



# Common Drug Review

*Request for Advice —  
CDEC Briefing Document*

April 2015

<b>Drug</b>	ingenol mebutate (Picato)
<b>Indication</b>	Topical treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.
<b>Manufacturer</b>	LEO Pharma Inc.
<b>Request for Advice Questions</b>	<ol style="list-style-type: none"><li>1. Can CDEC provide further clarity with regard to the comparative effectiveness and role of ingenol mebutate relative to appropriate comparators?</li><li>2. Ingenol mebutate is indicated for the topical treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults. The manufacturer's requested listing criteria were for "patients who have failed or are intolerant to 5-FU." Can CDEC confirm what consideration was given to both the full Health Canada-approved indication and the requested listing criteria for ingenol mebutate and whether there was consideration given to a listing recommendation in patients or a subset of patients if its cost-effectiveness could be improved relative to other clinical treatments?</li></ol>

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with [CDR Update — Issue 87](#), manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

The information in this report is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment with respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this document to ensure that its contents are accurate, complete, and up-to-date as of the date of publication, CADTH does not make any guarantee to that effect. CADTH is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in the source documentation. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the information in this document or in any of the source documentation.

This document is intended for use in the context of the Canadian health care system. Other health care systems are different; the issues and information related to the subject matter of this document may be different in other jurisdictions and, if used outside of Canada, it is at the user's risk. This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

CADTH takes sole responsibility for the final form and content of this document, subject to the limitations noted above. The statements and conclusions in this document are those of CADTH and not of its advisory committees and reviewers. The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada or any Canadian provincial or territorial government. Production of this document is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon.

You are permitted to make copies of this document for non-commercial purposes, provided it is not modified when reproduced and appropriate credit is given to CADTH. You may not otherwise copy, modify, translate, post on a website, store electronically, republish, or redistribute any material from this document in any form or by any means without the prior written permission of CADTH.

Please contact CADTH's Vice-President of Corporate Services at [corporateservices@cadth.ca](mailto:corporateservices@cadth.ca) with any inquiries about this notice or other legal matters relating to CADTH's services.

## TABLE OF CONTENTS

ABBREVIATIONS .....	ii
1. BACKGROUND .....	1
2. REQUEST FOR ADVICE .....	1
3. CDR APPROACH TO THE REQUEST FOR ADVICE .....	2
4. CLINICAL FINDINGS.....	2
4.1 Key Characteristics of Ingenol Mebutate and Appropriate Comparators.....	2
4.2 Summary of Results from the Systematic Review of the Efficacy and Safety of Ingenol Mebutate Contained in the Original 2013 CDR Clinical Review Report .....	5
4.3 Efficacy and Safety of Appropriate Comparators (5-Fluorouracil and Imiquimod).....	7
4.4 North American Guidelines for the Treatment of Actinic Keratosis .....	9
4.5 Patient Input Summary.....	11
4.6 Studies of Adherence to Topical Treatments for Actinic Keratosis Provided by the Manufacturer .....	11
5. COST INFORMATION.....	12
6. CONCLUSIONS .....	14
APPENDIX 1: METHODOLOGY.....	15
REFERENCES.....	17
<b>Tables</b>	
Table 1: Listing Criteria of 5-Fluorouracil and Imiquimod for Actinic Keratosis on Provincial Drug Plans.....	3
Table 2: Key Characteristics of Ingenol Mebutate, 5-Fluorouracil, and Imiquimod .....	4
Table 3: Proportion of Patients Achieving Complete Clearance of Actinic Keratosis Lesions at Day 57 in Non-head Studies.....	5
Table 4: Proportion of Patients Achieving Complete Clearance of Actinic Keratosis Lesions at Day 57 in Head Studies .....	6
Table 5: Subgroup Analyses of Complete Clearance Rate in Head Studies .....	7
Table 6: Summary of Pooled Analyses From Gupta et al. (2012) .....	8
Table 7: Treatment Recommendations for Managing Actinic Keratosis .....	10
Table 8: Cost Comparison Table for Ingenol Mebutate Gel.....	13
<b>Figures</b>	
Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of Guidelines .....	16

