# Common Drug Review
## *Clinical Review Report*

**February 2014**

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|---|---|
| **Drug** | ingenol mebutate (Picato) |
| **Indication** | Topical treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults. |
| **Listing request** | For patients who have failed or are intolerant to 5-fluorouracil (5-FU). |
| **Manufacturer** | Leo Pharma Inc. |

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# ABBREVIATIONS

| | |
|---|---|
| **5-FU** | 5-fluorouracil |
| **AE** | adverse event |
| **AK** | actinic keratosis |
| **ANOVA** | analysis of variance |
| **BCC** | basal cell carcinoma |
| **CMH** | Cochran-Mantel-Haenszel |
| **CDR** | Common Drug Review |
| **CI** | confidence interval |
| **DB** | double blind |
| **EMEA** | European Medicines Agency |
| **FDA** | Food and Drug Administration |
| **HRQoL** | health-related quality of life |
| **IQR** | interquartile range |
| **ITT** | intention-to-treat population |
| **LOCF** | last observation carried forward |
| **LSR** | local skin response |
| **MeSH** | medical subject headings |
| **MCID** | minimum clinically important difference |
| **NMSC** | non-melanoma skin cancer |
| **NNT** | number needed to treat |
| **PP** | per-protocol |
| **RCT** | randomized controlled trial |
| **RD** | risk difference |
| **RNA** | ribonucleic acid |
| **RR** | risk ratio |
| **SAE** | serious adverse event |
| **SCC** | squamous cell carcinoma |
| **SD** | standard deviation |
| **SF-36** | short form health survey |
| **TRAE** | treatment-related adverse event |
| **TSQM** | Treatment Satisfaction Questionnaire for Medication |
| **WDAE** | withdrawal due to adverse event |
| **UK** | United Kingdom |
| **UV** | ultraviolet |

# EXECUTIVE SUMMARY

## Introduction

Actinic keratosis (AK) is a precancerous skin condition that develops as a result of chronic ultraviolet (UV) exposure and was estimated to affect 1.5 million Canadians in 2011. AK is characterized by thickened, scaly lesions that are skin to reddish-brown in colour. The rate of progression from AK to squamous cell carcinoma (SCC) is estimated to be 0.025% to 20% per year for an individual lesion. The choice of treatment is guided by the clinical presentation of the condition, with lesion-directed therapies being appropriate for few and isolated lesions, and field-directed therapies being used for areas of skin with multiple lesions. Field-directed therapies include topical 5-fluorouracil (5-FU), imiquimod, and now ingenol mebutate. Ingenol mebutate is a diterpene ester purified from the *Euphorbia peplus* plant that induces cell death through cytotoxic and neutrophil-dependent inflammatory mechanisms. In Canada, ingenol mebutate is available as a 0.05% gel (once daily for two days, for trunk and extremities) or 0.015% gel (once daily for three days, for face and scalp), supplied in unit-dose tubes for topical application.

| Indication under review |
| --- |
| Topical treatment of non-hyperkeratotic, non-hypertrophic AK in adults. |
| **Listing criteria requested by sponsor** |
| For patients who have failed or are intolerant to 5-FU. |

The objective of this systematic review is to examine the beneficial and harmful effects of ingenol mebutate once daily for the topical treatment of non-hyperkeratotic, non-hypertrophic AK for the face and scalp (0.015% gel, three-day treatment) and for the trunk and extremities (0.05% gel, two-day treatment) in adult patients.

## Results and Interpretation

### Included Studies

Four 57-day, randomized, double-blind, vehicle-controlled trials met the inclusion criteria for this systematic review. PEP005-014 (N = 255) and PEP005-028 (N = 203) evaluated the efficacy and safety of ingenol mebutate gel, 0.05% for the treatment of AK on the trunk and extremities (non-head studies). PEP005-016 (N = 269) and PEP005-025 (N = 278) evaluated the efficacy and safety of ingenol mebutate gel, 0.015% for the treatment of AK on the face and scalp (head studies). All enrolled patients had four to eight AK lesions within a 25 $cm^2$ contiguous treatment area. Approximately 20% of patients in all trials had previously received treatment with topical 5-FU, however the prior treatment was not necessarily targeted toward the treatment area observed in the reviewed trials. The primary outcome in all trials was the proportion of patients achieving complete clearance of all clinically visible AK lesions at day 57. Other outcomes included the proportion of patients achieving partial clearance (defined as a reduction of ≥ 75% in the number of AK lesions in target treatment area), the per cent change from baseline in total number of AK lesions, the change in Skindex-16 Dermatological Survey score from baseline, and the Treatment Satisfaction Questionnaire for Medication (TSQM) score at day 57. The included trials are limited by their short duration, lack of an active comparator, and uncertain applicability to the manufacturer's requested listing criteria, since the majority of patients included in the trials had not failed or exhibited intolerance to 5-FU.

**Efficacy**

The intention-to-treat population was used in all efficacy analyses. In the non-head and head trials, the proportion of patients achieving complete clearance was statistically greater in the ingenol mebutate groups compared with vehicle groups; absolute risk differences versus vehicle ranged from 23.1% to 42.0%, and numbers needed to treat from three to five. Similarly, the proportion of patients achieving partial clearance of lesions was statistically greater in the ingenol mebutate groups compared with the vehicle groups; absolute risk differences versus vehicle ranged from 37.5% to 59.5%, and NNTs from two to three. In addition, patients treated with ingenol mebutate gel had a greater median percentage reduction in the number of AK lesions compared with baseline than patients treated with vehicle gel.

In all trials, the change from baseline in Skindex-16 Dermatological Survey Scores indicated that patients were significantly more bothered in the symptoms domain at day 8 in the ingenol mebutate groups than the vehicle groups ($P < 0.001$). Similarly, the TSQM scores at day 57 in the side effects domain were statistically significantly lower (less satisfied) in the ingenol mebutate groups than in the vehicle groups. The TSQM global satisfaction scores at day 57 were statistically significantly higher (more satisfied) in the ingenol mebutate groups than the vehicle groups.

The manufacturer conducted post-hoc subgroup analyses of pooled head, and pooled non-head trials, based on prior treatment with 5-FU. In the pooled head studies, ingenol mebutate-treated patients who had not previously received 5-FU were more likely to achieve complete clearance of AK lesions at day 57 compared with ingenol mebutate-treated patients who had previously received 5-FU; 45.9% versus 27.3% ($P = 0.014$). However, as previous treatment with 5-FU was not necessarily in the target treatment area that was subsequently treated with ingenol mebutate, the clinical relevance of this analysis is unclear.

**Harms**

Across all trials, the incidence of patients reporting adverse events and treatment-related adverse events was greater in the ingenol mebutate group compared with the vehicle group. The most commonly reported adverse events were related to administration site conditions, including pain, pruritus, and irritation. Composite local skin response (LSR) scores, post-baseline, were notably higher in the ingenol mebutate groups compared with vehicle gel in both non-head and head studies. LSR scores peaked at day 3 or day 8 for the non-head studies, and at day 4 for the head studies, with scores declining to near-baseline values by day 29. The incidence of serious adverse events and withdrawals due to adverse events was low and balanced between treatment groups. There were no deaths reported in any included study. There was a minimal change in pigmentation and scarring after treatment with ingenol mebutate or vehicle gel.

## Pharmacoeconomic Summary

Ingenol mebutate gel (Picato) is a topical cream that the manufacturer is requesting for use as a second-line treatment in patients with AK who have failed or are intolerant to 5-FU. Ingenol mebutate gel is available in two strengths — a 0.015% dose for lesions on the face and scalp and a 0.05% dose for lesions on the trunk and extremities. Both strengths cost $383.00 per treatment course. The manufacturer submitted a cost-minimization analysis against 5-FU in the trunk and extremity indication, and against 5-FU and imiquimod 5% in the face and scalp indication. No appropriate evidence of comparative effectiveness was presented.

The cost per course of treatment with ingenol mebutate ($383) is similar to that of imiquimod 5% depending on how it is dosed ($353 to $529),[1] but considerably higher than that of 5-FU ($34). Whether ingenol mebutate will generate savings or incur additional costs if listed by public plans depends on how ingenol mebutate will be utilized: if ingenol mebutate is used only by AK patients who have failed 5-FU treatment, listing ingenol mebutate may generate modest savings when compared with imiquimod 5%. However, if ingenol mebutate is used as a first-line therapy for AK (as per the Health Canada indication), listing ingenol mebutate would result in substantially higher costs incurred by public plans.

## Conclusions

Based on two each double-blind randomized controlled trials of adults with AK lesions on non-head and head locations, compared with no treatment (vehicle), treatment with ingenol mebutate resulted in a statistically greater proportion of patients achieving complete or partial clearance of AK lesions, but with an increase in LSRs. However, there are no trials comparing ingenol mebutate with other field-directed treatments (e.g., 5-FU or imiquimod). In addition, the trials comparing ingenol mebutate with no treatment (vehicle) are limited by their short duration and uncertain applicability to the manufacturer's requested listing criteria.

[1]These costs are based on a range of 12 weeks to 16 weeks treatment with imiquimod 5%. The low range of 12 weeks was provided by clinical expert advice where patients receive one 24-dose pack of imiquimod 5%, while the upper range is based on patients receiving a pack of 24 doses and a pack of 12 doses (total 36 doses) to cover 16 weeks of treatment; based on the pack size and treatment regimen specified in the imiquimod 5% Product Monograph.

**TABLE 1: SUMMARY OF RESULTS OF NON-HEAD STUDIES**

| Outcome | PEP005-014 | | PEP005-028 | |
|---|---|---|---|---|
| | Ingenol Mebutate (N = 126) | Vehicle (N = 129) | Ingenol Mebutate (N = 100) | Vehicle (N = 103) |
| **Complete Clearance of AK Lesions** | | | | |
| **n (%)** | 35 (27.8) | 6 (4.7) | 42 (42.0) | 5 (4.9) |
| **Risk Difference (95% CI)** | 23.1 (14.5 to 31.8) | | 37.2 (26.6 to 47.7) | |
| **Partial Clearance of AK Lesions** | | | | |
| **n (%)** | 56 (44.4) | 9 (7.0) | 55 (55.0) | 7 (6.8) |
| **Risk Difference (95% CI)** | 37.5 (27.7 to 47.2) | | 48.2 (37.3 to 59.1) | |
| **Per cent Reduction from Baseline in AK Lesion Count** | | | | |
| **N** | 120 | 128 | 100 | 101 |
| **Median (Range)** | 69.05 (–25.0 to 100) | 0 (–33.3 to 100) | 75.0 (0 to 100) | 0 (–33.3 to 100) |
| **Skindex-16 Dermatological Survey Mean Change from Baseline** | | | | |
| **Emotions** | | | | |
| **Day 8** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Day 29** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Day 57** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Functioning** | | | | |
| **Day 8** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Day 29** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Day 57** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Symptoms** | | | | |
| **Day 8** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Day 29** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Day 57** | [redacted] | [redacted] | [redacted] | [redacted] |
| **AEs** | | | | |
| **Total, N (%)** | 40 (32.0) | 37 (28.7) | 35 (35.0) | 26 (25.2) |
| **SAEs** | | | | |
| **Total, N (%)** | 1 (0.8) | 3 (2.3) | 2 (2.0) | 2 (1.9) |
| **WDAEs** | | | | |
| **Total, N (%)** | 2 (1.6) | 1 (0.8) | 0 | 1 (1.0) |
| **LSR Score, Mean (SD)** | | | | |
| **Baseline** | 1.0 (1.14) | 1.0 (1.13) | 1.00 (1.25) | 1.30 (1.51) |
| **Day 3** | 4.9 (2.96) | 1.1 (1.31) | 6.34 (3.25) | 1.33 (1.46) |
| **Day 8** | 5.4 (3.63) | 1.1 (1.21) | 6.11 (3.54) | 1.39 (1.49) |
| **Day 15** | 3.4 (2.20) | 1.1 (1.25) | 4.06 (2.21) | 1.17 (1.13) |
| **Day 29** | 1.6 (1.61) | 0.9 (1.04) | 1.51 (1.29) | 1.20 (1.30) |
| **Day 57** | 0.8 (1.50) | 0.7 (0.93) | 0.72 (0.84) | 1.02 (1.06) |

AE = adverse event; AK = actinic keratosis; CI = confidence interval; LSR = local skin response; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.

**TABLE 2: SUMMARY OF RESULTS OF HEAD STUDIES**

| Outcome | PEP005-016 | | PEP005-025 | |
|---|---|---|---|---|
| | Ingenol Mebutate (N = 135) | Vehicle (N = 134) | Ingenol Mebutate (N = 142) | Vehicle (N = 136) |
| **Complete Clearance of AK Lesions** | | | | |
| **n (%)** | 50 (37.0) | 3 (2.2) | 67 (47.2) | 7 (5.1) |
| **Risk Difference (95% CI)** | 34.8 (26.3 to 43.3) | | 42.0 (33.0 to 51.1) | |
| **Partial Clearance of AK Lesions** | | | | |
| **n (%)** | 81 (60.0) | 9 (6.7) | 96 (67.6) | 11 (8.1) |
| **Risk Difference (95% CI)** | 53.3 (44.0 to 62.6) | | 59.5 (50.6 to 68.5) | |
| **Per cent Reduction from Baseline in AK Lesion Count** | | | | |
| **n** | 131 | 133 | 142 | 136 |
| **Median (Range)** | 83.3 (–50.0 to 100.0) | 0 (–100.0 to 100.0) | 86.6 (–25.0, 100.0) | 0 (–100.0 to 100.0) |
| **Skindex-16 Dermatological Survey Mean Change from Baseline** | | | | |
| **Emotions** | | | | |
| **Day 8** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Day 29** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Day 57** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Functioning** | | | | |
| **Day 8** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Day 29** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Day 57** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Symptoms** | | | | |
| **Day 8** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Day 29** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Day 57** | [redacted] | [redacted] | [redacted] | [redacted] |
| **AEs** | | | | |
| **Total, N (%)** | 62 (47.0) | 31 (23.0) | 40 (28.2) | 29 (21.3) |
| **SAEs** | | | | |
| **Total, N (%)** | 2 (1.5) | 2 (1.5) | 1 (0.7) | 0 |
| **WDAEs** | | | | |
| **Total, N (%)** | 1 (0.8) | 1 (0.7) | 2 (1.4) | 0 |
| **LSR Score, Mean (SD)** | | | | |
| **Baseline** | 1.72 (1.74) | 1.21 (1.19) | 1.14 (1.17) | 1.08 (1.14) |
| **Day 4** | 9.47 (4.13) | 1.35 (1.36) | 8.08 (4.13) | 1.17 (1.26) |
| **Day 8** | 6.21 (3.60) | 1.42 (1.33) | 5.42 (3.64) | 1.12 (1.28) |
| **Day 15** | 1.93 (1.36) | 1.22 (1.27) | 1.94 (1.92) | 1.10 (1.06) |
| **Day 29** | 1.08 (1.06) | 1.17 (1.30) | 1.09 (1.31) | 1.00 (1.00) |
| **Day 57** | 0.80 (0.97) | 1.23 (1.48) | 0.55 (0.90) | 0.84 (0.95) |

AE = adverse event; AK = actinic keratosis; CI = confidence interval; LSR = local skin response; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.

# 1. INTRODUCTION

## 1.1 Disease Prevalence and Incidence

Actinic keratosis (AK) is a common, precancerous skin condition characterized by thickened, cornified, scaly lesions that develop as a result of chronic ultraviolet (UV) irradiation.[1] Risk factors for AK include fair skin types (Fitzpatrick skin type I or II), older age, and a history of chronic sun exposure.[2] Lesions are predominantly found on sun-exposed areas such as the face, bald scalp, ears, and forearms.[1] Approximately 60% of people older than 40 years old with a history of UV exposure have at least one AK lesion.[3] Since there is a lack of well-designed Canadian AK studies, the prevalence of AK in Canada in 2011 was estimated to be 4.4% using data from a German population-based study, affecting a total of 1.5 million people.[4]

According to the British Association of Dermatologists, 15% to 25% of AK lesions spontaneously resolve over a one-year period.[5] However, AK lesions may develop into invasive squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) if left untreated, which are the two main non-melanoma skin cancers (NMSCs).[6] The rate of progression from AK to SCC is estimated to be 0.025% to 20% per year for an individual lesion.[1,7] In Canada, 74,100 new cases of NMSCs and 270 deaths due to these cancers were predicted for 2011.[6]

AK typically manifests as 2 mm to 6 mm scaly macules, papules, or plaques that are skin to reddish-brown in colour.[1,8] Patients with AK are usually referred to dermatologists and diagnosis is frequently made on clinical appearance alone.[5] A skin biopsy may be required when there is clinical doubt or suspicion of invasive malignancy.[5,8] Detectable AK may be associated with a field change where the surrounding skin is also altered and subclinical lesions may be present.[6]

## 1.2 Standards of Therapy

No Canadian guidelines currently exist for the treatment of AK. The choice of treatment is generally guided by the clinical presentation of the condition and may include general measures such as sun protection.[9]

Treatment options for AK in Canada can be divided into two categories: lesion-directed therapies and field-directed therapies. Lesion-directed therapies include cryotherapy, surgical excision, curettage, and laser therapy.[1] Field-directed therapies include photodynamic therapy, chemical peels, imiquimod cream (5%, 3.75%, or 2.5%), and topical 5-fluorouracil (5-FU).[1]

Lesion-directed therapies are often used to treat isolated lesions that are few in number, with cryotherapy being the most commonly used method. Field-directed therapies may be used to treat extensive areas of affected skin or multiple lesions. Field-directed therapies can treat both visible and non-visible lesions in the actinic field and have the advantage of being noninvasive, with certain treatments that can be administered by the patient. Current approaches to the management of AK use both lesion-directed and field-directed methods as a strategy to increase the overall success of treatment.[3]

The clinical expert consulted for this review noted that the clinicians' choice of topical treatment would likely be based on their familiarity with a specific agent. The clinical expert also discussed that lesions that do not fully clear with initial treatment, or recurrent lesions, are typically retreated with the initial therapy.

