlin, Dublin 12
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-Authorisation safety study: In order to further investigate the incidence of treatment area skin malignancy, particularly squamous cell carcinoma, the MAH should conduct and submit the results of a randomised, double-blind, trial in patients treated with ingenol mebutate compared with vehicle control, over at least 18 months of follow-up. The study should be based on an agreed protocol. The final study report shall be submitted:	31 December 2024
Non-interventional Post-Authorisation safety study: In order to investigate the rate of skin malignancies (squamous cell carcinoma,	

Bowen's disease, basal cell carcinoma, keratoacanthoma, malignant melanoma) in patients with actinic keratosis treated with ingenol mebutate, the MAH should conduct and submit the results of a cohort study comparing patients treated with ingenol mebutate with patients exposed to other actinic keratosis treatments. The final study report shall be submitted:	 31 December 2020

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 150 mcg/g GEL

1. NAME OF THE MEDICINAL PRODUCT

Picato 150 micrograms/g gel
ingenol mebutate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gram of gel contains 150 micrograms of ingenol mebutate. Each tube contains 70 micrograms of ingenol mebutate in 0.47 g of gel.

3. LIST OF EXCIPIENTS

Isopropyl alcohol
Hydroxyethylcellulose
Citric acid monohydrate
Sodium citrate
Benzyl alcohol
Purified water

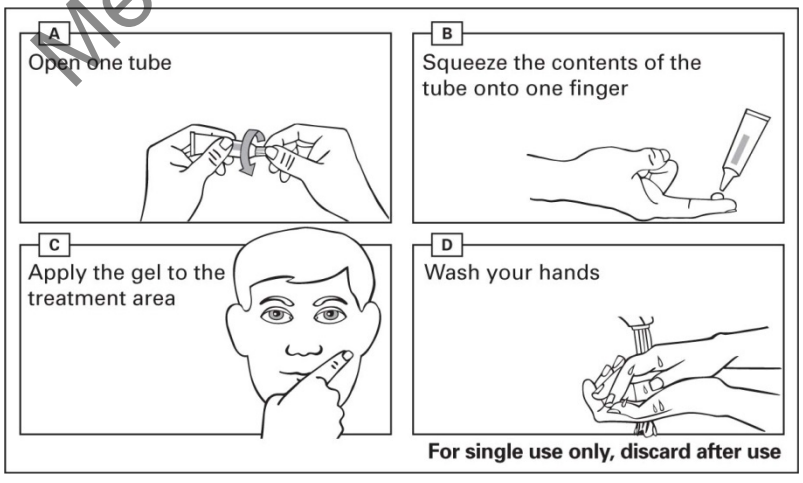
4. PHARMACEUTICAL FORM AND CONTENTS

gel
3 tubes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Read the package leaflet before use.
Cutaneous use

To be printed on the inside of the carton lid:



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

LEO Laboratories Ltd.
285 Cashel Road
Crumlin, Dublin 12
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/796/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Picato 150 mcg/g

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 500 mcg/g GEL

1. NAME OF THE MEDICINAL PRODUCT

Picato 500 micrograms/g gel
ingenol mebutate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gram of gel contains 500 micrograms of ingenol mebutate. Each tube contains 235 micrograms of ingenol mebutate in 0.47 g of gel.

3. LIST OF EXCIPIENTS

Isopropyl alcohol
Hydroxyethylcellulose
Citric acid monohydrate
Sodium citrate
Benzyl alcohol
Purified water