## **ABBREVIATIONS**

<b>5-FU</b>	5-fluorouracil
<b>AK</b>	actinic keratosis
<b>CDEC</b>	Canadian Drug Expert Committee
<b>CDR</b>	CADTH Common Drug Review
<b>CI</b>	confidence interval
<b>LSR</b>	local skin response
<b>OR</b>	odds ratio
<b>NCCN</b>	National Comprehensive Cancer Network
<b>NNT</b>	number needed to treat
<b>NMSC</b>	non-melanoma skin cancer
<b>NOC</b>	Notice of Compliance
<b>RCT</b>	randomized controlled trial
<b>RR</b>	risk ratio
<b>TSQM</b>	Treatment Satisfaction Questionnaire for Medication

## 1. BACKGROUND

The recommendation and the reasons for the recommendation sections in the 2014 Canadian Drug Expert Committee (CDEC) recommendation for ingenol mebutate (Picato) for the topical treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults state the following:

Recommendation
The Canadian Drug Expert Committee (CDEC) recommends that ingenol mebutate not be listed.
Reason(s) for Recommendation
<ul style="list-style-type: none"><li>• There was insufficient evidence from randomized controlled trials (RCTs) to assess the comparative clinical benefit of ingenol mebutate relative to other less costly treatments for actinic keratosis (AK).</li><li>• There were insufficient data in the four included RCTs (PEP005-014, PEP005-028, PEP005-016, AND PEP005-025) to suggest that the same AK lesions that fail to respond to 5-fluorouracil (5-FU), or recur following treatment with 5-FU, should be treated with ingenol mebutate.</li></ul>

The primary conclusions from the 2013 CADTH Common Drug Review (CDR) clinical review of ingenol mebutate (Picato) were as follows:

Based on two each double-blind RCTs 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 local skin responses (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.

## 2. REQUEST FOR ADVICE

The CDR-participating jurisdictions are requesting that CDEC provide advice with respect to the following questions:

1. Can CDEC provide further clarity with regard to the comparative effectiveness and role of ingenol mebutate relative to appropriate comparators?
2. Ingenol mebutate is indicated for the topical treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults. The manufacturer's requested listing criteria were for "patients who have failed or are intolerant to 5-FU." Can CDEC confirm what consideration was given to both the full Health Canada-approved indication and the requested listing criteria for ingenol mebutate and whether there was consideration given to a listing recommendation in patients or a subset of patients if its cost-effectiveness could be improved relative to other clinical treatments?

### **3. CDR APPROACH TO THE REQUEST FOR ADVICE**

To inform the Request for Advice regarding the comparative effectiveness of ingenol mebutate relative to appropriate comparators, relevant sections of the original 2013 CDR Clinical Review report for ingenol mebutate are provided, including:

- A table comparing and contrasting the key characteristics of ingenol mebutate with appropriate comparators
- A summary of the results of the systematic review of the efficacy and safety of ingenol mebutate contained in the original 2013 CDR Clinical Review report for ingenol mebutate that addresses both the patient population identified in the full Health Canada–approved indication and the manufacturer’s requested listing criteria (patients who have failed or are intolerant to 5-FU)
- A summary of evidence of the efficacy and safety for appropriate comparators (5-FU and imiquimod).

In addition, a revised cost comparison table for ingenol mebutate and appropriate comparators (5-FU and imiquimod) has been included in the present report. The revised cost table included updated costs for the comparators (5-FU and imiquimod), including costs for a newly available generic imiquimod product.

To inform the Request for Advice regarding the role of ingenol mebutate relative to appropriate comparators, a literature search was undertaken using established CDR methods to identify North American guidelines for the treatment of AK (details regarding the search methodology are provided in Appendix 1). In addition, patient group input relevant to the role of ingenol mebutate is summarized, as are two manufacturer-provided studies regarding adherence and persistence with topical treatments for AK.

### **4. CLINICAL FINDINGS**

#### **4.1 Key Characteristics of Ingenol Mebutate and Appropriate Comparators**

Appropriate comparators for ingenol mebutate were identified in the protocol of the original CDR review and included 5-FU and imiquimod. Imiquimod topical cream has a Notice of Compliance (NOC) from Health Canada for numerous dosage strengths (5%, 3.75%, and 2.5%); however, only the 5% appears to be a relevant comparator from the public drug plan perspective (3.75% and 2.5% cream are not listed in any of the relevant jurisdictions). 5-FU (Efudex) is listed on all CDR-participating provincial public drug plans as a full benefit (Table 1). Imiquimod 5% (Aldara) is listed in Alberta, Nova Scotia, New Brunswick, and Nova Scotia with specific criteria. Aldara is listed in Prince Edward Island as a full benefit.