## 1.3 Drug

Ingenol mebutate (Picato) is a diterpene ester extracted and purified from the sap of the *Euphorbia peplus* plant. The exact mechanism of action of ingenol mebutate is unknown, but it is able to induce rapid and direct cell death through immediate cytotoxicity and a neutrophil-dependent inflammatory response. Ingenol mebutate has a Health Canada indication for the topical treatment of non-hyperkeratotic, non-hypertrophic AK in adults. Ingenol mebutate is available in a topical gel formulation in concentrations of 0.05% (for trunk and extremities) or 0.015% (for face and scalp), supplied in unit-dose tubes for topical application.

| Indication under review |
|---|
| Topical treatment of non-hyperkeratotic, non-hypertrophic AK in adults. |
| Listing criteria requested by sponsor |
| For patients who have failed or are intolerant to 5-FU. |

**TABLE 3: KEY CHARACTERISTICS OF INGENOL MEBUTATE, 5-FU, AND IMIQUIMOD**

| | Ingenol mebutate | 5-FU | Imiquimod |
|---|---|---|---|
| **Mechanism of Action** | Unknown (cytotoxic and inflammatory mechanisms) | Competitive antagonist for uracil in formulation of RNA | Immune response modifier |
| **Related Indication** | Non-hyperkeratotic, non-hypertrophic AK | Premalignant keratosis and superficial BCC | Clinically typical, non-hyperkeratotic, non-hypertrophic AK on the face or balding scalp |
| **Dosage Form** | Topical, 0.05% and 0.015% gel | Topical, 5% cream | Topical, 5%, 3.75%, and 2.5% cream |
| **Recommended Dose** | Trunk and extremities: 0.05% gel once daily for 2 consecutive days<br><br>Face and scalp: 0.015% gel once daily for 3 consecutive days | Twice daily for 2 to 4 weeks | Face or balding scalp<br>5% cream: twice weekly for 16 weeks<br><br>3.75% or 2.5% cream: once daily for 2 treatment cycles of 2 weeks each separated by a 2-week no-treatment period |
| **Recommended Treatment Area** | 0.05% and 0.015% gel:<br>25 $cm^2$<br><br>Clinical data on treatment of more than one area are not available. | Entire affected area<br><br>No maximum recommended treatment area is suggested. | 5% cream: 25 $cm^2$<br>(safety applied to areas greater than 25 $cm^2$ for the treatment of AK has not been established.)<br><br>3.75% or 2.5% cream: up to 200 $cm^2$ (safety and efficacy applied to a larger area has not been established.) |

5-FU = 5-fluorouracil; AK = actinic keratosis; BCC = basal cell carcinoma; RNA = ribonucleic acid.
[a] Based on Health Canada-approved Product Monographs.

# 2. OBJECTIVES AND METHODS

## 2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of ingenol mebutate once daily for the topical treatment of non-hyperkeratotic, non-hypertrophic AK for the face and scalp (0.015% gel, three-day treatment) and for the trunk and extremities (0.05% gel, two-day treatment) in adult patients.

## 2.2 Methods

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 4.

**TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW**

| | |
|---|---|
| **Patient Population** | Adult patients (≥ 18 years of age) with non-hyperkeratotic, non-hypertrophic AK<br><br>Subpopulation: previous treatment of lesion/area with topical therapy (yes/no) |
| **Intervention** | Ingenol mebutate topical gel<br>Head (face and scalp): 0.015% gel daily for three consecutive days<br>Body (trunk and extremities): 0.05% gel daily for two consecutive days |
| **Comparators** | • 5-fluorouracil cream, 5%<br>• Imiquimod cream, 5%, 3.75%, or 2.5%[a] |
| **Outcomes** | ***Key efficacy outcomes:***<br>Complete clearance of AK lesions, partial clearance of AK lesions, reduction in number of AK lesions, health-related quality-of-life assessment (SF-36 or any valid scale)<br>***Other efficacy outcomes:***<br>Recurrence of AK lesions, progression to SCC, patient satisfaction<br>***Harms outcomes:***<br>AEs, SAEs, WDAEs, mortality, LSRs, pigmentation changes, and scarring |
| **Study Design** | Published and unpublished double-blind RCTs |

AE = adverse event; AK = actinic keratosis; DB = double blind; LSR = local skin response; RCT = randomized controlled trial; SAE = serious adverse event; SCC = squamous cell carcinoma; SF-36 = short form health survey; WDAE = withdrawal due to adverse event.
[a]Health Canada indication for the face and scalp.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946- ) with in-process records & daily updates through Ovid; Embase (1974- ) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Picato (ingenol mebutate).

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on June 13, 2013. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on October 16, 2013. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), which includes the websites of regulatory agencies, health technology assessment agencies, clinical trial registries, and professional associations. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

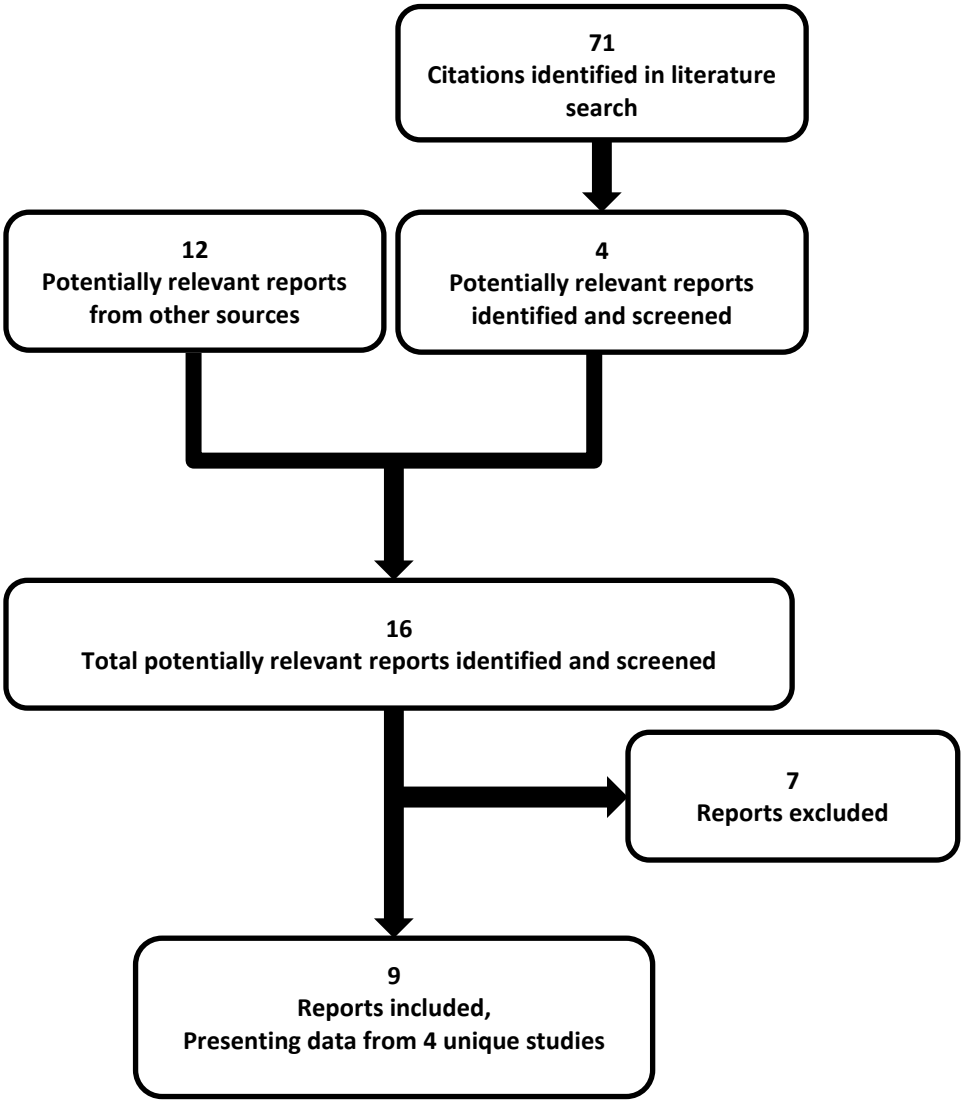
Two Common Drug Review clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 5; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

# 3. RESULTS

## 3.1 Findings From the Literature

A total of four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

**FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES**




QUOROM = Quality of Reporting of Meta-Analyses.

**TABLE 5: DETAILS OF INCLUDED STUDIES**

| | | PEP005-014 (REGION-I) | PEP005-028 (REGION-Ib) | PEP005-016 (REGION-IIa) | PEP005-025 (REGION-IIb) |
|---|---|---|---|---|---|
| Designs and Populations | **Study Design** | DB RCT | | | |
| | **Locations (# centres)** | US (18), Australia (2) | US (17) | US (19), Australia (2) | USA (19), Australia (2) |
| | **Randomized (N)** | 255 | 203 | 269 | 278 |
| | **Inclusion Criteria** | Patients ≥ 18 years with 4 to 8 clinically typical, visible, and discrete AK lesions within a contiguous 25 $cm^2$ treatment area on non-head locations (trunk and extremities). | | Patients ≥ 18 years with 4 to 8 clinically typical, visible, and discrete AK lesions within a contiguous 25 $cm^2$ treatment area on the head (face and scalp). | |
| | **Exclusion Criteria** | • Selected treatment area: within 5 cm of an incompletely healed wound; within 10 cm of a suspected BCC or SCC; previously treated with ingenol mebutate gel.<br>• Treatment area lesions with atypical clinical appearance (hypertrophic, hyperkeratotic, recalcitrant disease, cutaneous horns).<br>• History of other skin conditions that would interfere with evaluation of study medication.<br>• Anticipated excessive exposure to UV or use of tanning beds during study.<br>• Treatment with lesion-directed therapies (cryotherapy, surgical excision, curettage, laser therapy) within 2 cm of selected treatment area within 2 weeks prior to screening.<br>• Treatment with 5-FU, imiquimod, diclofenac, or photodynamic therapy within 2 cm of selected treatment area within 8 weeks prior to screening. | | | |
| Drugs | **Intervention** | Ingenol mebutate, 0.05% gel, daily for 2 consecutive days, topical | | Ingenol mebutate, 0.015% gel, daily for 3 consecutive days, topical | |
| | **Comparator(s)** | Vehicle gel, topical | | | |
| Duration | **Phase:** | | | | |
| | Double-blind | 57 days | | | |
| | Follow-up | – | 12 months (PEP005-032) | 12 months (PEP005-030) | |
| Outcomes | **Primary End Point** | Proportion of patients achieving complete clearance of all clinically visible AK lesions in the target treatment area at day 57 | | | |
| | **Other End Points** | • Proportion of patients achieving partial clearance (reduction of 75% or more in number of clinically visible AK lesions in the target treatment area) at day 57<br>• Per cent reduction in number of AK lesions from baseline at day 57<br>• Change in Skindex-16 Dermatology Survey score from baseline at days 8, 29 and 57<br>• TSQM score at day 57<br>• LSR score at baseline an days 8, 29, and 57 | | | |
| Notes | **Publications** | Lebwohl et al. (2012)[10] | | | |

5-FU = 5-fluorouracil; AK = actinic keratosis; BCC = basal cell carcinoma; DB = double blind; FDA = (US) Food and Drug Administration; LSR = local skin response; RCT = randomized controlled trial; SCC = squamous cell carcinoma; TSQM = Treatment Satisfaction Questionnaire for Medication; UV = ultraviolet.
Source: Clinical Study Reports,[11-14] CDR submission binder,[4] FDA Medical Review,[15] FDA Statistical Review,[16] Health Canada Reviewer's Report,[17] Lebwohl et al. (2012).[10]

## 3.2 Included Studies

### 3.2.1 Description of studies

Four multicentre, randomized, parallel-group, double-blind, vehicle-controlled trials met the inclusion criteria for this systematic review. PEP005-014 (N = 255) and PEP005-028 (N = 203) evaluated the efficacy and safety of ingenol mebutate gel, 0.05% for the treatment of AK on non-head locations (trunk and extremities; non-head studies).[11,14] PEP005-016 (N = 269) and PEP005-025 (N = 278) evaluated the efficacy and safety of ingenol mebutate gel, 0.015% for the treatment of AK on the head (face and scalp; head studies).[12,13]

All of the included trials were 57 days in duration and patients who achieved complete clearance of AK lesions were followed up for 12 months in study PEP005-032 (follow-up of PEP005-025) and study PEP005-030 (follow-up of PEP005-016 and PEP005-028). Results of these long-term follow-up trials are summarized in APPENDIX 6: LONG-TERM EFFICACY AND HARMS FROM EXTENSION STUDIES.

Patients were randomized in a 1:1 ratio with stratification by study site and anatomical location (arm, back of hand, chest, other locations; face or scalp) to ingenol mebutate gel or vehicle gel. In the non-head studies (PEP005-014 and PEP005-028), ingenol mebutate gel, 0.05% was applied topically once daily for two consecutive days to the selected treatment area by the patient at home. In the head studies (PEP005-016 and PEP005-025), ingenol mebutate gel, 0.015% was applied topically once daily for three consecutive days to the selected treatment area by the patient at home.

### 3.2.2 Populations

#### a) Inclusion and Exclusion Criteria

The main inclusion criterion was the presence of four to eight clinically typical, visible, and discrete AK lesions within a 25 $cm^2$ contiguous treatment area on the trunk and extremities (PEP005-014 and PEP005-028) or on the face and scalp (PEP005-016 and PEP005-025). The target treatment area was identified and documented using a three-point landmark technique study transparency, where three anatomical landmarks (e.g., scars, moles, birthmarks), the 25 $cm^2$ treatment area, and AK lesions were marked on a transparency using a marker.

Patients were excluded from the trial if the selected treatment area was within 5 cm of an incompletely healed wound or within 10 cm of a suspected basal cell or SCC, if they had been previously treated with ingenol mebutate, if the target treatment area contained hypertrophic or hyperkeratotic lesions, or if they had a history of other skin conditions or treatments that could interfere with the evaluation of study medication (e.g., topical medications, artificial tanners, immunosuppressive medications, immunomodulation agents, cytotoxic drugs, ultraviolet B phototherapy, other therapies for AK, or oral retinoids).

Patients who had received treatment with topical therapies such as 5-FU, imiquimod, and diclofenac within 2 cm of a selected treatment area within eight weeks before screening were excluded.

#### b) Baseline Characteristics

Baseline characteristics were generally well-balanced across treatment groups in the non-head studies (Table 6) and head studies (Table 7). In all studies, patients had a mean age of around 65 years and the majority of them were male (approximately 60% in non-head studies; approximately 80% in head studies).

All patients were white and their skin type was categorized according to the Fitzpatrick Scale, which is a numerical classification schema for the colour of skin with the following definitions: type I = burns easily, rarely tans; type II = burns easily, tans minimally; type III = burns moderately, tans gradually; type IV = burns minimally, tans well; type V = rarely burns, tans profusely; type VI = never burns, deeply pigmented.[18] In the non-head studies, the majority of patients had Fitzpatrick skin type II, followed by types I and III. In the head studies, the majority of patients had Fitzpatrick skin type II, followed by type III and then type I.

In the non-head studies, the location of AK treatment area was evenly distributed between ingenol mebutate and vehicle groups, with the majority of patients having lesions on the arm (approximately 60%) and back of the hand (20% to 30%). In the head studies, approximately 80% of patients had lesions on the face and 20% had lesions on the scalp.

More than 75% of patients in all of the studies had received previous treatment for AK with cryotherapy on any previous AK lesion, and a smaller percentage had received treatment with topical therapies. Approximately 20% of patients had previously received treatment with topical 5-FU. Subsequent to a request from the CDR, the manufacturer confirmed that the prior AK treatments and procedures were not specific to the lesions studied in the reviewed trials.

**TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS OF NON-HEAD STUDIES**

| Characteristics | PEP005-014 | | PEP005-028 | |
|---|---|---|---|---|
| | Ingenol Mebutate (N = 126) | Vehicle (N = 129) | Ingenol Mebutate (N = 100) | Vehicle (N = 103) |
| **Age, Year (SD)** | 67.3 (10.59) | 66.9 (9.89) | 65.3 (10.2) | 64.9 (10.7) |
| **Male, N (%)** | 86 (68.3) | 73 (56.6) | 59 (59.0) | 68 (66.0) |
| **Baseline BMI, kg/m$^2$ (SD)** | 28.0 (4.6) | 28.5 (5.4) | 28.5 (5.6) | 28.2 (5.5) |
| **Fitzpatrick Skin Type, N (%)** | | | | |
| **Type I** | 26 (20.6) | 31 (24.0) | 26 (26.0) | 24 (23.3) |
| **Type II** | 69 (54.8) | 73 (56.6) | 36 (36.0) | 45 (43.7) |
| **Type III** | 21 (16.7) | 21 (16.3) | 31 (31.0) | 27 (26.2) |
| **Type IV** | 10 (7.9) | 4 (3.1) | 5 (5.0) | 7 (6.8) |
| **Type V** | 0 | 0 | 2 (2.0) | 0 |
| **Location of Treatment Area, N (%)** | | | | |
| **Arm** | 84 (66.7) | 82 (63.6) | 59 (59.0) | 67 (65.0) |
| **Back of Hand** | 25 (19.8) | 29 (22.5) | 28 (28.0) | 27 (26.2) |
| **Chest** | 9 (7.1) | 8 (6.2) | 5 (5.0) | 3 (2.9) |
| **Leg** | 6 (4.8) | 5 (3.9) | 3 (3.0) | 5 (4.9) |
| **Back** | 2 (1.6) | 3 (2.3) | 3 (3.0) | 0 |
| **Shoulder** | 0 | 2 (1.6) | 2 (2.0) | 1 (1.0) |
| **Proportion of Patients with Prior AK Treatments and Procedures, N (%)** | | | | |
| **None** | 17 (13.5) | 20 (15.5) | 20 (20.0) | 14 (13.6) |
| **Cryotherapy** | 97 (77.0) | 99 (76.7) | 73 (73.0) | 79 (76.7) |
| **Surgical Excision or Curettage** | 12 (9.5) | 14 (10.9) | 12 (12.0) | 20 (19.4) |
| **5-FU** | 27 (21.4) | 30 (23.3) | 23 (23.0) | 26 (25.2) |
| **Imiquimod** | 14 (11.1) | 17 (13.2) | 7 (7.0) | 15 (14.6) |
| **Diclofenac** | 9 (7.1) | 8 (6.2) | 0 | 3 (2.9) |

5-FU = 5-fluorouracil; AK = actinic keratosis; BMI = body mass index; SD = standard deviation.

**TABLE 7: SUMMARY OF BASELINE CHARACTERISTICS OF HEAD STUDIES**

| Characteristics | PEP005-016 | | PEP005-025 | |
|---|---|---|---|---|
| | Ingenol Mebutate (N = 135) | Vehicle (N = 134) | Ingenol Mebutate (N = 142) | Vehicle (N = 136) |
| **Age, Year (SD)** | 63.5 (10.5) | 63.0 (10.0) | 64.8 (11.2) | 65.0 (10.1) |
| **Male, N (%)** | 116 (85.9) | 120 (89.6) | 117 (82.4) | 112 (82.4) |
| **Mean BMI, kg/m$^2$ (SD)** | 28.5 (5.1) | 28.0 (4.7) | 28.3 (4.4) | 28.1 (4.5) |
| **Fitzpatrick Skin Type, N (%)** | | | | |
| **Type I** | 24 (17.8) | 16 (11.9) | 27 (19.0) | 18 (13.2) |
| **Type II** | 58 (43.0) | 53 (39.6) | 65 (45.8) | 59 (43.4) |
| **Type III** | 44 (32.6) | 59 (44.0) | 40 (28.2) | 52 (38.2) |
| **Type IV** | 9 (6.7) | 6 (4.5) | 10 (7.0) | 7 (5.1) |
| **Location of Treatment Area, N (%)** | | | | |
| **Face** | 109 (80.7) | 109 (81.3) | 111 (78.2) | 111 (81.6) |
| **Scalp** | 26 (19.3) | 25 (18.7) | 31 (21.8) | 25 (18.4) |
| **Lesion Count, N (%)** | | | | |
| **4** | 27 (20.0) | 32 (23.9) | 21 (14.8) | 25 (18.4) |
| **5** | 36 (26.7) | 44 (32.8) | 39 (27.5) | 35 (25.7) |
| **6** | 28 (20.7) | 35 (26.1) | 28 (19.7) | 29 (21.3) |
| **7** | 27 (20.0) | 15 (11.2) | 27 (19.0) | 21 (15.4) |
| **8** | 17 (12.6) | 8 (6.0) | 27 (19.0) | 26 (19.1) |
| **Prior AK Treatments and Procedures, N (%)** | | | | |
| **None** | 16 (11.9) | 23 (17.2) | 25 (17.6) | 12 (8.8) |
| **Cryotherapy** | 111 (82.2) | 108 (80.6) | 112 (78.9) | 119 (87.5) |
| **Surgical Excision or Curettage** | 17 (12.6) | 14 (10.4) | 30 (21.1) | 29 (21.3) |
| **5-FU** | 26 (19.3) | 25 (18.7) | 29 (20.4) | 27 (19.9) |
| **Imiquimod** | 7 (5.2) | 15 (11.2) | 18 (12.7) | 16 (11.8) |
| **Diclofenac** | 2 (1.5) | 2 (1.5) | 3 (2.1) | 6 (4.4) |

5-FU = 5-fluorouracil; AK = actinic keratosis; BMI = body mass index; SD = standard deviation.