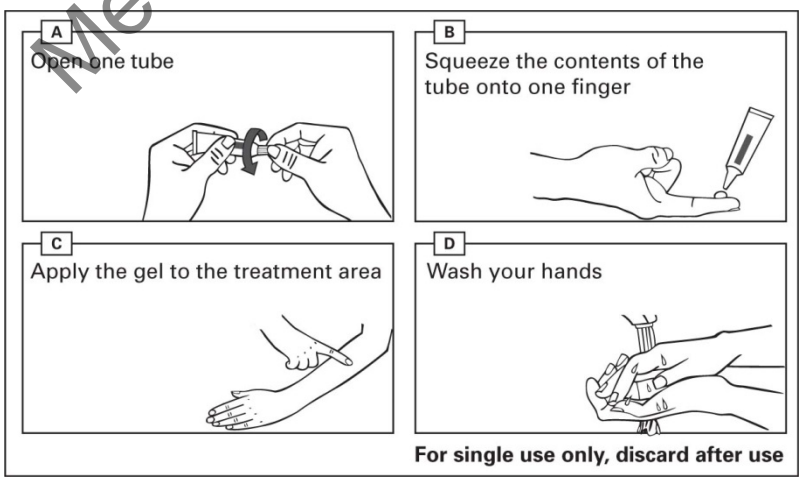
4. PHARMACEUTICAL FORM AND CONTENTS

gel
2 tubes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Read the package leaflet before use.
Cutaneous use

To be printed on the inside of the carton lid:



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

LEO Laboratories Ltd.
285 Cashel Road
Crumlin, Dublin 12
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/796/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Picato 500 mcg/g

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

TUBE 150 mcg/g GEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Picato 150 mcg/g gel
ingenol mebutate
Cutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.47 g

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

TUBE 500 mcg/g GEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Picato 500 mcg/g gel
ingenol mebutate
Cutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.47 g

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Picato 150 micrograms/gram gel
ingenol mebutate

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Picato is and what it is used for

Picato contains the active substance ingenol mebutate.
This medicine is used for topical (on the skin) treatment of actinic keratosis, also called solar keratosis, in adults. Actinic keratoses are rough areas of skin found in people who have been exposed to too much sunshine over the course of their lifetime. Picato 150 micrograms/gram gel is used for actinic keratosis on the face and scalp.

2. What you need to know before you use Picato

Do not use Picato
- If you are allergic to ingenol mebutate or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before using Picato.
- Do not get Picato in your eyes. Wash your hands thoroughly after you have applied the gel. Wash your hands again if you happen to touch the area where you applied the gel. Take care not to transfer gel from the treatment area into your eyes. In the event of accidental contact, remove the gel by rinsing with plenty of water and seek medical assistance as soon as possible.
- Do not swallow this medicine. Drink plenty of water if you accidentally swallow this medicine and seek medical assistance.
- Make sure that your skin has healed from any other treatments or surgery before using this medicine. Do not apply Picato on open-wounds or damaged skin.
- Do not apply this medicine internally, to the area near the eyes, to the inside of the nostrils, the inside of the ear or on the lips.
- Avoid sunlight as much as possible (including sunlamps and tanning beds).

- Be vigilant for any new scaly red patches, open sores, elevated or warty growths within the treatment area. Should any occur, talk to your doctor immediately.
- This medicine is intended to treat one area of 25 cm^2 for three days.
- Do not apply more gel than your doctor has advised.
- You should expect to get local skin reactions, such as reddening and swelling, after treatment with this medicine (see section 4). Contact your doctor if these local skin reactions get severe.

Children and adolescents
Actinic keratosis does not occur in children, and this medicine must not be used in children and adolescents under 18 years of age.

Other medicines and Picato
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

If you have previously used Picato or other similar medicines tell your doctor before starting the treatment.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. You should avoid the use of Picato if you are pregnant.
If you are breast-feeding, avoid physical contact between the baby and the treated area for 6 hours after application of this medicine.

Driving and using machines
This medicine does not have any effect on your ability to drive or to use machines.