**TABLE 1: LISTING CRITERIA OF 5-FLUORARACIL AND IMIQUIMOD FOR ACTINIC KERATOSIS ON PROVINCIAL DRUG PLANS**

Province	Efudex (5-FU)	Aldara (imiquimod 5%)
<b>BC</b>	Full benefit	Not a benefit
<b>AB</b>	Full benefit	For the treatment of AK located on the head and neck in patients who have failed treatment with cryotherapy (where appropriate) and 5-FU. Special authorization may be granted for 6 months <sup>a</sup>
<b>SK</b>	Full benefit	Not reimbursed for AK
<b>MB</b>	Full benefit	Not a benefit
<b>ON</b>	Full benefit	Not reimbursed for AK
<b>NB</b>	Full benefit	For the treatment of AK in patients who have failed treatment with 5-FU and cryotherapy <sup>a</sup>
<b>NS</b>	Full benefit	For the treatment of AK on the head and neck in patients who have failed treatment with 5-FU and cryotherapy
<b>PEI</b>	Full benefit	Full benefit
<b>NL</b>	Full benefit	For the treatment of AK on the head and neck in patients who have failed treatment with 5-FU and cryotherapy <sup>a</sup>
<b>YK</b>	Full benefit	For treatment of AK in patients who have failed treatment with cryotherapy (where appropriate) and 5-FU. Approval for 4 months <sup>a</sup>

5-FU = 5-fluorouracil; AK = actinic keratosis.

<sup>a</sup> APO-imiquimod 5% also reimbursed as per Aldara criteria.

As noted below, the relevant treatments differ based on Health Canada recommendations related to treatment site and duration (Table 2). While the manufacturer asserts that ingenol mebutate is the only treatment for AK indicated for use on both face and scalp, as well as trunk and extremities, it should be noted that the Health Canada–approved product monograph for 5-FU cream has no specific restrictions regarding site of administration. However, imiquimod is indicated only for treatment on the face or balding scalp. Health Canada–recommended treatment durations are noticeably shorter for ingenol mebutate (two or three days, depending on site of application), compared with 5-FU (two to four weeks) and imiquimod (16 weeks).

TABLE 2: KEY CHARACTERISTICS OF INGENOL MEBUTATE, 5-FLUOROURACIL, AND IMIQUIMOD

	Ingenol Mebutate <sup>a</sup>	5-FU <sup>a</sup>	Imiquimod <sup>a</sup>
<b>Mechanism of Action</b>	Unknown (cytotoxic and inflammatory mechanisms)	Competitive antagonist for uracil in formulation of DNA and RNA	Immune response modifier
<b>Related Indication</b>	Non-hyperkeratotic, non-hypertrophic AK	Premalignant keratoses and superficial BCC	Clinically typical, non-hyperkeratotic, non-hypertrophic AK on the face or balding scalp
<b>Dosage Form</b>	Topical, 0.05% and 0.015% gel	Topical, 5% cream	Topical, 5%, 3.75%, and 2.5% cream
<b>Recommended Dose</b>	<b>Trunk and extremities:</b> 0.05% gel once daily for 2 consecutive days  <b>Face and scalp:</b> 0.015% gel once daily for 3 consecutive days	Twice daily for 2 to 4 weeks	<b>Face or balding scalp</b> 5% cream: twice weekly for 16 weeks  3.75% or 2.5% cream: once daily for 2 treatment cycles of 2 weeks each separated by a 2-week no-treatment period
<b>Recommended Treatment Area</b>	<b>0.05% and 0.015% gel:</b> 25 cm <sup>2</sup>  Clinical data on treatment of more than one area are not available.  In a pharmacokinetic study, ingenol mebutate gel 0.05% was applied once daily to a 100 cm <sup>2</sup> area for 2 consecutive days. No systemic blood levels of ingenol mebutate or its 2 isomers were quantifiable.	Entire affected area (lesion)  No maximum recommended treatment area is suggested.	<b>5% cream:</b> 25 cm <sup>2</sup> (safety when applied to areas greater than 25 cm <sup>2</sup> for the treatment of AK has not been established).  <b>3.75% or 2.5% cream:</b> no maximum recommended treatment area is suggested. However, the safety and efficacy of imiquimod 3.75% or 2.5% cream applied to an area larger than the face or balding scalp (approximately 200 cm <sup>2</sup> ) have not been established.
<b>Most Common Adverse Events</b>	Erythema, flaking or scaling, swelling, vesiculation or pustulation, erosion or ulceration, application site pain, pruritus, irritation.	Pain, pruritus, hyperpigmentation, burning at site of application.	Erythema, flaking or scaling, dryness, scabbing, crusting, itching, burning at site of application, edema, weeping or exudate, erosion or ulceration.