### 3.2.3 Outcomes

The primary efficacy outcome was the proportion of patients achieving complete clearance of all clinically visible AK lesions in the target treatment area at day 57. Clinical AK lesion assessment was performed by a board certified dermatologist. The same dermatologist performing screening assessments was to perform all subsequent study assessments for each individual patient and across enrolled patients.

**Secondary outcomes of interest included the following:**

- Proportion of patients achieving partial clearance of AK lesions at day 57, defined as a reduction of 75% or more in the number of clinically visible AK lesions in the target treatment area.
- Percentage change from baseline in the total number of AK lesions (not pre-specified in the trial protocol). Change in Skindex-16 Dermatological Survey score from baseline at day 8, day 29, and day 57.
- The Treatment Satisfaction Questionnaire for Medication (TSQM) scores at day 57.

The Skindex-16 Dermatological Survey is a validated, 16-item, self-administered instrument that measures the effect of skin disease on patient quality of life. There are three domains: Symptoms (four items), Emotions (seven items), and Functioning (five items), and items are rated on a seven-point Likert-type scale, with higher scores indicating increased "bothersomeness." Each of the items was transformed to a 0 to 100-point scale, and the mean of the transformed scores was calculated for each domain.

TSQM is a validated, 14-item, self-administered instrument with four domains: Effectiveness (three items), Side Effects (five items), Convenience (three items), and Global Satisfaction (three items). Items were rated on a five or seven-point Likert-type scale, and the sum of the individual items comprising each of the four domains was transformed to a 0 to 100-point scale (least favourable to most favourable).

Adverse events were defined as any unfavourable and unintended sign, symptom, or disease temporarily associated with the use of a study medication, whether or not related to the investigational product. Pre-existing conditions that worsened during the treatment period were reported as adverse events. The relationship of an adverse event to the study medication was assessed by the investigator (treatment-related adverse events). An adverse event was considered a serious adverse event if it was fatal, life-threatening, required participant hospitalization or prolonged existing hospitalization, resulted in persistent or significant disability/incapacity, a congenital anomaly/birth defect, or a medically significant event.

Local skin responses (LSRs), including erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, or erosion/ulceration, were assigned a grade of 0 to 4 according to the LSR Grading Scale, with higher numbers indicating greater severity. A composite LSR score was calculated based on the sum of the six individual LSR scores and ranged from 0 to 24. A summary of the LSR grading criteria is presented in Table 8.

**TABLE 8: LOCAL SKIN RESPONSE GRADING CRITERIA**

| Local Skin Response | Grading Criteria | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| **Erythema** | Not present | Slight pink, < 50% | Pink or light red, > 50% | Red, restricted to treatment area | Red extending outside treatment area |
| **Flaking/Scaling** | Not present | Isolated scale, specific to lesion | Scale < 50% | Scale > 50% | Scaling extending outside treatment area |
| **Crusting** | Not present | Isolated crusting | Crusting < 50% | Crusting > 50% | Crusting extending outside treatment area |
| **Swelling** | Not present | Slight, lesion-specific edema | Palpable edema extending beyond individual lesions | Confluent and/or visible edema | Marked swelling extending outside treatment area |
| **Vesiculation/ Pustulation** | Not present | Vesicles only | Transudate or pustules, with or without vesicles, < 50% | Transudate or pustules, with or without vesicles, > 50% | Transudate or pustules, with or without vesicles, extending outside treatment area |
| **Erosion/ Ulceration** | Not present | Lesion-specific erosion | Erosion extending beyond individual lesions | Erosion > 50% | Black eschar or ulceration |

Pigmentation and scarring were assessed by presence and then graded. Hypopigmentation and hyperpigmentation were assigned a grade of 0 (not present) to 3 (darker pigment or depigmented); scarring was assigned a grade of 0 (not present) to 2 (entire treatment area).

For a more detailed description of study outcomes, see APPENDIX 5: VALIDITY OF OUTCOME MEASURES.

### 3.2.4 Statistical analysis

**a) Efficacy Criteria**

- A sample size of approximately 250 patients (PEP005-014, PEP005-016, PEP005-025) was determined to be sufficient to provide at least 90% power to detect at least a 20% difference in complete clearance rate of AK lesions at day 57 between-treatment groups (alpha = 0.05), assuming a 5% attrition rate. In PEP005-028, a sample size of approximately 200 patients was calculated to provide at least 90% power to detect this difference (alpha = 0.05), assuming a 10% complete clearance rate for the vehicle group as observed from PEP005-014.
- The primary analysis for the primary end point (complete clearance of AK) and key secondary end points (partial clearance of AK lesions, percentage change from baseline in number of AK lesions) was performed using the intention-to-treat (ITT) population.
- The per-protocol (PP) population was used for supportive efficacy analyses.
- Missing clinical AK lesion assessments at day 57 were imputed using the last observation carried forward (LOCF) method for complete and partial clearance analyses. An additional sensitivity analysis was performed for complete clearance rate, in which all missing or out-of-window observations were considered treatment failures.
- The Cochran-Mantel-Haenszel (CMH) test controlling for anatomical location was used to compare complete and partial clearance rates between-treatment groups. A logistic analysis of variance (ANOVA) model was used with treatment, anatomical location, and geographic location (Australia versus US) as factors to test for treatment effect in addition to the CMH test.
- For the per cent reduction from baseline in the number of AK lesions at day 57, mean percentage reduction with a 95% CI was summarized by treatment group. No imputation of missing data was performed.
- The Skindex-16 Dermatological Survey scores were transformed from the original scale of 0 to 6 to a linear scale of 0 to 100, with the mean of the transformed subscores computed for the domains (emotions, functioning, symptoms). If two or more responses were missing within a domain, that domain was considered missing. There was no imputation for missing data. The transformed scores at each scheduled visit (baseline, day 8, day 29, day 57) were treated as continuous variables and analyzed using ANOVA with treatment and analysis site as factors to test for treatment effect.
- The TSQM scores were transformed to a scale from 0 to 100 and summarized by treatment group for each domain (effectiveness, side effects, convenience, global satisfaction). If more than one item within a domain was missing, that domain was considered missing. There was no imputation for missing data. The transformed scores for each domain at day 57 were treated as continuous variables and analyzed using ANOVA with treatment and analysis site as factors to test for treatment effect.
- All hypotheses were tested for statistical significance using two-tailed P values. Results of all tests were considered statistically significant if their *P* value was less than or equal to 0.05. No adjustments for multiple testing were made.

**b) Analysis Populations**

In all four trials, the following data sets were defined:
**ITT population:** All patients randomized to receive study medication.

**PP population:** A subset of the ITT population that included all randomized patients considered to be sufficiently compliant with the protocol.

**Safety data set:** Patients who received at least one dose of study medication and had at least one post-baseline safety evaluation. Patients were counted in the group in which they were actually treated.

## 3.3 Patient Disposition

The disposition of patients in the non-head studies is presented in Table 9 and that of the head studies is presented in Table 10. The percentage of patients who withdrew from the trials was low (< 5%), and there were no notable between-treatment differences.

**TABLE 9: PATIENT DISPOSITION IN NON-HEAD STUDIES**

| Criteria, N (%) | PEP005-014 | | PEP005-028 | |
|---|---|---|---|---|
| | Ingenol Mebutate | Vehicle | Ingenol Mebutate | Vehicle |
| **Screened** | 324 | | 271 | |
| **Randomized** | 126 (100) | 129 (100) | 100 (100) | 103 (100) |
| **Discontinued** | 4 (3.2) | 1 (0.8) | 2 (2.0) | 4 (3.9) |
| • **Adverse Event** | 2 (1.6) | 1 | 0 | 1 (1.0) |
| • **Lost to Follow-up** | 1 (0.8) | 0 | 0 | 0 |
| • **Withdrew Consent** | 0 | 0 | 0 | 1 (1.0) |
| • **Protocol Violation** | 1 (0.8) | 0 | 1 (1.0) | 1 (1.0) |
| • **Other** | 0 | 0 | 1 (1.0) | 1 (1.0) |
| **ITT** | 126 (100) | 129 (100) | 100 (100) | 103 (100) |
| **PP** | 112 (88.9) | 113 (87.6) | 90 (90.0) | 95 (92.2) |
| **Safety** | 125 (99.2) | 129 (100) | 100 (100) | 103 (100) |

ITT = intention to treat; PP = per-protocol.

**TABLE 10: PATIENT DISPOSITION IN HEAD STUDIES**

| Criteria, N (%) | PEP005-016 | | PEP005-025 | |
|---|---|---|---|---|
| | Ingenol Mebutate | Vehicle | Ingenol Mebutate | Vehicle |
| **Screened** | 422 | | 406 | |
| **Randomized** | 135 (100) | 134 (100) | 142 (100) | 136 (100) |
| **Discontinued** | 3 (2.2) | 7 (5.2) | 0 | 1 (0.7) |
| • **Adverse Event** | 1 (0.7) | 1 (0.7) | 0 | 0 |
| • **Withdrew Consent** | 2 (1.5) | 5 (3.7) | 0 | 1 (0.7) |
| • **Protocol Violation** | 0 | 1 (0.7) | 0 | 0 |
| **ITT** | 135 (100) | 134 (100) | 142 (100) | 136 (100) |
| **PP** | 121 (89.6) | 125 (93.3) | 136 (95.8) | 130 (95.6) |
| **Safety** | 132a | 135b | 142 (100) | 136 (100) |

ITT = intention to treat; PP = per-protocol.
[a] Two patients never applied the study medication.
[b] One patient was dispensed the incorrect medication.

## 3.4 Exposure to Study Treatments

In all four included trials, all patients randomized to vehicle applied the gel for the required duration; whereas, a number of patients randomized to ingenol mebutate failed to apply the gel for the required duration (Table 11 and Table 12). In study PEP005-014, one patient did not apply the second dose of ingenol mebutate due to an AE, and another patient did not apply the second dose due to a LSR. In study PEP005-028, one patient missed the second dose of ingenol mebutate due to losing the study medication tube. In study PEP005-016, two patients applied one dose of ingenol mebutate and one patient applied two doses. In study PEP005-025, one patient applied one dose and another patient applied two doses of ingenol mebutate. Reasons for the lack of adherence to the prescribed administration in studies PEP005-016 and PEP005-025 were not reported.

**TABLE 11: EXTENT OF EXPOSURE IN NON-HEAD STUDIES**

| Days of Exposure, N (%) | PEP005-014 | | PEP005-028 | |
|---|---|---|---|---|
| | Ingenol Mebutate, 0.05% (N = 125) | Vehicle (N = 129) | Ingenol Mebutate, 0.05% (N = 100) | Vehicle (N = 103) |
| **1** | 2 (1.6) | 0 | 1 (1.0) | 0 |
| **2** | 123 (98.4) | 129 (100) | 99 (99.0) | 103 (100) |

**TABLE 12: EXTENT OF EXPOSURE IN HEAD STUDIES**

| Days of Exposure, N (%) | PEP005-016 | | PEP005-025 | |
|---|---|---|---|---|
| | Ingenol Mebutate, 0.015% (N = 135) | Vehicle (N = 134) | Ingenol Mebutate, 0.015% (N = 142) | Vehicle (N = 136) |
| **0** | 2 (1.5) | 0 | 0 | 0 |
| **1** | 2 (1.5) | 0 | 1 (0.7) | 0 |
| **2** | 1 (0.7) | 0 | 1 (0.7) | 0 |
| **3** | 130 (96.3) | 134 (100) | 140 (98.6) | 136 (100) |

## 3.5 Critical Appraisal

### 3.5.1 Internal validity

- The PEP005 trials employed appropriate methods of randomization and allocation concealment (randomized centrally with the manufacturer), and baseline characteristics were well-balanced across treatment groups. Patients, investigators, and study site personnel were blinded to treatment assignment. However, during the trials, the increased incidence of LSRs in patients receiving ingenol mebutate gel may have resulted in unblinding of patients and assessors, potentially influencing patient-reported outcomes (Skindex-16 Dermatology Survey and TSQM) and lesion assessments by assessors.
- Patients self-applied study medication, which may have resulted in varying practices and a lack of consistency. Treatment adherence was assessed simply by having the patients return the study medication kit with the tubes, which may not be sound evidence of adherence to treatment protocol.
- The frequency of study withdrawal was low (< 5%), and similar across treatment groups, in all trials, supportive of internal validity.
- Assessment of AK lesions at study entry and subsequent study visits were assessed by the same dermatologists across patients.
- No minimum clinically important difference (MCID) values were identified for Skindex-16 Dermatological Survey and TSQM scores for patients with AK.

### 3.5.2 External validity

- Ingenol mebutate gel was compared with vehicle gel and not with any other topical treatments for AK lesions.
- Inclusion criteria required patients to have four to eight lesions within a contiguous 25 $cm^2$ area, which may not be representative of what is seen in clinical practice. The clinical expert consulted for this review mentioned that patients with AK frequently have scattered lesions, rather than lesions localized within a small area.
- There was limited evidence for patients who had failed treatment with 5-FU, given that patients previously treated with 5-FU accounted for approximately 20% of trial participants and the response to prior treatment was not reported. In addition, prior 5-FU treatment was not necessarily specific to the lesions treated in the PEP005 trials.
- Partial clearance of AK lesions was not considered to be a relevant outcome by the clinical expert consulted for this review, as the treatment area would require retreatment if there were any remaining lesions. The FDA medical review of ingenol mebutate also questioned the clinical meaningfulness of this outcome, stating, "However, it is not clear that partial clearing (e.g., 75%) is clinically meaningful. For example, a 75% or greater reduction in the number of AK lesions could still leave the largest AK lesion in the treatment area unaffected, and the lesion could progress into a squamous cell carcinoma."[15]
- The duration of the trials is insufficient to provide long-term efficacy and safety specific to ingenol mebutate gel, particularly with regard to progression of AK lesions to SCC or BCC.

## 3.6 Efficacy

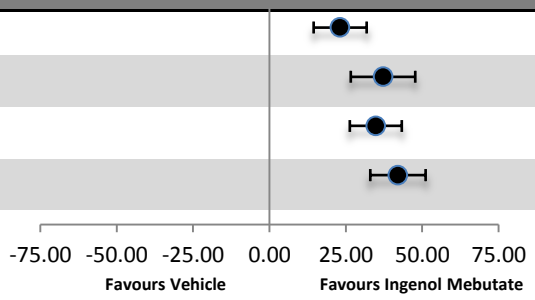
Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 4). See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data.

### 3.6.1 Complete clearance of AK lesions

The proportion of patients achieving complete clearance of all clinically visible AK lesions in the target treatment area at day 57 was statistically significantly higher in the ingenol mebutate group than the vehicle group in all studies. In the included trials, the proportion of patients achieving complete clearance of AK lesions at day 57 ranged from 27.8% to 47.2% with ingenol mebutate gel, and 2.2% to 5.1% with vehicle gel (Table 19 and Table 20). The risk difference of achieving complete clearance of AK lesions at day 57 with ingenol mebutate versus vehicle is presented in Table 13 along with numbers needed to treat. In all studies, the point estimates for risk difference favoured ingenol mebutate gel over vehicle gel.

**TABLE 13: INGENOL MEBUTATE VERSUS VEHICLE — COMPLETE CLEARANCE OF AK LESIONS AT DAY 57**

| Study | RD (95% CI)[a] | NNT[a] |
|---|---|---|
| PEP005-014 | 23.1 (14.5 to 31.8) | 5 |
| PEP005-028 | 37.2 (26.6 to 47.7) | 3 |
| PEP005-016 | 34.8 (26.3 to 43.3) | 3 |
| PEP005-025 | 42.0 (33.0 to 51.1) | 3 |



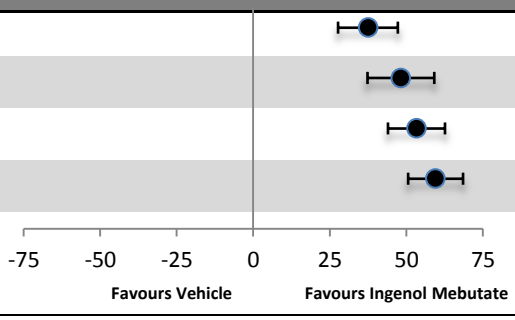

CI = confidence interval; NNT = number needed to treat; RD = risk difference.
[a] Calculated by CADTH (Revman 5).

### 3.6.2 Partial clearance of AK lesions

The proportion of patients achieving partial clearance of AK lesions (reduction of 75% or more in the number of clinically visible AK lesions in the target treatment area) was statistically significantly higher in the ingenol mebutate group than the vehicle group in all studies. In the included trials, the proportion of patients achieving partial clearance of AK lesions at day 57 ranged from 44.4% to 67.6% with ingenol mebutate gel, and 6.7% to 8.1% with vehicle gel. The risk difference of achieving complete clearance of AK lesions at day 57 with ingenol mebutate versus vehicle is presented in Table 14 along with NNTs. In all studies, the point estimates for risk difference favoured ingenol mebutate gel over vehicle gel. Additional details regarding partial clearance rates are presented in Table 21 and Table 22.

**TABLE 14: INGENOL MEBUTATE VERSUS VEHICLE — PARTIAL CLEARANCE OF AK LESIONS AT DAY 57**

| Study | RD (95% CI)[a] | NNT[a] |
|---|---|---|
| PEP005-014 | 37.5 (27.7, 47.2) | 3 |
| PEP005-028 | 48.2 (37.3, 59.1) | 3 |
| PEP005-016 | 53.3 (44.0, 62.6) | 2 |
| PEP005-025 | 59.5 (50.6, 68.5) | 2 |




CI = confidence interval; NNT = number needed to treat; RD = risk difference.
[a]Calculated by CADTH (Revman 5).