3. How to use Picato

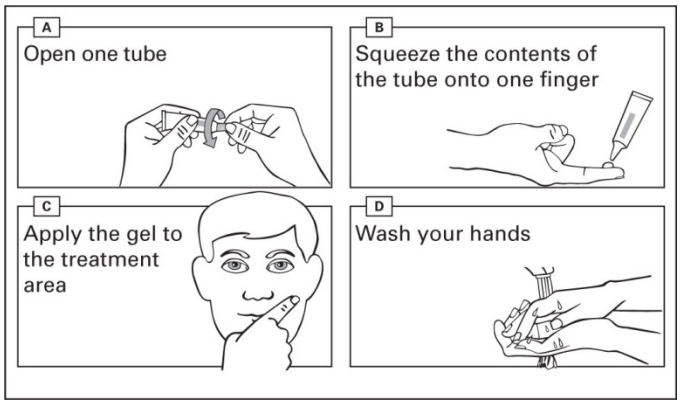
Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

If you have been prescribed two different strengths for treatment of two different areas you should make sure that you use the prescribed strength on the correct area. Do not apply the 500 mcg/g gel on the face or scalp as this could lead to intense local skin responses.

- Treatment of actinic keratosis on the face and scalp is one tube of Picato 150 micrograms/g gel (containing 70 micrograms of ingenol mebutate) once a day for 3 days in a row.

Instructions for use:
- Open a new tube each time you use this medicine. Remove the cap from the tube just before use.
- Squeeze the gel from one tube onto a fingertip.
- Apply the content of one tube to one area of 25 cm^2 (e.g. 5 cm x 5 cm).
- Gently rub the gel onto the treatment area.
- Allow the area to dry for 15 minutes. Avoid touching the treatment area for 6 hours after applying your medicine.
- Wash your hands with soap and water immediately after applying the gel, and also in between administrations if prescribed two different strengths for two different areas.
- Do not apply this medicine immediately after taking a shower or less than 2 hours before bedtime.
- Do not wash the areas where you applied the gel for at least 6 hours after you apply it.
- Do not touch the treatment area yourself or allow anyone or any pets to touch the treatment area for a period of 6 hours after applying the gel.
- Do not cover the treated area with air- or water-tight bandages after you have applied this medicine.

- The full effect of Picato can be evaluated approximately 8 weeks after treatment.



If you use Picato for treatment of the neck
If more than half of the treatment area is located in the *upper* part of the neck:
- Use Picato 150 mcg/g gel (face and scalp)

If more than half of the treatment area is located in the *lower* part of the neck:
- Use Picato 500 mcg/g gel (trunk and extremities)

If you use more Picato than you should
Wash the area with soap and water. Please contact your doctor or pharmacist if you experience severe skin reactions.

If you forget to use Picato
Please contact your doctor or pharmacist if you forget to use Picato.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Seek medical attention right away if you experience an allergic reaction that may include swelling of the mouth, tongue or throat when using this medicine. This side effect is uncommon.

After using this medicine the skin where you apply it is likely to get red, peel and have scabs. These side effects most often occur within one day after applying this medicine. The side effects may get worse for up to 1 week after you have stopped using this medicine. They will usually get better within 2 weeks from when you started the treatment.

Infection of the skin in the treatment area can occur (has been reported as a common side effect, which may affect up to 1 in 10 people, when treating the face and scalp).

Swelling of the application site is very common (has been reported in more than 1 in 10 people). Application site swelling on the face or scalp may gravitate to the eye area.

Should the symptoms described above intensify beyond the first week after you have stopped using this medicine, or if there is discharge of pus, you might have an infection and should contact your doctor or pharmacist.

<u>The most frequently occurring side effects when treating the face and scalp:</u>

Very common side effects on the treatment area, may affect more than 1 in 10 people:
On the treatment area:

- Some of the outer layer of your skin may wear away (erosion)
- Blisters (vesicles, pustules)
- Peeling (exfoliation)
- Scabs
- Redness due to widening of the small blood vessels (erythema)
- Pain (including application site burning)

The most frequently occurring side effects when treating the trunk and extremities:

Very common side effects on the treatment area, may affect more than 1 in 10 people:
On the treatment area:
- Some of the outer layer of your skin may wear away (erosion)
- Blisters (vesicles, pustules)
- Peeling (exfoliation)
- Scabs
- Redness due to widening of the small blood vessels (erythema)