5-FU = 5-fluorouracil; AK = actinic keratosis; BCC = basal cell carcinoma.

<sup>a</sup> Key characteristics based on Health Canada–approved product monographs.



#### 4.2 Summary of Results from the Systematic Review of the Efficacy and Safety of Ingenol Mebutate Contained in the Original 2013 CDR Clinical Review Report

The protocol for the systematic review identified the population of interest (adult patients with non-hyperkeratotic, non-hypertrophic AK). However, a subpopulation of interest was also identified (previous treatment with topical therapy). Comparators of interest included 5-FU and imiquimod.

No RCTs comparing ingenol mebutate with 5-FU or imiquimod were identified by CDR. However, four 57-day, randomized, double-blind, vehicle-controlled trials were identified and included in the systematic review.<sup>1</sup> PEP005-014 (N = 255) and PEP005-028 (N = 203) evaluated the efficacy and safety of ingenol mebutate gel, 0.05% once daily for two consecutive days 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% once daily for three consecutive days 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<sup>2</sup> contiguous treatment area. The primary outcome in all trials was the proportion of patients achieving complete clearance of all clinically visible AK lesions in the treatment area 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 the Skindex-16 Dermatological Survey score from baseline, and the Treatment Satisfaction Questionnaire for Medication (TSQM) score at day 57.

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 (NNTs) from three to five (Table 3 and Table 4). 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.

**TABLE 3: PROPORTION OF PATIENTS ACHIEVING COMPLETE CLEARANCE OF ACTINIC KERATOSIS LESIONS AT DAY 57 IN NON-HEAD STUDIES**

Complete Clearance	PEP005-014		PEP005-028	
	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) <sup>a</sup>	23.1 (14.5 to 31.8)		37.2 (26.6 to 47.7)	
P value	< 0.0001		< 0.001	

CI = confidence interval.

<sup>a</sup> Calculated by CADTH (RevMan 5).

**TABLE 4: PROPORTION OF PATIENTS ACHIEVING COMPLETE CLEARANCE OF ACTINIC KERATOSIS LESIONS AT DAY 57 IN HEAD STUDIES**

Complete Clearance	PEP005-016		PEP005-025	
	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) <sup>a</sup>	34.8 (26.3 to 43.3)		42.0 (33.0 to 51.1)	
P value	< 0.001		< 0.001	

CI = confidence interval.

<sup>a</sup> Calculated by CADTH (RevMan 5).

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.

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 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.

Patients who achieved complete clearance of lesions at the target area at day 57 were eligible for enrolment in two 12-month observational follow-up studies: PEP005-030 (head studies, PEP005-016 and PEP005-025) and PEP005-032 (non-head study, PEP005-028).<sup>2</sup> The frequency of recurrence was defined as any identified AK lesion in the target treatment area. Of patients with head AK lesions treated with ingenol mebutate who attained complete clearance ( $n = 108$ ), an estimated 53.9% (95% confidence interval [CI], 44.3 to 63.5) experienced a recurrence within 12 months of follow-up. Of patients with non-head AK lesions treated with ingenol mebutate 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.

#### 4.2.1 Listing Criteria Requested by Sponsor

In its original 2013 submission to CDR, the manufacturer had requested listing for patients who have failed or are intolerant to 5-FU. 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 manufacturer conducted post hoc subgroup analyses of pooled head, and pooled non-head trials, based on prior treatment with 5-FU. Compared with vehicle, ingenol mebutate resulted in a statistically significantly greater proportion of patients achieving complete clearance in both 5-FU-naive and 5-FU-experienced patients in both the head and non-head studies. 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% ( $P = 0.014$ ) (Table 5). 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. Further, in the pooled non-head studies, the proportion of ingenol mebutate-treated patients who achieved complete clearance was similar for those who had and had not been previously treated with 5-FU: 36.0% and 33.5%, respectively.

**TABLE 5: SUBGROUP ANALYSES OF COMPLETE CLEARANCE RATE IN HEAD STUDIES**

PEP005-016 + PEP005-025			
	Complete Clearance, n/N [95% CI]		
Prior 5-FU	Ingenol Mebutate, 0.015% (N = 277)	Vehicle (N = 270)	Risk Difference (95% CI) <sup>a</sup>
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, 49.3)

5-FU = 5 fluorouracil; CI = confidence interval.