### 3.6.3 Per cent reduction from baseline in AK lesion count

The median reduction in the number of AK lesions compared with baseline at day 57 was 0% in the vehicle groups in all studies (Table 23 and Table 24). In the non-head studies, the median reduction in the number of AK lesions from baseline was 69% in study PEP005-014 and 75% in study PEP005-028 (Table 23). In the head studies, the median reduction in the number of AK lesions from baseline was 83% in study PEP005-016 and 87% in study PEP005-025 (Table 24). No analyses to determine the statistical significance of these findings were reported by the manufacturer.

### 3.6.4 Health-related quality of life

A summary of the Skindex-16 Dermatological Survey change in scores from baseline at days 8, 29, and 57 for the three domains (emotions, functioning, symptoms) is presented in Table 15 for the non-head studies and Table 16 for the head studies. Higher scores indicate greater patient concern, or "bothersomeness." Change from baseline was calculated by subtracting the baseline score from the post-baseline score, thereby making a negative change an improvement in(health-related quality-ofe-life (HRQoL), and a positive change a decline or deterioration in HRQoL.

[redacted]

[redacted]

Skindex-16 Dermatology Survey scores at baseline and day 57 are summarized in Table 25, Table 26, Table 27, and Table 28.

**TABLE 15: SKINDEX-16 DERMATOLOGICAL SURVEY CHANGE FROM BASELINE; MEAN (SD) AT DAYS 8, 29, AND 57 IN NON-HEAD STUDIES[a]**

| | PEP005-014 | | | PEP005-028 | | |
|---|---|---|---|---|---|---|
| | Ingenol Mebutate (N = 126) | Vehicle (N = 129) | *P* Value | Ingenol Mebutate (N = 100) | Vehicle (N = 103) | *P* Value |
| **Emotions** | | | | | | |
| Baseline Score, Mean (SD) | [redacted] | [redacted] | - | [redacted] | [redacted] | - |
| Day 8 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Day 29 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Day 57 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Functioning** | | | | | | |
| Baseline Score, Mean (SD) | [redacted] | [redacted] | - | [redacted] | [redacted] | - |
| Day 8 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Day 29 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Day 57 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Symptoms** | | | | | | |
| Baseline Score, Mean (SD) | [redacted] | [redacted] | - | [redacted] | [redacted] | - |
| Day 8 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Day 29 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Day 57 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

[a]Calculated as post-baseline value minus baseline value.

**TABLE 16: SKINDEX-16 DERMATOLOGICAL SURVEY CHANGE FROM BASELINE; MEAN (SD) AT DAYS 8, 29, AND 57 IN HEAD STUDIES[a]**

| | PEP005-016 | | | PEP005-025 | | |
|---|---|---|---|---|---|---|
| | Ingenol Mebutate (N = 135) | Vehicle (N = 134) | *P* Value | Ingenol Mebutate (N = 142) | Vehicle (N = 136) | *P* Value |
| **Emotions** | | | | | | |
| Baseline Score, Mean (SD) | [redacted] | [redacted] | - | [redacted] | [redacted] | - |
| Day 8 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Day 29 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Day 57 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Functioning** | | | | | | |
| Baseline Score, Mean (SD) | [redacted] | [redacted] | - | [redacted] | [redacted] | - |
| Day 8 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Day 29 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Day 57 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Symptoms** | | | | | | |
| Baseline Score, Mean (SD) | [redacted] | [redacted] | - | [redacted] | [redacted] | - |
| Day 8 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Day 29 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Day 57 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

[a]Calculated as post-baseline value minus baseline value.

### 3.6.5 Treatment Satisfaction Questionnaire for Medication

TSQM domain scores were transformed to a 0 to 100-point scale with higher scores indicating greater satisfaction. TSQM scores at day 57 for the non-head and head studies are presented in Table 29 and Table 30.

[redacted]

[redacted]

[redacted]

### 3.6.6 Subgroup analyses

A post-hoc subgroup analysis of complete clearance in patients who had received previous treatment with cryotherapy, imiquimod, and 5-FU was conducted by the manufacturer using the pooled RCTs for the non-head studies (PEP005-014 and PEP005-028) and the head studies (PEP005-016 and PEP005-025). Results of this analysis are presented in Table 31 and Table 32.

Prior AK topical treatments were not specific to the target treatment area or lesions of interest in the included studies. Data on prior AK topical treatments specific to the target treatment area were requested from the manufacturer, but this information was not collected in the included studies.

Among ingenol mebutate-treated patients in the pooled non-head studies, there were no statistical differences in the proportion of patients achieving complete clearance based on prior treatment with cryotherapy, imiquimod, or 5-FU.

Among ingenol mebutate-treated patients in the pooled head studies, patients previously treated with 5-FU were less likely to achieve complete clearance than patients not previously treated with 5-FU: 27.3% versus 45.9% ($P$ = 0.014). There was no statistical difference in the proportion of patients achieving complete clearance based on prior treatment with cryotherapy or imiquimod.

### 3.6.7 Progression to SCC

In study PEP005-014, one patient in the vehicle group developed a SCC in the target treatment area. In study PEP005-028, one patient in the ingenol mebutate group and two patients in the vehicle group developed a SCC, but it was unclear whether these were in the target treatment area. No cases of progression to SCC were reported in the head studies.

### 3.6.8 Recurrence of AK lesions

In study PEP005-014, one patient in the vehicle group experienced proliferation of AK lesions in the target treatment area. Recurrence of AK lesions was assessed in the follow-up studies of patients who achieved complete clearance in the included studies (APPENDIX 6: LONG-TERM EFFICACY AND HARMS FROM EXTENSION STUDIES).

## 3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2, Protocol).

### 3.7.1 Adverse events

Across all studies, the proportion of patients that reported at least one adverse event was greater in the ingenol mebutate group compared with the vehicle group: PEP005-014, 32.0% versus 28.7%; PEP005-028, 35.0% versus 25.2%; PEP005-016, 47.0% versus 23.0%; PEP005-025, 28.2% versus 21.3% (Table 33 and Table 34). In the non-head and head studies, the most commonly reported adverse events fell in the categories of infections and infestations, and general disorder and administration site conditions for patients treated with ingenol mebutate gel. The proportion of patients that reported at least one adverse event that fell into the category of general disorder and administration site conditions was greater in the ingenol mebutate group compared with the vehicle group: PEP005-014, 4.0% versus 0%; PEP005-028, 24.0% versus 5.8%; PEP005-016, 24.2% versus 3.0%; PEP005-025, 14.1% versus 2.2%. In the

head studies, the proportion of patients who experienced any ocular AEs was higher in the ingenol mebutate group compared with the vehicle group (PEP005-016, 3.8% versus 0.7%; PEP005-025, 3.5% versus 0.7%).

A greater number of patients who received ingenol mebutate gel experienced at least one AE considered by the investigator to be related to treatment compared with patients who received vehicle gel. The most frequently reported treatment-related adverse events included general disorder and administration site conditions such as application site pruritus, application site pain, and application site irritation. Patients treated on the face or scalp had eye-associated disorders such as eyelid edema and periorbital edema.

### 3.7.2 Serious adverse events (SAEs)

The percentage of patients who experienced at least one serious adverse event was < 3% in all treatment groups in all trials, and did not differ noticeably between treatments.

### 3.7.3 Withdrawals due to adverse events (WDAEs)

The percentage of patients who discontinued due to adverse events was < 2% across all studies and treatment groups.

### 3.7.4 Mortality

No deaths were reported in any of the included trials.

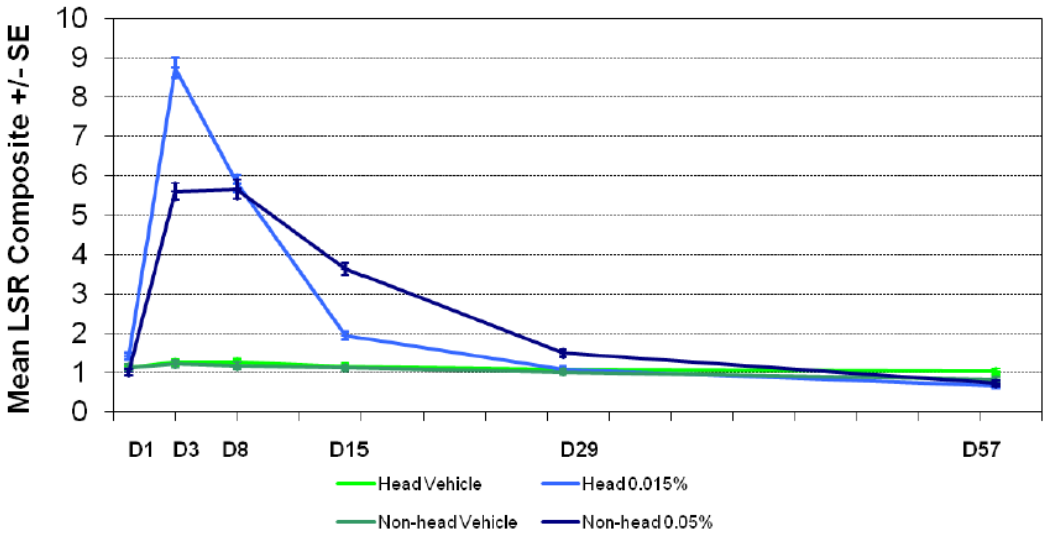
### 3.7.5 Notable harms

### 3.7.6 Local skin responses

The mean composite LSR scores for patients treated with ingenol mebutate gel and vehicle gel at baseline and days 3, 8, 15, 29 and 57 are presented in Table 35 and Table 36). In all trials baseline mean LSR scores in both treatment groups were greater than zero, indicating a localized irritation at the lesion sites which was predominantly attributed to erythema and flaking/scaling. In the ingenol mebutate groups across all studies, the composite mean LSR scores peaked at the first or second assessment post-baseline: day 3 or day 8 for non-head studies; day 4 for head studies, before returning to approximately baseline values at day 29. In all trials, mean LSR scores in the vehicle groups were relatively stable at all time points.

A graphed time-course of the mean composite LSR scores for the pooled non-head and pooled head studies depicts this increase and decrease in patients treated with ingenol mebutate gel (Figure 2).

**FIGURE 2: TIME COURSE OF MEAN COMPOSITE LSR SCORES**




Source: Health Canada Module 2.7.4.[19]

### 3.7.7 Pigmentation and scarring

In all studies, the majority of patients showed no hypopigmentation, hyperpigmentation, or scarring at baseline or at day 57 in all treatment groups (Table 17 and Table 18). Generally, hypopigmentation, hyperpigmentation, or scarring that was present at baseline remained unchanged at the end of the study. A greater proportion of patients who had hypo or hyperpigmentation at baseline was absent at the end of the study in ingenol mebutate-treated patients than with vehicle-treated patients. A small proportion of patients that had no pigmentation or scarring at baseline showed pigmentation or scarring at the end of the study.

**TABLE 17: INCIDENCE OF PATIENTS WITH PIGMENTATION AND SCARRING CHANGE FROM BASELINE AT DAY 57 FOR NON-HEAD STUDIES**

| Grade, N (%) | PEP005-014 | | | | PEP005-028 | | | |
|---|---|---|---|---|---|---|---|---|
| | Ingenol Mebutate (N = 125) | | Vehicle (N = 129) | | Ingenol Mebutate (N = 100) | | Vehicle (N = 103) | |
| **Hypopigmentation** | | | | | | | | |
| | **Baseline** | **Day 57** | **Baseline** | **Day 57** | **Baseline** | **Day 57** | **Baseline** | **Day 57** |
| **0** | 122 (97.6) | 123 (98.4) | 121 (93.8) | 129 (100) | 95 (95.0) | 88 (88.0) | 95 (92.2) | 95 (92.2) |
| **1** | 3 (2.4) | 2 (1.6) | 4 (3.1) | 0 | 5 (5.0) | 12 (12.0) | 7 (6.8) | 6 (5.8) |
| **2** | 0 | 0 | 1 (0.8) | 0 | 0 | 0 | 0 | 0 |
| **3** | 0 | 0 | 1 (0.8) | 0 | 0 | 0 | 0 | 0 |
| **Hyperpigmentation** | | | | | | | | |
| | **Baseline** | **Day 57** | **Baseline** | **Day 57** | **Baseline** | **Day 57** | **Baseline** | **Day 57** |
| **0** | 123 (98.4) | 122 (97.6) | 120 (93.0) | 126 (97.7) | 92 (92.0) | 98 (98.0) | 91 (88.3) | 94 (91.3) |
| **1** | 1 (0.8) | 2 (1.6) | 7 (5.4) | 3 (2.3) | 8 (8.0) | 2 (2.0) | 11 (10.7) | 7 (6.8) |
| **2** | 1 (0.8) | 1 (0.8) | 0 | 0 | 0 | 0 | 1 (1.0) | 0 |
| **3** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Scarring** | | | | | | | | |
| | **Baseline** | **Day 57** | **Baseline** | **Day 57** | **Baseline** | **Day 57** | **Baseline** | **Day 57** |
| **0** | 120 (96.0) | 122 (97.6) | 121 (93.8) | 124 (96.1) | 99 (99.0) | 99 (99.0) | 103 (100) | 101 (98.1) |
| **1** | 5 (4.0) | 3 (2.4) | 6 (4.7) | 5 (3.9) | 1 (1.0) | 0 | 0 | 0 |
| **2** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**TABLE 18: INCIDENCE OF PATIENTS WITH PIGMENTATION AND SCARRING CHANGE FROM BASELINE AT DAY 57 FOR HEAD STUDIES**

| Grade, N (%) | PEP005-016 | | | | PEP005-025 | | | |
|---|---|---|---|---|---|---|---|---|
| | Ingenol Mebutate (N = 132) | | Vehicle (N = 135) | | Ingenol Mebutate (N = 142) | | Vehicle (N = 136) | |
| **Hypopigmentation** | | | | | | | | |
| | **Baseline** | **Day 57** | **Baseline** | **Day 57** | **Baseline** | **Day 57** | **Baseline** | **Day 57** |
| **0** | 113 (85.6) | 126 (95.5) | 124 (91.9) | 128 (94.8) | 131 (92.3) | 138 (97.2) | 123 (90.4) | 122 (89.7) |
| **1** | 15 (11.4) | 5 (3.8) | 11 (8.1) | 6 (4.4) | 11 (7.7) | 4 (2.8) | 11 (8.1) | 13 (9.6) |
| **2** | 3 (2.3) | 0 | 0 | 0 | 0 | 0 | 2 (1.5) | 1 (0.7) |
| **3** | 1 (0.8) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Hyperpigmentation** | | | | | | | | |
| | **Baseline** | **Day 57** | **Baseline** | **Day 57** | **Baseline** | **Day 57** | **Baseline** | **Day 57** |
| **0** | 114 (86.4) | 124 (93.9) | 122 (90.4) | 129 (95.6) | 124 (87.3) | 130 (91.5) | 123 (90.4) | 124 (91.2) |
| **1** | 15 (11.4) | 7 (5.3) | 13 (9.6) | 5 (3.7) | 18 (12.7) | 12 (8.5) | 13 (9.6) | 12 (8.8) |
| **2** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **3** | 3 (2.3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Scarring** | | | | | | | | |
| | **Baseline** | **Day 57** | **Baseline** | **Day 57** | **Baseline** | **Day 57** | **Baseline** | **Day 57** |
| **0** | 127 (96.2) | 130 (98.5) | 134 (99.3) | 134 (99.3) | 141 (99.3) | 142 (100) | 131 (96.3) | 132 (97.1) |
| **1** | 3 (2.3) | 0 | 1 (0.7) | 0 | 1 (0.7) | 0 | 5 (3.7) | 4 (2.9) |
| **2** | 2 (1.5) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

# 4. DISCUSSION

## 4.1 Summary of Available Evidence

Four 57-day, double-blind RCTs comparing ingenol mebutate gel with vehicle gel in adults with AK were included in the systematic review. PEP005-014 (N = 225) and PEP005-028 (N = 203) evaluated the efficacy and safety of ingenol mebutate gel, 0.05%, once daily for two days, on non-head locations (trunk and extremities). PEP005-016 (N = 269) and PEP005-025 (N = 278) evaluated the efficacy and safety of ingenol mebutate gel, 0.015%, once daily for three days on the head (face and scalp). Included patients had four to eight clinically typical, visible, and discrete AK lesions within a 25 $cm^2$ contiguous treatment area. No active-comparator trials met the inclusion criteria for this review.

## 4.2 Interpretation of Results

### 4.2.1 Efficacy

In both the non-head and head studies, the proportion of patients achieving complete clearance of all AK lesions at day 57 was statistically significantly greater in the ingenol mebutate gel groups compared with the vehicle gel groups; Absolute risk differences ranged from 23.1% to 42.0% across the included trials. Efficacy results from the individual trials are similar to that of a published pooled analysis of the non-head and head studies.[10] The proportion of patients achieving partial clearance (reduction of 75% or more in the number of lesions) at day 57 was naturally higher than those achieving complete clearance, but between-treatment differences were also higher than those observed for complete clearance; absolute-risk differences ranged from 37.5% to 59.5%. However, partial clearance of AK lesions was considered to be of lesser clinical importance by the clinical expert consulted for this review, as residual lesions in the treatment area would require retreatment. Similarly, the FDA medical review for ingenol mebutate stated that it wasn't clear that partial clearance is clinically meaningful, as a 75% or greater reduction in the number of AK lesions could leave the largest AK lesion in the treatment area unaffected, which could then progress to SCC.[15]

[redacted]

[redacted] This may be associated with the increased severity of LSRs observed during or shortly following treatment with ingenol mebutate (Section 4.2.2 Harms).

While the reviewed trials provide support for the efficacy of ingenol mebutate versus no treatment (vehicle), in terms of clearance of lesions, the available evidence has a number of limitations, including the lack of an active comparator, the short duration of the trials, and uncertain applicability to the manufacturer's requested listing criteria. No RCTs comparing ingenol mebutate with other topical treatments for AK were identified. Ingenol mebutate has a shorter course of treatment compared with 5-FU and imiquimod, which may potentially impact treatment adherence and outcome. A cross-sectional online/telephone survey of 300 adults with AK living in the UK found that rates of non-adherence and non-persistence increased with increasing lengths of treatment regimens.[20] However, given the lack of active-comparator trials, the comparative efficacy of ingenol mebutate is unknown. A recent Cochrane review[21] of interventions for AK concluded that field-directed treatments (including ingenol mebutate, imiquimod, and 5-FU) have similar efficacy. However, the between-trial heterogeneity makes direct comparisons challenging.

Trials included in the present review were of short duration (57 days) and do not provide evidence of long-term efficacy or whether ingenol mebutate reduces the risk of progression to SCC. Two observational, 12-month follow-up studies reported that approximately 50% of patients who achieved complete clearance in studies PEP005-028, PEP005-016, and PEP005-025 experienced at least one new or recurrent AK lesion within the treatment area (APPENDIX 6: LONG-TERM EFFICACY AND HARMS FROM EXTENSION STUDIES). The clinical expert consulted for this review noted that this is consistent with what is observed in clinical practice with other topical treatments for AK.