Other possible side effects when treating the face and scalp:

Common side effects, may affect up to 1 in 10 people:
On the treatment area:
- Itching (pruritus)
- Irritation

Other side effects:
- Swelling of the area around the eye (periorbital oedema)
- Swelling (oedema) of your eye lid
- Headache

Uncommon side effects, may affect up to 1 in 100 people:
On the treatment area:
- Tingling or numbness (paraesthesia)
- Open sores (ulcer)
- Discharge (secretion) of fluid
- Change in skin colour (pigmentation change)

Other side effects:
- Eye pain
- Injury or irritation to the surface of the eye (cornea, conjunctiva) following accidental exposure

Rare side effects, may affect up to 1 in 1000 people:
On the treatment area:
- Scarring

Other possible side effects when treating the trunk and extremities:

Common side effects, may affect up to 1 in 10 people:
On the treatment area:
- Itching (pruritus)
- Irritation
- Pain (including application site burning)

Uncommon side effects, may affect up to 1 in 100 people:
On the treatment area:
- Tingling or numbness (paraesthesia)
- Open sores (ulcer)
- Change in skin colour (pigmentation change)

- Warmth

Other side effects:
- Injury or irritation to the surface of the eye (cornea, conjunctiva) following accidental exposure

Rare side effects, may affect up to 1 in 1000 people:
On the treatment area:
- Scarring

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Picato

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and tube after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C-8°C).

For single use only. Do not re-use the tubes once opened.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Picato contains
- The active substance is ingenol mebutate. Each gram of gel contains 150 micrograms of ingenol mebutate. Each tube contains 70 micrograms of ingenol mebutate in 0.47 g of gel.

- The other ingredients are isopropyl alcohol, hydroxyethylcellulose, citric acid monohydrate, sodium citrate, benzyl alcohol, purified water.

What Picato looks like and contents of the pack
Picato 150 micrograms/g gel is clear and colourless and each carton contains 3 tubes with 0.47 g of gel each.

Marketing Authorisation Holder
LEO Laboratories Ltd.
285 Cashel Road
Crumlin, Dublin 12
Ireland

Manufacturer
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This leaflet was last revised in.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

Package leaflet: Information for the patient

Picato 500 micrograms/gram gel
ingenol mebutate

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Picato is and what it is used for

Picato contains the active substance ingenol mebutate.
This medicine is used for topical (on the skin) treatment of actinic keratosis, also called solar keratosis, in adults. Actinic keratoses are rough areas of skin found in people who have been exposed to too much sunshine over the course of their lifetime. Picato 500 micrograms/gram gel is used for actinic keratosis on the body, arms, hands and legs.

2. What you need to know before you use Picato

Do not use Picato
- If you are allergic to ingenol mebutate or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before using Picato.
- Do not get Picato in your eyes. Wash your hands thoroughly after you have applied the gel. Wash your hands again if you happen to touch the area where you applied the gel. Take care not to transfer gel from the treatment area into your eyes. In the event of accidental contact, remove the gel by rinsing with plenty of water and seek medical assistance as soon as possible.
- Do not swallow this medicine. Drink plenty of water if you accidentally swallow this medicine and seek medical assistance.
- Make sure that your skin has healed from any other treatments or surgery before using this medicine. Do not apply Picato on open-wounds or damaged skin.
- Do not apply this medicine internally, to the area near the eyes, to the inside of the nostrils, the inside of the ear or on the lips.
- Avoid sunlight as much as possible (including sunlamps and tanning beds).
- Be vigilant for any new scaly red patches, open sores, elevated or warty growths within the treatment area. Should any occur, talk to your doctor immediately.

- This medicine is intended to treat one area of 25 cm^2 for two days.
- Do not apply more gel than your doctor has advised.
- You should expect to get local skin reactions, such as reddening and swelling, after treatment with this medicine (see section 4). Contact your doctor if these local skin reactions get severe.