<sup>a</sup> Calculated by CADTH.

### 4.3 Efficacy and Safety of Appropriate Comparators (5-Fluorouracil and Imiquimod)

The CDR systematic review identified no RCTs comparing ingenol mebutate with appropriate comparators (5-FU or imiquimod). However, CDR identified and critically appraised a recent Cochrane systematic review of treatments for AK by Gupta et al.<sup>3</sup>

The Cochrane review included numerous treatments and dosages that were not specifically relevant to this CDR review; i.e., they were not considered appropriate comparators based on the CDR systematic review protocol for ingenol mebutate. Findings below are specific to Health Canada-approved field-directed pharmacotherapies for AK; 5-FU (5%), and imiquimod (5%, 3.75%, and 2.5%). However, of the imiquimod results, only the 5% dosage form is relevant to the public drug plans, given that the lesser strengths are not reimbursed.

Gupta et al. performed pooled analyses based on RCTs for each of the above treatments (Table 6). The systematic review 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, three included a dose of 3.75%, and two included a dose of 2.5%. Three studies were consistent with the Health Canada-recommended dosing regimen of imiquimod 5%, and two studies were consistent with the Health Canada-recommended dosing regimens for both imiquimod 5% and 2.5%. Of the two RCTs comparing 5-FU 5% with imiquimod 5%, only one study (Tanghetti and Werschler<sup>4</sup>) employed Health Canada-recommended dosage regimens of both drugs, whereas the Krawtchenko et al.<sup>5</sup> study employed a non-Health Canada dosing regimen of imiquimod.

The primary outcome was complete clearance of AK lesions (Table 6). From pooled analyses, patients were statistically significantly more likely to achieve complete clearance with 5% imiquimod compared with placebo (risk ratio [RR] 7.70; 95% CI, 4.63 to 12.79). 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, which may be due to the variability in dosing regimens. The 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 interpreted with caution. As few studies were consistent with Health Canada dosing regimens, the generalizability of these results in Canada is uncertain.

**TABLE 6: 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
<b>imiquimod 5% versus placebo</b>					
Chen et al. 2003 <sup>6</sup>	39	8/29 (27.6)	1/10 (10.0)	NA	
Gebauer et al. 2009 <sup>7</sup>	149	6/120 (5.0)	0/29 (0)	22/120 (18.3)	0/29 (0)
Korman et al. 2005 <sup>8</sup>	492	117/242 (48.3)	18/250 (7.2)	23/242 (9.5)	10/250 (4.0)
Lebwohl et al. 2004 <sup>9</sup>	436	97/215 (45.1)	7/221 (3.2)	7/215 (3.3)	2/221 (0.9)
NCT00828568 Aldara <sup>10</sup>	213	74/180 (41.1)	3/30 (10.0)	11/183 (6.0)	1/30 (3.3)
NCT00828568 Taro <sup>10</sup>	209	64/176 (36.4)	3/30 (10.0)	8/179 (4.5)	1/30 (3.3)
Ooi et al. 2006 <sup>11</sup>	17	5/11 (45.5)	0/6 (0)	NA	
Stockfleth et al. 2002 <sup>12</sup>	36	21/25 (84.0)	0/11 (0)	NA	
Szeimies et al. 2004 <sup>13</sup>	286	84/147 (57.1)	3/139 (2.2)	15/147 (10.2)	4/139 (2.9)
Alomar et al. 2007 <sup>14</sup>	259	NA		2/129 (1.6)	0/130 (0)
Jorizzo et al. 2007 <sup>15</sup>	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)	
<b>imiquimod 3.75% versus placebo</b>					
Hanke et al. 2010 <sup>16</sup>	244	55/162 (34.0)	4/82 (4.9)	4/162 (2.5)	1/82 (1.2)
Jorizzo et al. 2010 <sup>17</sup>	247	43/126 (34.1)	6/121 (5.0)	NA	
Swanson et al. 2010a <sup>18</sup>	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)	
<b>imiquimod 2.5% versus placebo</b>					
Hanke et al. 2010 <sup>16</sup>	246	41/164 (25.0)	5/82 (6.1)	2/164 (1.2)	1/82 (1.2)
Swanson et al. 2010a <sup>18</sup>	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)	