The manufacturer is requesting that ingenol mebutate be listed for patients who have failed or are intolerant to 5-FU, however the included trials are not specific to this subpopulation of patients. Approximately 20% of patients in the reviewed trials had received prior AK treatment with 5-FU. The manufacturer provided pooled post-hoc subgroup analyses comparing the incidence of complete clearance between treatment-naive and previously treated patients. However, the subgroup analyses suffer from a number of limitations, including not being pre-planned or having used stratified randomization, and uncertain statistical power and a lack of adjustment for multiple comparisons. In addition, as previous treatment with 5-FU was not necessarily in the target treatment area that was subsequently treated with ingenol mebutate, it is difficult to glean useful information from this analysis. Finally, the clinical expert consulted for this review indicated that, while failure to achieve lesion clearance in clinical practice would prompt retreatment, it would not necessarily prompt a change in treatment.

The reviewed trials enrolled patients with four to eight AK lesions within a 25 $cm^2$ contiguous area. However, the clinical expert consulted for this review indicated that this would not be typically seen in clinical practice, where AK patients may have scattered lesions not necessarily within a contiguous area. The Health Canada-approved product monograph indicates that ingenol mebutate gel should be applied to a treatment field area of 25 $cm^2$, and that clinical data on treatment of more than one area are not available.

Although ingenol mebutate gel is indicated for the treatment of AK, the clinical expert consulted on this review indicated that the potential for off-label use is high due to misdiagnosis of lesions that are similar in appearance to AK. These lesions include irritated seborrheic keratosis, psoriasis, lichen planus, traumatic lesions, and eczema. Clinical trials are currently being conducted investigating the effect of ingenol mebutate on other indications such as SCC, BCC, and seborrheic keratosis. The clinical expert

also noted that the definition for non-hyperkeratotic, non-hypertrophic AK, the Health Canada-approved indication for ingenol mebutate, may be difficult to interpret and will likely vary between clinicians.

### 4.2.2 Harms

The overall safety results in the non-head and head studies revealed an increase in the incidence of adverse events with the application of ingenol mebutate gel compared with vehicle gel. The most common treatment-related adverse events were administration site conditions, including pain, pruritus, and irritation. In the studies looking at the face and scalp, there was an increased incidence of ocular adverse events in the ingenol mebutate group compared with the vehicle group, possibly due to the proximity of the target treatment area to the eye in the face and scalp studies. The incidence of serious adverse events and withdrawals due to adverse events was low and balanced between treatment groups. There were no deaths reported in all included studies. In all included studies, there was minimal change in hypopigmentation, hyperpigmentation, and scarring after treatment with ingenol mebutate or vehicle gel.

Composite LSR scores (erythema, flaking or scaling, crusting, swelling, vesiculation or pustulation, erosion or ulceration) at the application site were reported at each study visit. Composite LSR scores, post-baseline, were notably higher in the ingenol mebutate groups compared with vehicle gel in both non-head and head studies. LSR scores peaked at day three or day eight for the non-head studies, and at day four for the head studies, with scores declining to near-baseline values by day 29. The maximum mean composite LSR score in the head studies was higher than that of the non-head studies. The clinical expert consulted for this review stated that this is due to the skin on the face and scalp being more delicate and more susceptible to swelling.

The types of local skin reactions experienced with ingenol mebutate are comparable to those reported for other topical therapies for AK such as 5-FU and imiquimod.[22-24] Patient input indicated that these adverse skin reactions made it difficult to complete the full course of treatment with 5-FU and imiquimod due to increasing discomfort.

# 5. CONCLUSIONS

Based on two each double-blind randomized controlled trials of adults with AK lesions on non-head and head locations, compared with no treatment (vehicle), treatment with ingenol mebutate resulted in a statistically greater proportion of patients achieving complete or partial clearance of AK lesions, but with an increase in LSRs. However, there are no trials comparing ingenol mebutate with other field-directed treatments (e.g., 5-FU or imiquimod). In addition, the trials comparing ingenol mebutate with no treatment (vehicle) are limited by their short duration and uncertain applicability to the manufacturer's requested listing criteria.

# APPENDIX 1: PATIENT INPUT SUMMARY

*This section was summarized by CDR staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.*

### 1. Brief Description of Patient Group(s) Supplying Input

A joint submission was made by the Canadian Skin Patient Alliance and the Save Your Skin Foundation.

The Canadian Skin Patient Alliance is a non-profit patient-centred organization serving patient needs to enhance care, promote skin health, and find cures for Canadian skin patients by providing education, information, and a supportive online community and by acting as an umbrella organization for affiliated skin-disease-specific organizations including the Save Your Skin Foundation. The Canadian Skin Patient Alliance has received unrestricted grants from Leo Pharma, Amgen, AbbVie, Galderma, GlaxoSmithKline, Merck, Novartis, Triton Pharma, and Valeant Canada.

The Save Your Skin Foundation is a patient-led non-profit organization dedicated to raising awareness of melanoma and NMSCs, which provides patients with access to information about treatment options as well as emotional and financial support to patients and caregivers. The Save Your Skin Foundation has received unrestricted grants from Leo Pharma, Merck, Roche, and Bristol-Myers Squibb.

### 2. Condition and Current Therapy-related Information

Information was gathered by conducting interviews with six patients who had used ingenol mebutate for actinic keratosis (AK) to determine treatment satisfaction, effectiveness, ease of use, side effects, and impact on day-to-day living. Additionally, an online survey was used to collect patient experiences with AK and AK treatments. Six people responded to the survey and their experiences echoed those of the interviewed patients.

AK is a precancerous skin condition usually caused by cumulative sun exposure. It is most common among those older than 65 and its prevalence is increasing as the Canadian population ages. AK shows up as lesions or rough scaly patches on the skin. If untreated, AK can progress to NMSC which can have a profound impact on the individual, including dealing with treatments, cancer-related stress and anxiety, general comorbidities, and the potential for it to spread; some NMSCs can lead to death. There is no way to predict which AK lesions will progress to NMSC.

There are some major concerns with current treatments, including the inability to finish treatment cycles due to extreme side effects, the negative impact of side effects on quality of life during treatment, the length of treatment (up to 12 weeks), severe discomfort, and treatment effectiveness. The reaction to treatment caused anxiety and stress for some patients.

*"When I need to have it burned off, the site blisters and looks horrible, weeping, etc. Yuk. I have been told that if it recurs again, I will need surgery, and they will take skin from my cheek up to my nose to accomplish this…very ugly!"*

Five patients who had used treatments other than ingenol mebutate were interviewed. These patients all said they experienced discomfort or suffering caused by the treatment. Side effects with treatments like fluorouracil and imiquimod include skin irritation, burning, redness, dryness, pain, swelling, tenderness, blistering, and changes in skin colour. One patient was unable to complete treatment as his

lip hurt so much he was unable to eat. In addition, he compared the side effects to what it must be like to have leprosy and said that he took time off work to avoid showing his face in public. Others complain of extreme pain and bleeding sores with treatment. Patients find that completing a 12-week course of imiquimod difficult to cope with because the discomfort increases as treatment progresses. In terms of effectiveness, many patients found that even if they were able to complete a treatment course, they did not experience a complete resolution of their AK lesions.

While many AK patients are self-sufficient and need minimal help from caregivers, those who are elderly may need a caregiver to apply their treatment, which can be distressing when the patient is already suffering from inflamed and painful skin. Additionally, patients may stay home from work or stop participating in social and recreational activities, which can impact the entire family.

## 3. Related Information about the Drug Being Reviewed

AK is not generally perceived as being as serious as other NMSCs and many patients are reluctant to complete the currently available long and debilitating treatment courses to reduce their risk of cancer. A shorter treatment with reduced trauma to the skin will be more acceptable to the growing population of patients diagnosed with AK. The short length of treatment (two to three days) with ingenol mebutate and more tolerable side effects will have a real impact on patients who have felt stress, anxiety, and pain related to their past AK treatments. As patients need only apply ingenol mebutate for two to three days, their skin will have less time to react. Side effects include pain and redness that develops after the last application of the ointment and lasts up to two weeks. This shortened period of adverse effects is considered positive and acceptable considering the alternatives. Compliance with ingenol mebutate is high, leading to improved patient long-term health and well-being as the risk of skin cancer at the lesion site is addressed. Patients will be able to avoid more time off work, stay more productive, use fewer pain medications, and experience considerably less stress.

Patients with experience with ingenol mebutate found it to be effective and less painful than other treatments:

*"I had some light blistering two or three days after treatment, which went away very quickly. Very little soreness or itching, I didn't have to put anything on it."*

"*Extremely easy, I went through other drugs before and compared to that it was a walk in the park."*

Because of the effectiveness and ability to complete the treatment cycle, all of the interviewed patients agreed that they felt peace of mind knowing they were preventing their AK lesions from potentially developing into NMSC. All patients said they would use ingenol mebutate again, and they would speak to their doctors about receiving that treatment over and above another one.

# APPENDIX 2: LITERATURE SEARCH STRATEGY

| OVERVIEW | |
|---|---|
| Interface: | Ovid |
| Databases: | Embase 1974 to present<br>MEDLINE Daily and Ovid MEDLINE 1946 to Present<br>MEDLINE In-Process & Other Non-Indexed Citations<br>**Note:** Subject headings have been customized for each database.<br>Duplicates between databases were removed in Ovid. |
| Date of Search: | June 13, 2013 |
| Alerts: | Weekly search updates until October 16, 2013 |
| Study Types: | No search filters were applied |
| Limits: | No date or language limits were used<br>Human filter was applied<br>Conference abstracts were excluded |

| SYNTAX GUIDE | |
|---|---|
| / | At the end of a phrase, searches the phrase as a subject heading |
| .sh | At the end of a phrase, searches the phrase as a subject heading |
| MeSH | Medical Subject Heading |
| exp | Explode a subject heading |
| * | Before a word, indicates that the marked subject heading is a primary topic;<br>or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings |
| adj | Requires words are adjacent to each other (in any order) |
| adj# | Adjacency within # number of words (in any order) |
| .rn | CAS registry number |
| .nm | Name of substance word |
| .ti | Title |
| .ot | Original title |
| .ab | Abstract |
| .hw | Heading Word; usually includes subject headings and controlled vocabulary |
| .pt | Publication type |
| .po | Population group [PsychInfo only] |
| pmez | Ovid database code; MEDLINE(R) In-Process & Other Non-Indexed Citations<br>MEDLINE Daily and Ovid MEDLINE 1946 to Present |
| oemezd | Ovid database code; Embase 1974 to present, updated daily |

| OVID Strategy |
|---|
| 1 75567-37-2.rn,nm. |
| 2 (picato or ingenol mebutate or PEP005 or "PEP 005" or ingenol angelate or ingenol 3 angelate or 3- Angeloylingenol or Euphorbia factor An1 or Euphorbia factor H1).ti,ot,ab,sh,rn,hw,nm. |
| 3 1 or 2 |
| 4 3 use pmez |
| 5 *ingenol mebutate/ |
| 6 (picato or ingenol mebutate or PEP005 or "PEP 005" or ingenol angelate or ingenol 3 angelate or 3-Angeloylingenol or Euphorbia factor An1 or Euphorbia factor H1).ti,ab. |
| 7 5 or 6 |
| 8 7 use oemezd |
| 9 conference abstract.pt. |
| 10 8 not 9 |
| 11 4 or 10 |
| 12 exp animals/ |
| 13 exp animal experimentation/ or exp animal experiment/ |
| 14 exp models animal/ |
| 15 nonhuman/ |
| 16 exp vertebrate/ or exp vertebrates/ |
| 17 animal.po. |
| 18 or/12-17 |
| 19 exp humans/ |
| 20 exp human experimentation/ or exp human experiment/ |
| 21 human.po. |
| 22 or/19-21 |
| 23 18 not 22 |
| 24 11 not 23 |
| 25 remove duplicates from 24 |

| OTHER DATABASES | |
|---|---|
| PubMed | Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used. |
| Trial registries (Clinicaltrials.gov and other) | Same keywords, limits used as per MEDLINE search. |

### Grey Literature

| | |
|---|---|
| Dates for Search: | June 2013 |
| Keywords: | Picato and synonyms, actinic keratosis |
| Limits: | No date or language limits used |

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Databases (free)
- Internet Search.

# APPENDIX 3: EXCLUDED STUDIES

| Reference | Reason for Exclusion |
|---|---|
| Clinical study report: PEP005-030[25] | Study design |
| Clinical study report: PEP005-031[26] | |
| Clinical study report: PEP005-032[27] | |
| Clinical study report: PEP005-020[28] | |
| Lebwohl et al. (2013)[29] | |
| Anderson et al. (2009)[30] | Head and non-head indications not separated in results |
| Siller et al. (2009)[31] | |

# APPENDIX 4: DETAILED OUTCOME DATA

## Complete Clearance of AK Lesions

**TABLE 19: PROPORTION OF PATIENTS ACHIEVING COMPLETE CLEARANCE OF AK LESIONS AT DAY 57 IN NON-HEAD STUDIES**

| | PEP005-014 | | PEP005-028 | |
|---|---|---|---|---|
| Complete Clearance | Ingenol Mebutate (N = 126) | Vehicle (N = 129) | Ingenol Mebutate (N = 100) | Vehicle (N = 103) |
| N (%) | 35 (27.8) | 6 (4.7) | 42 (42.0) | 5 (4.9) |
| Risk Difference (95% CI)[a] | 23.1 (14.5 to 31.8) | | 37.2 (26.6 to 47.7) | |
| *P* Value | < 0.0001 | | < 0.001 | |

CI = confidence interval.
[a]Calculated by CADTH (Revman 5).

**TABLE 20: PROPORTION OF PATIENTS ACHIEVING COMPLETE CLEARANCE OF AK LESIONS AT DAY 57 IN HEAD STUDIES**

| | PEP005-016 | | PEP005-025 | |
|---|---|---|---|---|
| Complete Clearance | Ingenol Mebutate (N = 135) | Vehicle (N = 134) | Ingenol Mebutate (N = 142) | Vehicle (N = 136) |
| N (%) | 50 (37.0) | 3 (2.2) | 67 (47.2) | 7 (5.1) |
| Risk Difference (95% CI)[a] | 34.8 (26.3 to 43.3) | | 42.0 (33.0 to 51.1)) | |
| *P* Value | < 0.001 | | < 0.001 | |

CI = confidence interval.
[a]Calculated by CADTH (Revman 5).

## Partial Clearance of AK Lesions

**TABLE 21: PROPORTION OF PATIENTS ACHIEVING PARTIAL CLEARANCE OF AK LESIONS AT DAY 57 IN NON-HEAD STUDIES**

| | PEP005-014 | | PEP005-028 | |
|---|---|---|---|---|
| Partial Clearance | Ingenol Mebutate (N = 126) | Vehicle (N = 129) | Ingenol Mebutate (N = 100) | Vehicle (N = 103) |
| N (%) | 56 (44.4) | 9 (7.0) | 55 (55.0) | 7 (6.8) |
| Risk Difference (95% CI)[a] | 37.5 (27.7 to 47.2) | | 48.2 (37.3 to 59.1) | |
| *P* Value | < 0.0001 | | < 0.001 | |

CI = confidence interval.
[a]Calculated by CADTH (Revman 5).

**TABLE 22: PROPORTION OF PATIENTS ACHIEVING PARTIAL CLEARANCE OF AK LESIONS AT DAY 57 IN HEAD STUDIES**

| | PEP005-016 | | PEP005-025 | |
|---|---|---|---|---|
| Partial Clearance | Ingenol Mebutate (N = 135) | Vehicle (N = 134) | Ingenol Mebutate (N = 142) | Vehicle (N = 136) |
| N (%) | 81 (60.0) | 9 (6.7) | 96 (67.6) | 11 (8.1) |
| Risk Difference (95% CI)[a] | 53.3 (44.0 to 62.6) | | 59.5 (50.6 to 68.5) | |
| *P* Value | < 0.001 | | < 0.001 | |

CI = confidence interval.
[a]Calculated by CADTH (Revman 5).

## Per cent Reduction from Baseline in AK Lesion Count

**TABLE 23: PER CENT REDUCTION FROM BASELINE IN AK LESION COUNT AT DAY 57 IN NON-HEAD STUDIES**

| | PEP005-014 | | PEP005-028 | |
|---|---|---|---|---|
| | Ingenol Mebutate (N = 126) | Vehicle (N = 129) | Ingenol Mebutate (N = 100) | Vehicle (N = 103) |
| n | 120 | 128 | 100 | 101 |
| Median (Range) | 69.05 (–25.0 to 100) | 0 (–33.3 to 100) | 75.0 (0 to 100) | 0 (–33.3 to 100) |
| Baseline Lesion Count, Mean (SD) | NR | NR | 5.3 (1.3) | 5.7 (1.4) |
| Day 57 Lesion Count, Mean (SD) | NR | NR | 1.7 (1.9) | 5.0 (2.1) |
| Baseline Lesion Count, Median (Range) | NR | NR | 5 (4 to 8) | 6 (4 to 8) |
| Day 57 Lesion Count, Median (Range) | NR | NR | 1 (0 to 8) | 5 (0 to 10) |

AK = actinic keratosis; NR = not reported; SD = standard deviation.

**TABLE 24: PER CENT REDUCTION FROM BASELINE IN AK LESION COUNT AT DAY 57 IN HEAD STUDIES**

| | PEP005-016 | | PEP005-025 | |
|---|---|---|---|---|
| | Ingenol Mebutate (N = 135) | Vehicle (N = 134) | Ingenol Mebutate (N = 142) | Vehicle (N = 136) |
| n | 131 | 133 | 142 | 136 |
| Median (Range) | 83.3 (–50.0 to 100.0) | 0 (–100.0 to 100.0) | 86.6 (–25.0 to 100.0) | 0 (–100.0 to 100.0) |
| Baseline Lesion Count, Mean (SD) | 5.8 (1.3) | 5.4 (1.1) | 6.0 (1.4) | 5.9 (1.4) |
| Day 57 Lesion Count, Mean (SD) | 1.6 (1.8) | 4.5 (1.9) | 1.7 (2.3) | 5.2 (2.4) |
| Baseline Lesion Count, Median (Range) | 6 (4 to 8) | 5 (4 to 8) | 6 (4 to 8) | 6 (4 to 8) |
| Day 57 Lesion Count, Median (Range) | 1 (0 to 8) | 5 (0 to 9) | 1 (0 to 9) | 5 (0 to 14) |

AK = actinic keratosis; SD = standard deviation.

## Skindex-16 Dermatological Survey Scores

**TABLE 25: SKINDEX-16 DERMATOLOGICAL SURVEY SCORES AT BASELINE IN NON-HEAD STUDIES**

| | PEP005-014 | | PEP005-028 | |
|---|---|---|---|---|
| Skindex-16 Score | Ingenol Mebutate (N = 126) | Vehicle (N = 129) | Ingenol Mebutate (N = 100) | Vehicle (N = 103) |
| **Emotions** | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median (Range) | [redacted] | [redacted] | [redacted] | [redacted] |
| **Functioning** | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median (Range) | [redacted] | [redacted] | [redacted] | [redacted] |
| **Symptoms** | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median (Range) | [redacted] | [redacted] | [redacted] | [redacted] |

SD = standard deviation.