Children and adolescents
Actinic keratosis does not occur in children, and this medicine must not be used in children and adolescents under 18 years of age.

Other medicines and Picato
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

If you have previously used Picato or other similar medicines tell your doctor before starting the treatment.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. You should avoid the use of Picato if you are pregnant.
If you are breast-feeding, avoid physical contact between the baby and the treated area for 6 hours after application of this medicine.

Driving and using machines
This medicine does not have any effect on your ability to drive or to use machines.

3. How to use Picato

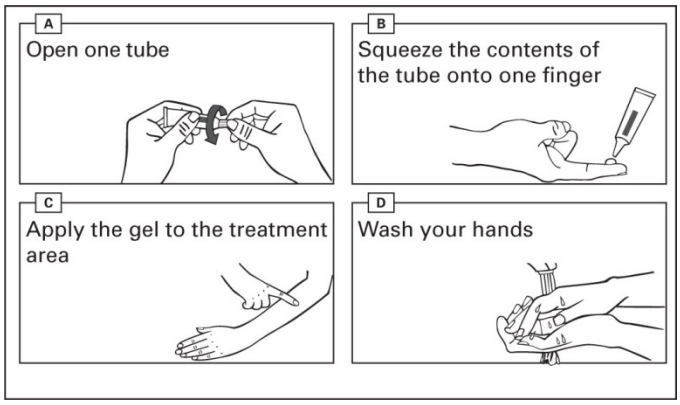
Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

If you have been prescribed two different strengths for treatment of two different areas you should make sure that you use the prescribed strength on the correct area. Do not apply the 500 mcg/g gel on the face or scalp as this could lead to intense local skin responses.

- Treatment of actinic keratosis on the body, arms, hands and legs is one tube of Picato 500 micrograms/g gel (containing 235 micrograms of ingenol mebutate) once a day for 2 days in a row.

Instructions for use:
- Open a new tube each time you use this medicine. Remove the cap from the tube just before use.
- Squeeze the gel from one tube onto a fingertip.
- Apply the content of one tube to one area of 25 cm^2 (e.g. 5 cm x 5 cm).
- Gently rub the gel onto the treatment area.
- Allow the area to dry for 15 minutes. Avoid touching the treatment area for 6 hours after applying your medicine.
- Wash your hands with soap and water immediately after applying the gel, and also in between administrations if prescribed two different strengths for two different areas. If you are treating your hands you should only wash the fingertip which you used for applying the gel.
- Do not apply this medicine immediately after taking a shower or less than 2 hours before bedtime.
- Do not wash the areas where you applied the gel for at least 6 hours after you apply it.
- Do not touch the treatment area yourself or allow anyone or any pets to touch the treatment area for a period of 6 hours after applying the gel.
- Do not cover the treated area with air- or water-tight bandages after you have applied this medicine.

- The full effect of Picato can be evaluated approximately 8 weeks after treatment.



If you use Picato for treatment of the neck
If more than half of the treatment area is located in the *upper* part of the neck:
- Use Picato 150 mcg/g gel (face and scalp)

If more than half of the treatment area is located in the *lower* part of the neck:
- Use Picato 500 mcg/g gel (trunk and extremities)

If you use more Picato than you should
Wash the area with soap and water. Please contact your doctor or pharmacist if you experience severe skin reactions.

If you forget to use Picato
Please contact your doctor or pharmacist if you forget to use Picato.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Seek medical attention right away if you experience an allergic reaction that may include swelling of the mouth, tongue or throat when using this medicine. This side effect is uncommon.

After using this medicine the skin where you apply it is likely to get red, peel and have scabs. These side effects most often occur within one day after applying this medicine. The side effects may get worse for up to 1 week after you have stopped using this medicine. They will usually get better within 4 weeks from when you started the treatment.

Infection of the skin in the treatment area can occur (has been reported as a common side effect, which may affect up to 1 in 10 people, when treating the face and scalp).