**TABLE 26: SKINDEX-16 DERMATOLOGICAL SURVEY SCORES AT BASELINE IN HEAD STUDIES**

| | PEP005-016 | | PEP005-025 | |
|---|---|---|---|---|
| Skindex-16 Score | Ingenol Mebutate (N = 135) | Vehicle (N = 134) | Ingenol Mebutate (N = 142) | Vehicle (N = 136) |
| **Emotions** | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median (Range) | [redacted] | [redacted] | [redacted] | [redacted] |
| **Functioning** | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median (Range) | [redacted] | [redacted] | [redacted] | [redacted] |
| **Symptoms** | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median (Range) | [redacted] | [redacted] | [redacted] | [redacted] |

SD = standard deviation.

**TABLE 27: SKINDEX-16 DERMATOLOGICAL SURVEY SCORES AT DAY 57 IN NON-HEAD STUDIES**

| | PEP005-014 | | PEP005-028 | |
|---|---|---|---|---|
| Skindex-16 Score | Ingenol Mebutate (N = 126) | Vehicle (N = 129) | Ingenol Mebutate (N = 100) | Vehicle (N = 103) |
| **Emotions** | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median (Range) | [redacted] | [redacted] | [redacted] | [redacted] |
| **Functioning** | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median (Range) | [redacted] | [redacted] | [redacted] | [redacted] |
| **Symptoms** | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median (Range) | [redacted] | [redacted] | [redacted] | [redacted] |

SD = standard deviation.

**TABLE 28: SKINDEX-16 DERMATOLOGICAL SURVEY SCORES AT DAY 57 IN HEAD STUDIES**

| | PEP005-016 | | PEP005-025 | |
|---|---|---|---|---|
| Skindex-16 Score | Ingenol Mebutate (N = 135) | Vehicle (N = 134) | Ingenol Mebutate (N = 142) | Vehicle (N = 136) |
| **Emotions** | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median (Range) | [redacted] | [redacted] | [redacted] | [redacted] |
| **Functioning** | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median (Range) | [redacted] | [redacted] | [redacted] | [redacted] |
| **Symptoms** | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median (Range) | [redacted] | [redacted] | [redacted] | [redacted] |

SD = standard deviation.

## Treatment Satisfaction Questionnaire for Medication Scores

**TABLE 29: TREATMENT SATISFACTION QUESTIONNAIRE FOR MEDICATION SCORE AT DAY 57 IN NON-HEAD STUDIES**

| | PEP005-014 | | PEP005-028 | |
|---|---|---|---|---|
| | Ingenol Mebutate (N = 126) | Vehicle (N = 129) | Ingenol Mebutate (N = 100) | Vehicle (N = 103) |
| **Effectiveness** | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| *P* Value | [redacted] | | [redacted] | |
| **Side Effects** | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| *P* Value | [redacted] | | [redacted] | |
| **Convenience** | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| *P* Value | [redacted] | | [redacted] | |
| **Global Satisfaction** | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| *P* Value | [redacted] | | [redacted] | |

SD = standard deviation.

**TABLE 30: TREATMENT SATISFACTION QUESTIONNAIRE FOR MEDICATION SCORE AT DAY 57 IN HEAD STUDIES**

| | PEP005-016 | | PEP005-025 | |
|---|---|---|---|---|
| | Ingenol Mebutate (N = 135) | Vehicle (N = 134) | Ingenol Mebutate (N = 142) | Vehicle (N = 136) |
| **Effectiveness** | | | | |
| n | | | | |
| Mean (SD) | | | | |
| *P* Value | | | | |
| **Side Effects** | | | | |
| n | | | | |
| Mean (SD) | | | | |
| *P* Value | | | | |
| **Convenience** | | | | |
| n | | | | |
| Mean (SD) | | | | |
| *P* Value | | | | |
| **Global Satisfaction** | | | | |
| n | | | | |
| Mean (SD) | | | | |
| *P* Value | | | | |

SD = standard deviation.

## Subgroup Analysis of Complete Clearance

**TABLE 31: SUBGROUP ANALYSES OF COMPLETE CLEARANCE RATE IN NON-HEAD STUDIES**

| PEP005-014 and PEP005-028 | | | |
|---|---|---|---|
| | Complete Clearance, n/N (95% CI) | | |
| | Ingenol Mebutate, 0.05% (N = 226) | Vehicle (N = 232) | Risk Difference (95% CI)[a] |
| **Prior Cryotherapy** | | | |
| Yes | 54/170 (31.8) (24.8 to 39.3) | 7/178 (3.9) (1.6 to 7.9) | 27.8 (20.3 to 35.4) |
| No | 23/56 (41.1) (28.1 to 55.0) | 4/54 (7.4) (2.1 to 17.9) | 33.7 (19.0 to 48.3) |
| **Prior Imiquimod** | | | |
| Yes | 10/21 (47.6) (25.7 to 70.2) | 1/32 (3.1) (0.1 to 16.2) | 44.5 (22.3 to 66.7) |
| No | 67/205 (32.7) (26.3 to 39.6) | 10/200 (5.0) (2.4 to 9.0) | 27.7 (20.6 to 34.8) |
| **Prior 5-FU** | | | |
| Yes | 18/50 (36.0) (22.9 to 50.8) | 2/56 (3.6) (0.4 to 12.3) | 32.4 (18.3 to 46.6) |
| No | 59/176 (33.5) (26.6 to 41.0) | 9/176 (5.1) (2.4 to 9.5) | 28.4 (20.7 to 36.1) |

5-FU = 5-flurorouracil; CI = confidence interval.
[a] Calculated by CADTH.

**TABLE 32: SUBGROUP ANALYSES OF COMPLETE CLEARANCE RATE IN HEAD STUDIES**

| PEP005-016 and PEP005-025 | | | |
|---|---|---|---|
| | Complete Clearance, n/N (95% CI) | | |
| | Ingenol Mebutate, 0.015% (N = 277) | Vehicle (N = 270) | Risk Difference (95% CI)[a] |
| **Prior Cryotherapy** | | | |
| Yes | 90/224 (40.2) (33.7 to 46.9) | 10/227 (4.4) (2.1 to 8.0) | 35.7 (28.8 to 42.7) |
| No | 27/53 (50.9) (36.8 to 64.9) | 0/43 (0.0) (–, 8.2) | 50.9 (37.3 to 64.6) |
| **Prior Imiquimod** | | | |
| Yes | 9/25 (36.0) (18.0 to 57.5) | 3/31 (9.7) (2.0 to 25.8) | 26.3 (4.8 to 47.8) |
| No | 108/252 (42.9) (36.7 to 49.2) | 7/239 (2.9) (1.2 to 5.9) | 39.9 (33.5 to 46.4) |
| **Prior 5-FU** | | | |
| Yes | 15/55 (27.3) (16.1 to 41.0) | 2/52 (3.8) (0.5 to 13.2) | 23.4 (10.6 to 36.3) |
| No | 102/222 (45.9) (39.3 to 52.7) | 8/218 (3.7) (1.6 to 7.1) | 42.3 (35.3 to 49.3) |

5-FU = 5-flurorouracil; CI = confidence interval.
[a] Calculated by CADTH.

## Harms

**TABLE 33: HARMS FOR NON-HEAD STUDIES**

| | PEP005-014 | | PEP005-028 | |
|---|---|---|---|---|
| | Ingenol Mebutate (N = 125) | Vehicle (N = 129) | Ingenol Mebutate (N = 100) | Vehicle (N = 103) |
| **AEs** | | | | |
| Subjects with > 0 AEs, N (%) | 40 (32.0) | 37 (28.7) | 35 (35.0) | 26 (25.2) |
| **Most Common AEs**[a] | | | | |
| Infections and infestations | 11 (8.8) | 12 (9.3) | 4 (4.0) | 3 (2.9) |
| General disorder and administration site conditions | 5 (4.0) | 0 | 24 (24.0) | 6 (5.8) |
| Cardiac disorders | 7 (5.6) | 6 (4.7) | 0 | 2 (1.9) |
| Investigations | 7 (5.6) | 6 (4.7) | 3 (3.0) | 3 (2.9) |
| Benign, malignant, and unspecified neoplasms | 3 (2.4) | 6 (4.7) | 3 (3.0) | 5 (4.9) |
| Skin and subcutaneous tissue disorders | 7 (5.6) | 6 (4.7) | 4 (4.0) | 1 (1.0) |
| Injury, poisoning, and procedural complications | 5 (4.0) | 2 (1.6) | 3 (3.0) | 1 (1.0) |
| Respiratory, thoracic, and mediastinal disorders | 3 (2.4) | 2 (1.6) | 2 (2.0) | 4 (3.9) |
| Musculoskeletal and connective tissue disorders | 3 (2.4) | 2 (1.6) | 3 (3.0) | 1 (1.0) |
| **TRAEs** | | | | |
| Subjects with > 0 TRAEs, N (%) | 7 (5.6) | 1 (0.8) | 22 (22.0) | 1 (1.0) |
| **Most Common AEs**[a] | | | | |
| General disorders and administration site conditions | 5 (4.0) | 0 | 20 (20.0) | 1 (1.0) |
| Skin and subcutaneous tissue disorders | 2 (1.6) | 0 | 3 (3.0) | 0 |
| **SAEs** | | | | |
| Subjects with > 0 SAEs, N (%) | 1 (0.8) | 3 (2.3) | 2 (2.0) | 2 (1.9) |
| **WDAEs** | | | | |
| WDAEs, N (%) | 2 (1.6) | 1 (0.8) | 0 | 1 (1.0) |
| **Deaths** | | | | |
| Number of deaths, N (%) | 0 | 0 | 0 | 0 |

AE = adverse event; SAE = serious adverse event; TRAE = treatment-related adverse event; WDAE = withdrawal due to adverse event.
Note: Outcomes identified as important to the review (see Table 2 for review protocol).
[a]Frequency ≥ 3%.

**TABLE 34: HARMS FOR HEAD STUDIES**

| | PEP005-016 | | PEP005-025 | |
|---|---|---|---|---|
| | Ingenol Mebutate (N = 132) | Vehicle (N = 135) | Ingenol Mebutate (N = 142) | Vehicle (N = 136) |
| **AEs** | | | | |
| Subjects with > 0 AEs, N (%) | 62 (47.0) | 31 (23.0) | 40 (28.2) | 29 (21.3) |
| **Most Common AEs**[a] | | | | |
| General disorder and administration site conditions | 32 (24.2) | 4 (3.0) | 20 (14.1) | 3 (2.2) |
| Infections and infestations | 14 (10.6) | 8 (5.9) | 6 (4.2) | 4 (2.9) |
| Injury, poisoning, and procedural complications | 6 (4.5) | 9 (6.7) | 4 (2.8) | 6 (4.4) |
| Nervous system disorders | 7 (5.3) | 4 (3.0) | 4 (2.8) | 2 (1.5) |
| Skin and subcutaneous tissue disorders | 7 (5.3) | 3 (2.2) | 2 (1.4) | 0 |
| Investigations | 3 (2.3) | 5 (3.7) | 2 (1.4) | 3 (2.2) |
| Eye disorders | 5 (3.8) | 1 (0.7) | 5 (3.5) | 1 (0.7) |
| **TRAEs** | | | | |
| Subjects with > 0 TRAEs, N (%) | 46 (34.8) | 7 (5.2) | 26 (18.3) | 4 (2.9) |
| **Most Common AEs**[a] | | | | |
| General disorders and administration site conditions | 31 (23.5) | 3 (2.2) | 20 (14.1) | 1 (0.7) |
| Nervous system disorders | 5 (3.8) | 1 (0.7) | 0 | 0 |
| Eye disorders | 5 (3.8) | 0 | 4 (2.8) | 1 (0.7) |
| Infections and infestations | 5 (3.8) | 0 | 2 (1.4) | 0 |
| Skin and subcutaneous tissue disorders | 5 (3.8) | 0 | 0 | 0 |
| **SAEs** | | | | |
| Subjects with > 0 SAEs, N (%) | 2 (1.5) | 2 (1.5) | 1 (0.7) | 0 |
| **WDAEs** | | | | |
| WDAEs, N (%) | 1 (0.8) | 1 (0.7) | 2 (1.4) | 0 |
| **Deaths** | | | | |
| Number of deaths, N (%) | 0 | 0 | 0 | 0 |
| **Notable Harms** | | | | |
| Application site or skin AE | 40 (30.3) | 5 (3.7) | 22 (15.5) | 1 (0.7) |
| Ocular AEs | 5 (3.8) | 1 (0.7) | 5 (3.5) | 1 (0.7) |

AE = adverse event; SAE = serious adverse event; TRAE = treatment-related adverse event; WDAE = withdrawal due to adverse event.
Note: Outcomes identified as important to the review (see Table 2 for review protocol).
[a]Frequency ≥ 3%.

## Local Skin Response Scores

**TABLE 35: LOCAL SKIN RESPONSE SCORES FOR NON-HEAD STUDIES**

| LSR Score, Mean (SD) | PEP005-014 | | PEP005-028 | |
|---|---|---|---|---|
| | Ingenol Mebutate (N = 125) | Vehicle (N = 129) | Ingenol Mebutate (N = 100) | Vehicle (N = 103) |
| **Baseline** | 1.0 (1.14) | 1.0 (1.13) | 1.00 (1.25) | 1.30 (1.51) |
| **Day 3** | 4.9 (2.96) | 1.1 (1.31) | 6.34 (3.25) | 1.33 (1.46) |
| **Day 8** | 5.4 (3.63) | 1.1 (1.21) | 6.11 (3.54) | 1.39 (1.49) |
| **Day 15** | 3.4 (2.20) | 1.1 (1.25) | 4.06 (2.21) | 1.17 (1.13) |
| **Day 29** | 1.6 (1.61) | 0.9 (1.04) | 1.51 (1.29) | 1.20 (1.30) |
| **Day 57** | 0.8 (1.50) | 0.7 (0.93) | 0.72 (0.84) | 1.02 (1.06) |

LSR = local skin response; SD = standard deviation.

**TABLE 36: LOCAL SKIN RESPONSE SCORES FOR HEAD STUDIES**

| LSR Score, Mean (SD) | PEP005-016 | | PEP005-025 | |
|---|---|---|---|---|
| | Ingenol Mebutate (N = 132) | Vehicle (N = 135) | Ingenol Mebutate (N = 142) | Vehicle (N = 136) |
| **Baseline** | 1.72 (1.74) | 1.21 (1.19) | 1.14 (1.17) | 1.08 (1.14) |
| **Day 4** | 9.47 (4.13) | 1.35 (1.36) | 8.08 (4.13) | 1.17 (1.26) |
| **Day 8** | 6.21 (3.60) | 1.42 (1.33) | 5.42 (3.64) | 1.12 (1.28) |
| **Day 15** | 1.93 (1.36) | 1.22 (1.27) | 1.94 (1.92) | 1.10 (1.06) |
| **Day 29** | 1.08 (1.06) | 1.17 (1.30) | 1.09 (1.31) | 1.00 (1.00) |
| **Day 57** | 0.80 (0.97) | 1.23 (1.48) | 0.55 (0.90) | 0.84 (0.95) |

LSR = local skin response; SD = standard deviation.

# APPENDIX 5: VALIDITY OF OUTCOME MEASURES

### Aim

To summarize the validity of the following outcome measures:

- Skindex-16 questionnaire
- TSQM.

### Findings

| Instrument | Type | Validated? | MCID | References |
|---|---|---|---|---|
| Skindex-16 | 0 to 100 score for each scale | Yes | Unknown | Chren et al. (2001)[32]<br>Chren et al. (2012)[33] |
| TSQM | 0 to 100 score for each scale | Yes | Unknown | Atkinson et al. (2004)[34] |

HRQoL = health-related quality of life; MCID = minimum clinically important difference; TSQM = Treatment Satisfaction Questionnaire for Medication.

### Skindex-16

The Skindex-16 questionnaire is a generic health-related quality-of-life instrument that, according to the developers, can be used with skin diseases of any sort.[33] The questionnaire is self-administered and is intended for an adult population. Skindex-16 consists of 16 items with a recall period of four weeks. Skindex-16 has three domains that address symptoms (four items), emotions (seven items), and functioning (five items). Using a continuous bipolar scale anchored by seven boxes with the words "Never Bothered" and "Always Bothered" at each end, item scores are transformed to a linear scale (0 to 100, with 0 representing "never bothered" and 100 representing "always bothered").[33] Domain scores are calculated as the average of the transformed item scores. A total score is calculated as the average of all 16 items.

Skindex-16 was developed in 2001 by Chren et al. (2001).[32] The Skindex-16 questionnaire is a refined version of the original 65-item Skindex-65 and the 29-item Skindex-29.[33] Skindex-16 includes additional items that were not included in Skindex-29, as well as the items that had the best performance in the previous versions. The validation study[32] assessed the questionnaire among 692 patients waiting for dermatology appointments in clinics. A total of 64 participants reported having AK as their primary dermatologic diagnosis. Among participants with AK, the mean (± standard deviation [SD]) for the "Symptoms" domain was 24 (± 23), 35 (± 29) for the "Emotions" domain, and 14 (± 23) for the "Functioning" domain. The author concluded that scores for each domain were reproducible after 72 hours (Pearson correlation coefficient = 0.88 to 0.90) and internally reliable (Cronbach's alpha = 0.86 to 0.93). Furthermore, the instrument demonstrated content and construct validity as items in the questionnaire captured information from an open-ended item, "What is it about your skin problem that bothers you the most?" For patients who reported that their skin had improved or remained the same, mean domain scores were consistent with these changes.

Skindex-16 appears to be adaptable cross-culturally as Higaki et al. (2002)[35] revealed similar results with the Japanese version. One hundred patients and 30 healthy adults responded to the Japanese Skindex-16. Similar to Chren et al. (2001),[32] Higaki et al. (2002)[35] concluded that scores for each domain were internally reliable (Cronbach's alpha = 0.83 to 0.92), while also revealing strong construct and content validity. As expected, mean global scores (± SD) for healthy adults (1 ± 2) were lower than scores

for dermatological patients (36 ± 23) (P < 0.001). No MCID for this scale was identified by CDR for patients being treated for AK.

### Treatment Satisfaction Questionnaire for Medication

The TSQM is a generic instrument that measures patients' satisfaction with medication and can be used with diseases of any sort according to the developers.[34] The questionnaire is self-administered and is intended for an adult population. The TSQM consists of 14 items with a recall period of two to three weeks or since the last medication use. The TSQM has four domains that address effectiveness (three items), side effects (five items), convenience (three items), and global satisfaction (three items). Using a continuous bipolar scale anchored by seven boxes with the words "Extremely Satisfied" and "Extremely Dissatisfied" at each end, item scores are summed within domains and transformed to a linear scale of 0 to 100 (with higher scores representing higher satisfaction in each domain).[34]

The TSQM was developed by Atkinson et al. (2004).[34] The validation study assessed the questionnaire among 567 patients from eight diverse patient groups (arthritis, asthma, major depression, type I diabetes, high cholesterol, hypertension, migraine, and psoriasis). Patients were recruited from a national longitudinal panel study of chronic illness and were randomized to complete the questionnaire using either Visual Analogue or Likert-type scaling methods. Statistical analyses supported the reliability and construct validity of the TSQM. Two separate multi-step exploratory factor analyses were employed. Overall, the four domains possessed good psychometric properties, and the Likert-type scaling method was superior to the Visual Analogue Scale method. Statistically significant differences in TSQM scores were found when factors such as level of illness severity, length and time on medication, and route of medication administration were assessed. No MCID for the TSQM was identified by CDR for patients being treated for AK.