Swelling of the application site is very common (has been reported in more than 1 in 10 people). Application site swelling on the face or scalp may gravitate to the eye area.

Should the symptoms described above intensify beyond the first week after you have stopped using this medicine, or if there is discharge of pus, you might have an infection and should contact your doctor or pharmacist.

<u>The most frequently occurring side effects when treating the face and scalp:</u>

Very common side effects on the treatment area, may affect more than 1 in 10 people:
On the treatment area:

- Some of the outer layer of your skin may wear away (erosion)
- Blisters (vesicles, pustules)
- Peeling (exfoliation)
- Scabs
- Redness due to widening of the small blood vessels (erythema)
- Pain (including application site burning)

The most frequently occurring side effects when treating the trunk and extremities:

Very common side effects on the treatment area, may affect more than 1 in 10 people:
On the treatment area:
- Some of the outer layer of your skin may wear away (erosion)
- Blisters (vesicles, pustules)
- Peeling (exfoliation)
- Scabs
- Redness due to widening of the small blood vessels (erythema)

Other possible side effects when treating the face and scalp:

Common side effects, may affect up to 1 in 10 people:
On the treatment area:
- Itching (pruritus)
- Irritation

Other side effects:
- Swelling of the area around the eye (periorbital oedema)
- Swelling (oedema) of your eye lid
- Headache

Uncommon side effects, may affect up to 1 in 100 people:
On the treatment area:
- Tingling or numbness (paraesthesia)
- Open sores (ulcer)
- Discharge (secretion) of fluid
- Change in skin colour (pigmentation change)

Other side effects:
- Eye pain
- Injury or irritation to the surface of the eye (cornea, conjunctiva) following accidental exposure

Rare side effects, may affect up to 1 in 1000 people:
On the treatment area:
- Scarring

Other possible side effects when treating the trunk and extremities:

Common side effects, may affect up to 1 in 10 people:
On the treatment area:
- Itching (pruritus)
- Irritation
- Pain (including application site burning)

Uncommon side effects, may affect up to 1 in 100 people:
On the treatment area:
- Tingling or numbness (paraesthesia)
- Open sores (ulcer)
- Change in skin colour (pigmentation change)

- Warmth

Other side effects:
- Injury or irritation to the surface of the eye (cornea, conjunctiva) following accidental exposure.

Rare side effects, may affect up to 1 in 1000 people:
On the treatment area:
- Scarring

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Picato

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and tube after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C-8°C).

For single use only. Do not re-use the tubes once opened.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Picato contains
- The active substance is ingenol mebutate. Each gram of gel contains 500 micrograms of ingenol mebutate. Each tube contains 235 micrograms of ingenol mebutate in 0.47 g of gel.

- The other ingredients are isopropyl alcohol, hydroxyethylcellulose, citric acid monohydrate, sodium citrate, benzyl alcohol, purified water.

What Picato looks like and contents of the pack
Picato 500 micrograms/g gel is clear and colourless and each carton contains 2 tubes with 0.47 g of gel each.

Marketing Authorisation Holder
LEO Laboratories Ltd.
285 Cashel Road
Crumlin, Dublin 12
Ireland

Manufacturer
LEO Laboratories Ltd.
285 Cashel Road, Crumlin, Dublin 12
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in.

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu/

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for ingenol mebutate, the scientific conclusions of CHMP are as follows:

Taking into account the treatment purpose for actinic keratosis, which is prevention of skin malignancy, and considering the number of skin tumour cases reported to ingenol mebutate in clinical trials and post-marketing, the PRAC has serious concerns about the impact of the risk of skin tumours on the benefit risk balance of Picato. The PRAC is of the opinion that a thorough review is needed of the impact of all available data related to skin malignancies, including the results of study LP0041-63, on the benefit risk balance of Picato. Additionally, the product information should be varied concerning ingenol mebutate use and the risk of skin malignancy. The PRAC also agreed that a DHPC is needed in order to mitigate this risk.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for ingenol mebutate the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing ingenol mebutate is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.