### Conclusions

Both the Skindex-16 and the TSQM are validated patient-reported instruments. Evidence of both instruments suggests that they are valid and reliable, though no evidence was found validating their use in AK specifically. Furthermore, no MCID for either instrument was identified.

# APPENDIX 6: LONG-TERM EFFICACY AND HARMS FROM EXTENSION STUDIES

### Aim

Additional information on the safety and tolerability of ingenol mebutate is available from two long-term observational follow-up studies; PEP005-030[25] and PEP005-032.[27] The results of the trials are summarized in this section to complement the information derived from short-term RCTs.

### Findings

Studies PEP005-030[25] and PEP005-032[27] were multicentre, 12-month observational follow-up studies which assessed the efficacy and safety of ingenol mebutate in the treatment of AK.

Patients with face or scalp AK, treated with 0.015% ingenol mebutate or vehicle gel for three days, were eligible to participate in PEP005-030[25] if they achieved complete clearance of lesions in the target treatment area at day 57 in PEP005-016[12] and PEP005-025.[13] A total of 117 (108 in the ingenol mebutate group and 9 in the vehicle group) of the 127 participants in PEP005-016[12] and PEP005-025[13] that achieved complete clearance at day 57 were enrolled in the follow-up study. One hundred eight participants (92.3%) completed the study through the 12-month follow-up assessment.

Patients with AK in non-head locations (trunk and extremities) treated with 0.05% ingenol mebutate or vehicle gel for two days were eligible to participate in in PEP005-032 if they achieved complete clearance of lesions in the selected treatment area by day 57 in PEP005-028.[14] A total of 43 (38 in the ingenol mebutate group and 5 in the vehicle group) of the 47 participants in PEP005-028[14] that achieved complete clearance at day 57 were enrolled in the follow-up study. Forty-two participants (97.7%) completed the study through the 12-month follow-up assessment.

Recurrence was defined as any identified AK lesion in the target treatment area in patients who achieved complete clearance at day 57 in the previous studies. The frequency of recurrence with 95% confidence intervals was estimated by the Kaplan-Meier method, at days 91 (3-month follow-up), 183 (6-month follow-up), 274 (9-month follow-up), and 365 (12-month follow-up).

### Study PEP005-030[25]

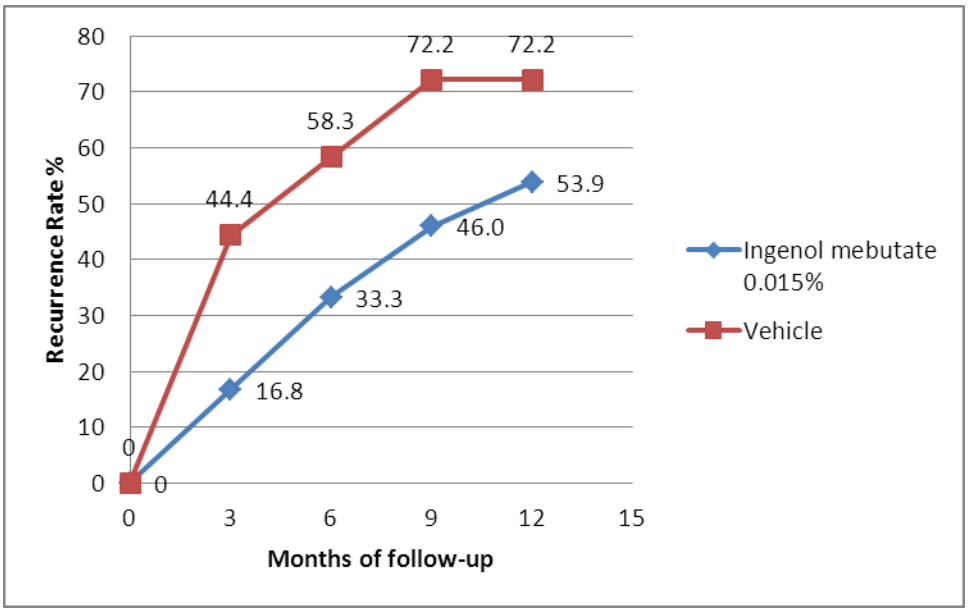
Of patients with face or scalp AK treated with ingenol mebutate who attained complete clearance (n = 108), an estimated 53.9% (95% CI 44.3 to 63.5) experienced a recurrence within 12 months of follow-up (Table 37). The estimated median (interquartile range [IQR]) time to recurrence was 365 (183 to > 365) days. Among the vehicle treatment group (N = 9), an estimated 72.2% (95% CI, 40.5 to 103.9) experienced a recurrence (Table 37). The estimated median (IQR) time to recurrence was 183 (91 to > 183) days. One adverse event, mild sunburn, which was deemed unrelated to the study drug, was reported during the 12-month follow-up.

**TABLE 37: RECURRENCE IN PATIENTS RECEIVING 0.015% INGENOL MEBUTATE AND VEHICLE IN PEP005-030**

| Previous Treatment in PEP005-016[12] and PEP005-025[13] | | | | | | |
|---|---|---|---|---|---|---|
| | Ingenol Mebutate 0.015% | | | Vehicle | | |
| Follow-Up | N[a] | Recurrence (%)[a] | 95% CI | N | Recurrence (%)[b] | 95% CI |
| 3 months | 107 | 16.8 | 9.7 to 23.9 | 9 | 44.4 | 12.0 to 76.9 |
| 6 months | 86 | 33.3 | 24.2 to 42.3 | 4 | 58.3 | 24.4 to 92.2 |
| 9 months | 68 | 46.0 | 36.4 to 55.6 | 3 | 72.2 | 40.5 to 103.9 |
| 12 months | 55 | 53.9 | 44.3 to 63.5 | 2 | 72.2 | 40.5 to 103.9 |

CI = confidence interval.
[a] N = number of patients at risk at the start of the visit window.
[b] Frequency of recurrence estimated by the Kaplan-Meier method.
Source: Clinical Study Report.[25]

**FIGURE 3: OVERALL RECURRENCE IN PATIENTS RECEIVING 0.015% INGENOL MEBUTATE AND VEHICLE IN PEP005-030[25]**




## Study PEP005-032[27]

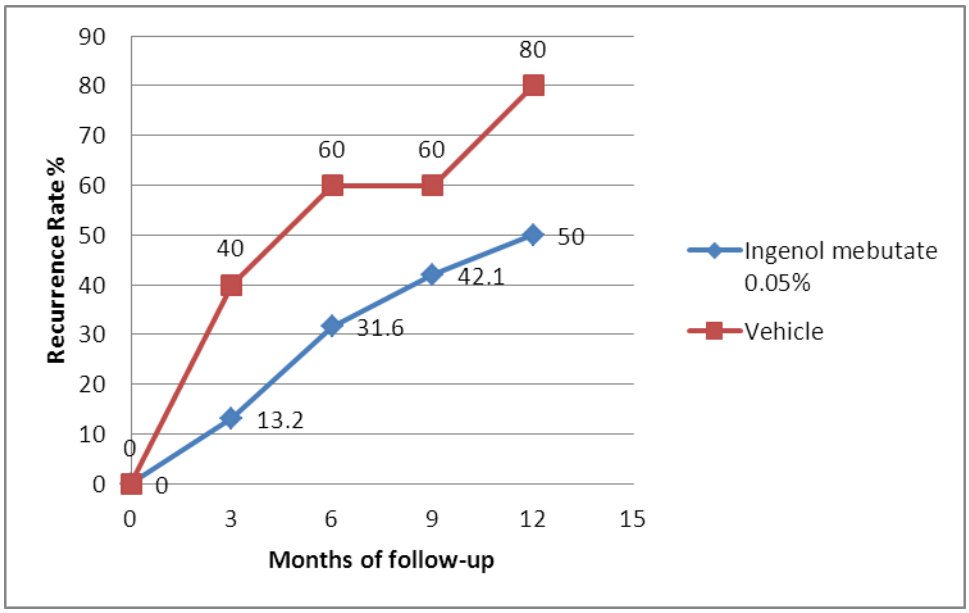
Of patients with AK treated with ingenol mebutate on non-head locations (trunk and extremities) who attained complete clearance (n = 38), an estimated 50% (95% CI, 34.1 to 65.9) experienced a recurrence within 12 months of follow-up (Table 38). The estimated median (IQR) time to lesion recurrence was greater than 183 (183 to > 183) days. Among the vehicle treatment group (N = 5), an estimated 80% (95% CI, 44.9 to 100.0) experienced recurrence (Table 38). The estimated median (IQR) time to lesion recurrence was 183 (91 to 365) days. One adverse event, a mild rash, which was deemed unrelated to the study drug, was reported during the 12-month follow-up.

**TABLE 38: RECURRENCE IN PATIENTS RECEIVING 0.05% INGENOL MEBUTATE AND VEHICLE IN PEP005-032**

| Previous Treatment in PEP005-028[14] | | | | | | |
|---|---|---|---|---|---|---|
| | Ingenol Mebutate 0.05% | | | Vehicle | | |
| Follow-Up | N[a] | Recurrence (%)[b] | 95% CI | N[a] | Recurrence (%)[b] | 95% CI |
| 3 months | 38 | 13.2 | 2.4, 23.9 | 5 | 40.0 | 0.0 to 82.9 |
| 6 months | 33 | 31.6 | 16.8, 46.4 | 3 | 60.0 | 17.1 to 100.0 |
| 9 months | 26 | 42.1 | 26.4, 57.8 | 2 | 60.0 | 17.1 to 100.0 |
| 12 months | 22 | 50.0 | 34.1, 65.9 | 2 | 80.0 | 44.9 to 100.0 |

CI = confidence interval.
[a]N = number of patients at risk at the start of the visit window.
[b]Frequency of recurrence estimated by the Kaplan-Meier method.
Source: Clinical Study Report[27]

**FIGURE 4: OVERALL RECURRENCE RATE OF INDIVIDUALS RECEIVING 0.05% INGENOL MEBUTATE AND VEHICLE IN PEP005-032[27]**




## Conclusion

The overall results of the follow-up studies suggest that recurrence is common among participants treated with ingenol mebutate and that treatment is well-tolerated by participants, with minimal adverse events being reported. The follow-up studies are limited by the ability to track specific lesions over a period of time and an uncertainty regarding whether lesions were recurring or were new lesions. The limited number of participants in the vehicle groups of PEP005-030[25] and PEP005-032[27] do not support between-group comparisons of safety and efficacy during the 12-month study.

# APPENDIX 7: SUMMARY OF COMPARATORS

**Aim**

To provide a summary of the efficacy and safety of topical comparator agents indicated for the treatment of AK.

**Summary of Study Characteristics**

Gupta et al. (2012)[21] reported on a systematic review of numerous treatments for AK. This summary of the findings of the systematic review is specific to 5-FU 5% and imiquimod (5%, 3.75%, and 2.5%). The systematic review[21] included 20 RCTs published between 2002 and 2010 that compared imiquimod (5%, 3.75%, and 2.5%) with placebo (18 studies) and imiquimod 5% with 5-FU 5% (two studies). Of the 18 studies comparing imiquimod with placebo, 15 used a 5% dose of imiquimod, 3 included a dose of 3.75%, and 2 included a dose of 2.5%. Three of the 15 studies comparing imiquimod 5% with placebo, two of which included an intra-individual design wherein patients applied imiquimod to lesions on one side of the body and vehicle cream to the other side, and one which included only immunosuppressed participants (organ transplant recipients), are not discussed, given that they were excluded from the pooled analyses and did not measure primary outcomes. There were no studies which compared 5-FU 5% with placebo. The participant characteristics in the included trials were generally similar. All studies included adult participants, with the majority being males with mean ages between 60 and 70 years.

Twelve studies comparing imiquimod 5% with placebo targeted the face, scalp, trunk, and extremities, with the number of doses per week ranging from two to seven. The duration of treatment ranged from 3 to 16 weeks and the total number of doses ranged from 9 to 56. The time of assessment ranged from immediately following treatment to eight weeks after the end of treatment. Proportion of patients achieving complete clearance and withdrawal due to adverse events were assessed in these studies (Table 39).

Three studies comparing imiquimod 3.75% with placebo targeted the face or scalp with all studies using seven doses per week. The duration of treatment ranged from four to six weeks and the total number of doses ranged from 28 to 42. The time of assessment ranged from 8 to 20 weeks after end of treatment. Proportion of patients achieving complete clearance and per cent mean reduction in lesion counts were assessed in these studies. Withdrawal due to adverse events was only assessed in two of the three studies (Table 39). Two of the three studies also compared imiquimod 2.5% with placebo.

Two trials comparing imiquimod 5% with 5-FU 5% targeted the head, neck, face, or scalp. The two trials used different dosing regimens which are summarized in Table 39. Assessments for both treatments were performed eight weeks after end of treatment. The proportion of patients achieving complete clearance, and withdrawal due to adverse events was assessed in both studies, while the mean per cent reduction in lesion count was reported for one of the two studies.

**TABLE 39: SUMMARY OF INCLUDED STUDY CHARACTERISTICS**

| Study | Doses per Week | Number of Weeks | Assessment Time | Anatomical Locations |
|---|---|---|---|---|
| **Imiquimod 5% Versus Placebo** | | | | |
| Chen et al., 2003[36] | 3 | 3 or 6 | At the end of the 12- week treatment | Face, forehead and temples, cheeks |
| Gebauer et al., 2009[37] | 2, 3, 5, 7 | 8 | 8 weeks after end of treatment | Dorsal of one or both forearms and hands |
| Korman et al., 2005[38] | 3 | 16 | 8 weeks after end of treatment | Face or bald scalp |
| Lebwohl et al., 2004[39] | 2 | 16 or less | 8 weeks after end of treatment | Face or scalp |
| NCT00828568 Aldara[40] | 2 | 16 | 8 weeks after end of treatment | Face or bald scalp |
| NCT00828568 Taro[40] | 2 | 16 | 8 weeks after end of treatment | Face or bald scalp |
| Ooi et al., 2006[41] | 3 | 16 or less | At the end of treatment | Scalp, extremities, or upper trunk |
| Stockfleth et al., 2002[42] | 3 | 12 or less | At the end of the 12- week treatment | Face, scalp, forehead, dorsal forearm, neck, back of hands |
| Szeimies et al., 2004[43] | 3 | 16 or less | 8 weeks after end of treatment | Face or bald scalp |
| Alomar et al., 2007[44] | 3 | 4 or 8 | 4 weeks after end of treatment | Face or bald scalp |
| Jorizzo et al., 2007[45] | 3 | 4 or 8 | 8 weeks after end of treatment | Face or bald scalp |
| **Imiquimod 3.75% Versus Placebo** | | | | |
| Hanke et al., 2010[46] | 7 | 6 (3 on , 3 off, 3 on) | 8 weeks after end of treatment | Face or bald scalp |
| Jorizzo et al., 2010[47] | 7 | 4 (2 on, 2 off, 2 on) | 20 weeks after end of treatment | Face |
| Swanson et al., 2010a[48] | 7 | 4 (2 on, 2 off, 2 on) | 8 weeks after end of treatment | Face or bald scalp |
| **Imiquimod 2.5% Versus Placebo** | | | | |
| Hanke et al., 2010[46] | 7 | 6 (3 on , 3 off, 3 on) | 8 weeks after end of treatment | Face or bald scalp |
| Swanson et al., 2010a[48] | 7 | 4 (2 on, 2 off, 2 on) | 8 weeks after end of treatment | Face or bald scalp |
| **5-FU 5% Versus Imiquimod 5%** | | | | |
| Krawtchenko et al., 2007[49] | Imiquimod: 3<br>5-FU: 14 | Imiquimod: 8 (4 on, 4 off)<br>5-FU: 4 | Imiquimod: 8 weeks<br>5-FU: 4 weeks | Head, neck or décolleté |
| Tanghetti et al., 2007[50] | Imiquimod: 2<br>5-FU: 14 | Imiquimod: 16<br>5-FU: 2 to 4 | 8 weeks after end of treatment | Face, forehead, or scalp |

5-FU = 5-fluorouracil.

**Summary of Findings**

Gupta et al. (2012)[21] reported that imiquimod 5% was favoured over placebo for complete clearance of AK based on pooled results from nine RCTs (n = 1,871, risk ratio [RR] 7.70 95%CI, 4.63 to 12.79) (Table 40). Complete clearance rates ranged from 5% to 84 % among the imiquimod 5% groups and 0% to 10% among the placebo groups. In eight RCTs, withdrawal due to adverse events was significantly higher in the 5% imiquimod group when compared with placebo (n = 2,290, RR 2.59, 95% CI, 1.59 to 4.23). The proportion of individuals who withdrew from the study due to adverse events ranged from 1.6% to 18.3% among the imiquimod 5% groups and 0% to 4% among the placebo groups.

Imiquimod 3.75% was favoured over placebo for complete clearance of AK (Table 40). Three RCTs provided pooled data for complete clearance (n = 730, RR 6.45, 95% CI, 3.87 to 10.73). Complete clearance rates ranged from 34.0% to 35.6% among the imiquimod 3.75% groups and 4.9% to 6.3% among the placebo groups. In two RCTs (n = 483), the difference in withdrawal due to adverse events was not statistically significantly different between imiquimod 3.75% and placebo based on pooled data.

Imiquimod 2.5% was favoured over placebo for complete clearance of AK (Table 40). Two RCTs provided pooled data for complete clearance (n = 486, RR 4.49, 95% CI, 2.40 to 8.39). Complete clearance rates ranged from 25.0% to 30.6% among the imiquimod 2.5% groups and 6.1% to 6.3% among the placebo groups. The incidence of withdrawal due to adverse events did not differ statistically between treatments.

Results of the two trials comparing imiquimod 5% with 5-FU 5% for complete clearance were not pooled due to the high level of heterogeneity between the trials ($I^2$ statistic = 93%). Variability in the dosing regimens employed in the two trials may partially explain the considerable disparity in results, wherein one trial reported statistical significance favouring 5-FU 5% over imiquimod 5% for complete clearance (n = 39, RR 0.31, 95% CI, 0.14 to 0.67) and the other trial reported no statistically significant between-treatment difference.

**TABLE 40: SUMMARY OF POOLED ANALYSES FROM GUPTA ET AL. (2012)**

| Study | Number Of Participants | Complete Clearance Rate n/N (%) | | Withdrawal Due to Adverse Events n/N (%) | |
|---|---|---|---|---|---|
| | | Imiquimod | Placebo | Imiquimod | Placebo |
| **Imiquimod 5% Versus Placebo** | | | | | |
| Chen et al., 2003[36] | 39 | 8/29 (27.6) | 1/10 (10.0) | NA | |
| Gebauer et al., 2009[37] | 149 | 6/120 (5.0) | 0/29 (0) | 22/120 (18.3) | 0/29 (0) |
| Korman et al., 2005[38] | 492 | 117/242 (48.3) | 18/250 (7.2) | 23/242 (9.5) | 10/250 (4.0) |
| Lebwohl et al., 2004[39] | 436 | 97/215 (45.1) | 7/221 (3.2) | 7/215 (3.3) | 2/221 (0.9) |
| NCT00828568 Aldara[40] | 213 | 74/180 (41.1) | 3/30 (10.0) | 11/183 (6.0) | 1/30 (3.3) |
| NCT00828568 Taro[40] | 209 | 64/176 (36.4) | 3/30 (10.0) | 8/179 (4.5) | 1/30 (3.3) |
| Ooi et al., 2006[41] | 17 | 5/11 (45.5) | 0/6 (0) | NA | |
| Stockfleth et al., 2002[42] | 36 | 21/25 (84.0) | 0/11 (0) | NA | |
| Szeimies et al., 2004[43] | 286 | 84/147 (57.1) | 3/139 (2.2) | 15/147 (10.2) | 4/139 (2.9) |
| Alomar et al., 2007[44] | 259 | NA | | 2/129 (1.6) | 0/130 (0) |
| Jorizzo et al., 2007[45] | 246 | NA | | 2/123 (1.6) | 2/123 (1.6) |
| Pooled analysis Effect size (95% CI) | | N = 1,871 (9 studies) RR 7.70 (4.63 to 12.79) | | N = 2,290 (8 studies) RR 2.59 (1.59 to 4.23) | |
| **Imiquimod 3.75% Versus Placebo** | | | | | |
| Hanke et al., 2010[46] | 244 | 55/162 (34.0) | 4/82 (4.9) | 4/162 (2.5) | 1/82 (1.2) |
| Jorizzo et al., 2010[47] | 247 | 43/126 (34.1) | 6/121 (5.0) | NA | |
| Swanson et al., 2010a[48] | 239 | 57/160 (35.6) | 5/79 (6.3) | 2/160 (1.3) | 2/79 (2.5) |
| Pooled analysis Effect size (95% CI) | | N = 730 (3 studies) RR 6.45 (3.87 to 10.73) | | N = 483 (2 studies) RR 0.92 (0.22 to 3.93) | |
| **Imiquimod 2.5% Versus Placebo** | | | | | |
| Hanke et al., 2010[46] | 246 | 41/164 (25.0) | 5/82 (6.1) | 2/164 (1.2) | 1/82 (1.2) |
| Swanson et al., 2010a[48] | 240 | 49/160 (30.6) | 5/80 (6.3) | 1/160 (0.6) | 2/80 (2.5) |
| Pooled analysis Effect size (95% CI) | | N = 486 (2 studies) RR 4.49 (2.40 to 8.39) | | N = 486 (2 studies) RR 0.50 (0.09 to 2.70) | |
| **Imiquimod 5% Versus 5-FU 5%** | | | | | |
| | | **Imiquimod** | **5-FU** | **Imiquimod** | **5-FU** |
| Krawtchenko et al., 2007[49] | 50 | 22/26 (84.6) | 23/24 (95.8) | 0/26 | 0/24 (0) |
| Tanghetti et al., 2007[50] | 39 | 5/19 (26.3) | 17/20 (85.0) | 0/19 | 0/20 (0) |
| Pooled analysis Effect size (95% CI) | NA | | | | |

CI = confidence interval; 5-FU = 5-fluorouracil; NA = not applicable; RR = risk ratio.
Source: Gupta et al. (2012).[21]

### Critical Appraisal of Systematic Review

We assessed the systematic review methods used by Gupta et al. using the AMSTAR instrument. The systematic review included a comprehensive literature search, and study selection and data extraction were performed by two independent reviewers. A list of included and excluded studies was provided and the scientific quality of the included studies was assessed and documented. The systematic review was limited by the heterogeneity and low methodological quality of the included studies. Several studies did not distinguish between the physical locations of the AK lesion on the body. The authors of the systematic review reported the possibility of performance, detection, attrition, and reporting biases in numerous studies that compared imiquimod with placebo and 5-FU. Results should therefore be interpreted with caution.

Complete clearance rates and withdrawals due to adverse events for the imiquimod 5% studies varied, and were likely reflective of the heterogeneity of the dosing regimens, assessment periods, and treatment locations. The majority of trials assessing complete clearance of AK lesions using imiquimod 5% used two or three doses per week, typically over 16 weeks or less, targeted the face or bald scalp, and participants were assessed eight weeks after the end of treatment. Two studies that demonstrated different results were Gebauer et al. (2009)[37] and Stockfleth et al. (2002.)[42]

Compared with the other studies, Gebauer et al. (2009)[37] reported lower clearance rates among both groups and more withdrawals due to adverse events among the imiquimod 5% group. Gebauer et al. (2009)[37] included four groups receiving two, three, five, and seven doses of imiquimod 5% per week over eight weeks and targeted the dorsal of one or both forearms and hands. The study had an overall low risk of bias. Potential sources of bias included uncertainty regarding allocation concealment, and although the study was double-blinded for the intervention versus control, it was not blinded for the frequency of application. Imiquimod appeared to be most effective in Stockfleth et al. (2002),[42] though the study included a small sample size (n = 36) with patients assessed immediately after the 12-week treatment period, and included lesions on the head, neck, forearms, and hands. The study had an overall low risk of bias though there was insufficient detail regarding the method used to generate the allocation sequence.

Only three studies[39,40] were consistent with the Health Canada recommended dosing regimen of imiquimod 5% (twice weekly for 16 weeks).[22] Two studies[47,48] were consistent with the Health Canada recommended dosing regimen of imiquimod 3.75% and 2.5% (once daily for two treatment cycles of two weeks each, separated by a two-week no-treatment period).[23] Only Tanghetti et al. (2007)[50] followed the Health Canada recommended dosing regimens for both imiquimod 5% and 5-FU 5%. Since few studies were consistent with Health Canada dosing regimens, the generalizability of these results in Canada is uncertain.

## Conclusions

A recent systematic review of treatments for AK by Gupta et al. (2012)[21] reported that, compared with placebo, imiquimod (5%, 3.75%, and 2.5%) produced a statistically significantly greater proportion of patients achieving complete clearance. Withdrawals due to adverse events were more common with a higher dose of imiquimod (5%) when compared with placebo, while there was no statistically significant difference in withdrawal due to adverse events when lower doses (3.75% and 2.5%) of imiquimod were compared with placebo. There is insufficient evidence to support the superiority of 5-FU over imiquimod for the treatment of AK given the conflicting results from two small trials. The systematic review identified no RCTs comparing 5-FU or imiquimod with ingenol mebutate, and given the between-trial heterogeneity, any comparisons between treatments that have not been directly compared should be made with caution.

# REFERENCES


1. Ghuznavi N, Nocera NF, Guajardo AR, Weinberg JM. Emerging medical treatments for actinic keratoses, squamous cell carcinoma and basal cell carcinoma. Clinical Investigation. 2012;2(9):909-21.
2. Jacks S, Kudrewicz K, Carr DR. Ingenol mebutate: an emerging therapy in the treatment of actinic keratoses. Current Dermatology Reports. 2013;2(2):113-7.
3. Berman B. New developments in the treatment of actinic keratosis: focus on ingenol mebutate gel. Clin Cosmet Investig Dermatol [Internet]. 2012 [cited 2013 Jun 18];5:111-22. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3430094/pdf/ccid-5-111.pdf
4. CDR submission binder: Picato® (ingenol mebutate) topical gel 0.015% and 0.05% [**CONFIDENTIAL** manufacturer's submission]. Thornhill (ON): LEO Pharma Inc; 2013 May.
5. de Berker D, McGregor JM, Hughes BR. Guidelines for the management of actinic keratoses. Br J Dermatol [Internet]. 2007 [cited 2013 Jul 18];156:222-30. Available from: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Actinic%20Keratoses.pdf
6. Gupta AK, Paquet M. Ingenol mebutate: a promising treatment for actinic keratoses and nonmelanoma skin cancers. J Cutan Med Surg. 2013 May;17(3):173-9.
7. Stockfleth E. The paradigm shift in treating actinic keratosis: a comprehensive strategy. J Drugs Dermatol. 2012 Dec;11(12):1462-7.
8. Stockfleth E, Terhorst D, Braathen L, Cribier B, Cerio R, Ferrandiz C, et al. Guideline on Actinic Keratoses [Internet]. Zurich (CH): European Dermatology Forum; 2010 Oct 20. [cited 2013 Jul 18]. Available from: http://www.euroderm.org/images/stories/guidelines/guideline_Management_Actinic_Keratoses-update2011.pdf
9. National Institute for Health and Care Excellence. ESNM14: Actinic keratosis: ingenol mebutate gel [Internet]. London: The Institute; 2013 Mar 19. [cited 2013 Jul 30]. (Evidence summary: new medicine). Available from: http://publications.nice.org.uk/esnm14-actinic-keratosis-ingenol-mebutate-gel-esnm14/overview
10. Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratosis. N Engl J Med. 2012 Mar 15;366(11):1010-9.
11. Clinical study report PEP005-014: A multi-center, randomized, parallel group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of PEP005 (ingenol mebutate) gel, 0.05% in patients with actinic keratoses on non-head locations (REGION-I) [**CONFIDENTIAL** internal manufacturer's report]. Bowen Hills, QLD (Australia): Peplin Operations Pty Ltd; 2010 Sep 16.
12. Clinical study report PEP005-016: A multi-center, randomized, parallel group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of PEP005 (ingenol mebutate) gel, 0.015% in patients with actinic keratoses on the head (face or scalp) (REGION-IIa) [**CONFIDENTIAL** internal manufacturer's report]. Bowen Hills, QLD (Australia): Peplin Operations Pty Ltd; 2010 Sep 8.
13. Clinical study report PEP005-025: A multi-center, randomized, parallel-group, double-blind, vehicle controlled study to evaluate the efficacy and safety of PEP005 (ingenol mebutate) gel, 0.015% in patients with actinic keratoses on the head (face or scalp) (REGION-IIb) [**CONFIDENTIAL** internal manufacturer's report]. Bowen Hills, QLD (Australia): Peplin Operations Pty Ltd; 2010 Sep 8.

14. Clinical study report PEP005-028: A multi-center, randomized, parallel group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of PEP005 (ingenol mebutate) gel, 0.05% in patients with actinic keratoses on non-head locations (REGIONIb) [**CONFIDENTIAL** internal manufacturer's report]. Bowen Hills, QLD (Australia): Peplin Operations Pty Ltd; 2010 Sep 8.

15. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s) [Internet]. In: Picato (ingenol mebutate) gel. Company: Leo Pharma. Application No.: 202833. Approval Date: 1/23/2012. Rockville (MD): The Center; 2012 [cited 2013 Jun 3]. (FDA approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202833Orig1s000TOC.cfm.

16. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s) [Internet]. In: Picato (ingenol mebutate) gel. Company: Leo Pharma. Application No.: 202833. Approval Date: 1/23/2012. Rockville (MD): The Center; 2012 [cited 2013 Jun 3]. (FDA approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202833Orig1s000TOC.cfm.

17. Health Canada reviewer's report: Picato® (ingenol mebutate) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutic Products Directorate, Health Canada; 2013 Jan 28.

18. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol. 1988 Jun;124(6):869-71.

19. Health Canada module 2.7.4: summary of clinical safety for actinic keratosis. In: CDR submission binder: Picato® (ingenol mebutate) topical gel 0.015% and 0.05% [**CONFIDENTIAL** manufacturer's submission]. Thornhill (ON): LEO Pharma Inc; 2011 Dec 13. Figure 2, Mean composite LSR score on each observation day; p. 98.

20. Adherence and health-related quality of life in patients with actinic keratosis: executive summary and full report. London: Hamell Communications; 2012. Unpublished report prepared for LEO Pharma.

21. Gupta AK, Paquet M, Villanueva E, Brintnell W. Interventions for actinic keratoses. Cochrane Database Syst Rev. 2012;12:CD004415.

22. Aldara (imiquimod) cream, 5% [product monograph]. Montreal: Valeant Canada; 2013 Feb 26.

23. Zyclara (imiquimod) cream, 2.5% and 3.75% [product monograph]. Montreal: Valeant Canada; 2013 Feb 27.

24. Efudex (flourouracil) topical cream [product monograph]. Montreal: Valeant Canada; 2004 Dec 15.

25. Clinical study report PEP005-030: A 12-month, long-term follow-up study of patients with actinic keratoses on the head (face or scalp) who have completed day 57 in studies PEP005-016 or PEP005-025 (REGION IIa and IIb) [**CONFIDENTIAL** intenal manufacturer's report]. Bowen Hills, QLD (Australia): Peplin Operations Pty Ltd; 2011 Mar 28.

26. Clinical study report PEP005-031: A 12-month, long-term follow-up study of patients with actinic keratosis on non-head areas (trunk and extremities) who have completed day 57 in study PEP005-020 [**CONFIDENTIAL** internal manufacturer's report]. Bowen Hills, QLD (Australia): Peplin Operations Pty Ltd; 2011 Mar 28.

27. Clinical study report PEP005-032: A 12 month, long-term follow-up study of patients with actinic keratosis on non-head locations (trunk and extremities) who have completed day 57 in study PEP005-028 [**CONFIDENTIAL** internal manufacturer's report]. Bowen Hills, QLD (Australia): Peplin Operations Pty Ltd; 2011 Mar 28.

28. Clinical study report PEP005-020: A multi-center, open-label study to evaluate the safety and efficacy of PEP005 (ingenol mebutate) gel, 0.05% in patients with actinic keratoses on non-head locations (trunk and extremities) [**CONFIDENTIAL** internal manufacturer's report]. Bowen Hills, QLD (Australia): Peplin Operations Pty Ltd; 2010 May 24.

29. Lebwohl M, Shumack S, Gold LS, Melgaard A, Larsson T, Tyring SK. Long-term Follow-up Study of Ingenol Mebutate Gel for the Treatment of Actinic Keratoses. JAMA Dermatol. 2013 Mar 20;1-5.

30. Anderson L, Schmieder GJ, Werschler WP, Tschen EH, Ling MR, Stough DB, et al. Randomized, double-blind, double-dummy, vehicle-controlled study of ingenol mebutate gel 0.025% and 0.05% for actinic keratosis. J Am Acad Dermatol. 2009 Jun;60(6):934-43.

31. Siller G, Gebauer K, Welburn P, Katsamas J, Ogbourne SM. PEP005 (ingenol mebutate) gel, a novel agent for the treatment of actinic keratosis: results of a randomized, double-blind, vehicle-controlled, multicentre, phase IIa study. Australas J Dermatol. 2009 Feb;50(1):16-22.

32. Chren MM, Lasek RJ, Sahay AP, Sands LP. Measurement properties of Skindex-16: a brief quality-of-life measure for patients with skin diseases. J Cutan Med Surg. 2001 Mar;5(2):105-10.

33. Chren MM. The Skindex instruments to measure the effects of skin disease on quality of life. Dermatol Clin [Internet]. 2012 Apr [cited 2013 Jul 11];30(2):231-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3269028/pdf/nihms345852.pdf

34. Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes [Internet]. 2004 Feb 26 [cited 2013 Jul 11];2:12. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC398419/pdf/1477-7525-2-12.pdf

35. Higaki Y, Kawamoto K, Kamo T, Horikawa N, Kawashima M, Chren MM. The Japanese version of Skindex-16: a brief quality-of-life measure for patients with skin diseases. J Dermatol. 2002 Nov;29(11):693-8.

36. Chen K, Yap LM, Marks R, Shumack S. Short-course therapy with imiquimod 5% cream for solar keratoses: a randomized controlled trial. Australas J Dermatol. 2003 Nov;44(4):250-5.

37. Gebauer K, Shumack S, Cowen PS. Effect of dosing frequency on the safety and efficacy of imiquimod 5% cream for treatment of actinic keratosis on the forearms and hands: a phase II, randomized placebo-controlled trial. Br J Dermatol. 2009 Oct;161(4):897-903.

38. Korman N, Moy R, Ling M, Matheson R, Smith S, McKane S, et al. Dosing with 5% imiquimod cream 3 times per week for the treatment of actinic keratosis: results of two phase 3, randomized, double-blind, parallel-group, vehicle-controlled trials. Arch Dermatol. 2005 Apr;141(4):467-73.

39. Lebwohl M, Dinehart S, Whiting D, Lee PK, Tawfik N, Jorizzo J, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. J Am Acad Dermatol. 2004 May;50(5):714-21.

40. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. NCT00828568, A therapeutic equivalence study of two imiquimod cream 5% treatments for patients with actinic keratosis; 2009 Nov 30 [cited 2013 Jul 29]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT00828568

41. Ooi T, Barnetson RS, Zhuang L, McKane S, Lee JH, Slade HB, et al. Imiquimod-induced regression of actinic keratosis is associated with infiltration by T lymphocytes and dendritic cells: a randomized controlled trial. Br J Dermatol. 2006 Jan;154(1):72-8.

42. Stockfleth E, Meyer T, Benninghoff B, Salasche S, Papadopoulos L, Ulrich C, et al. A randomized, double-blind, vehicle-controlled study to assess 5% imiquimod cream for the treatment of multiple actinic keratoses. Arch Dermatol. 2002 Nov;138(11):1498-502.

43. Szeimies RM, Gerritsen MJ, Gupta G, Ortonne JP, Serresi S, Bichel J, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from a phase III, randomized, double-blind, vehicle-controlled, clinical trial with histology. J Am Acad Dermatol. 2004 Oct;51(4):547-55.
44. Alomar A, Bichel J, McRae S. Vehicle-controlled, randomized, double-blind study to assess safety and efficacy of imiquimod 5% cream applied once daily 3 days per week in one or two courses of treatment of actinic keratoses on the head. Br J Dermatol. 2007 Jul;157(1):133-41.
45. Jorizzo J, Dinehart S, Matheson R, Moore JK, Ling M, Fox TL, et al. Vehicle-controlled, double-blind, randomized study of imiquimod 5% cream applied 3 days per week in one or two courses of treatment for actinic keratoses on the head. J Am Acad Dermatol. 2007 Aug;57(2):265-8.
46. Hanke CW, Beer KR, Stockfleth E, Wu J, Rosen T, Levy S. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: results of two placebo-controlled studies of daily application to the face and balding scalp for two 3-week cycles. J Am Acad Dermatol. 2010 Apr;62(4):573-81.
47. Jorizzo JL, Markowitz O, Lebwohl MG, Bourcier M, Kulp J, Meng TC, et al. A randomized, double-blinded, placebo-controlled, multicenter, efficacy and safety study of 3.75% imiquimod cream following cryosurgery for the treatment of actinic keratoses. J Drugs Dermatol. 2010 Sep;9(9):1101-8.
48. Swanson N, Abramovits W, Berman B, Kulp J, Rigel DS, Levy S. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: results of two placebo-controlled studies of daily application to the face and balding scalp for two 2-week cycles. J Am Acad Dermatol. 2010 Apr;62(4):582-90.
49. Krawtchenko N, Roewert-Huber J, Ulrich M, Mann I, Sterry W, Stockfleth E. A randomised study of topical 5% imiquimod vs. topical 5-fluorouracil vs. cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up. Br J Dermatol. 2007 Dec;157 Suppl 2:34-40.
50. Tanghetti E, Werschler P. Comparison of 5% 5-fluorouracil cream and 5% imiquimod cream in the management of actinic keratoses on the face and scalp. J Drugs Dermatol. 2007 Feb;6(2):144-7.