Study	Number of Participants	Complete Clearance Rate n/N (%)		Withdrawal Due to Adverse Events n/N (%)	
		Imiquimod	Placebo	Imiquimod	Placebo
<b>Imiquimod 5% versus 5-FU 5%</b>					
		Imiquimod	5-FU	Imiquimod	5-FU
Krawtchenko et al. 2007 <sup>5</sup>	50	22/26 (84.6)	23/24 (95.8)	0/26	0/24 (0)
Tanghetti and Werschler 2007 <sup>4</sup>	39	5/19 (26.3)	17/20 (85.0)	0/19	0/20 (0)
Pooled analysis Effect size (95% CI)		NA			

5-FU = 5 fluorouracil; CI = confidence interval; RR = risk ratio.

#### 4.4 North American Guidelines for the Treatment of Actinic Keratosis

A literature search was performed to identify evidence-based guidelines from North America on the management of AK. One evidence-based guideline from the National Comprehensive Cancer Network (NCCN, 2014) was identified.<sup>19</sup> The NCCN is a not-for-profit alliance of 25 cancer centres across the US and guidelines developed by the NCCN are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatments. The NCCN guidelines focused on the diagnosis and treatment of basal cell and squamous cell cancers and were developed by a team of physicians specializing in dermatology and various oncology fields. The NCCN guidelines also provided guidance on the treatment of AK.

According to the NCCN:

- “Actinic keratosis should be treated aggressively at first development.
  - Accepted treatment modalities include cryotherapy, topical 5-FU, topical imiquimod, photodynamic therapy (e.g., aminolevulinic acid, porfimer sodium), and curettage and electrodesiccation.
  - Other modalities that may be considered include diclofenac, chemical peel (trichloroacetic acid) and ablative skin resurfacing (laser, dermabrasion).
- Actinic keratoses that have an atypical clinical appearance or do not respond to appropriate therapy should be biopsied for histologic evaluation.”

As indicated by the guideline authors, the recommendations above, other than diclofenac, were based on lower-level evidence, with uniform NCCN consensus that the intervention is appropriate. It was not noted what was meant by “lower-level evidence.” The recommendation of diclofenac was also based upon lower-level evidence, with NCCN consensus that was not necessarily uniform. The NCCN guidelines did not mention ingenol mebutate in their recommendations of treatment for AK.

In addition to the above guidelines identified by CDR, the manufacturer provided unpublished draft guidelines on the diagnosis and management of non-melanoma skin cancer (NMSC) that were developed by a team of 10 Canadian dermatologists and dermatologic surgeons in 2014.<sup>20</sup> These guidelines have been finalized, but are currently unpublished. Authors performed a systematic literature search and the quality of each included study and strength of each recommendation were evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. A “high” level of evidence indicates that further research is very unlikely to change the confidence in the estimate of effect; a “moderate” and “low” level of evidence indicates that further research is likely or very likely to have an important impact on the confidence in the estimate of effect; and a “very low”

level of evidence indicates that any estimate of effect is very uncertain. A “strong” recommendation for an intervention indicates that desirable effects outweigh undesirable effects, and a “weak” recommendation for an intervention indicates that desirable effects probably outweigh undesirable effects.

The authors state that endorsers and sponsors were not party to the development of the guidelines and were not involved in the literature search, the selection of committee members, or the drafting of text, recommendations, or algorithms.

With regard to the management of AK, the draft Canadian guidelines recommend that [REDACTED]

[REDACTED]

**TABLE 7: TREATMENT RECOMMENDATIONS FOR MANAGING ACTINIC KERATOSIS**

Treatment Recommendation	Level of Evidence	Strength of Recommendation
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	T	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

#### **4.5 Patient Input Summary**

Two patient groups responded to the CDR call for patient input for ingenol mebutate. Patients' concerns with current treatments include the inability to finish treatment cycles due to side effects, the negative impact of these side effects on quality of life, the length of treatment (up to 12 weeks), severe discomfort during treatment, and the effectiveness of treatments. The side effects of current treatments caused stress and anxiety for some patients. Five patients who had used treatments other than ingenol mebutate said that they experienced skin irritation, burning, redness, dryness, pain, swelling, tenderness, blistering, and changes in skin colour with their treatment. Patients also found that even if they were able to complete a treatment course, they did not experience a complete resolution of their AK lesions.

Patients felt that the short treatment duration of ingenol mebutate (two to three days) would be a benefit and that it may improve treatment adherence. The six individuals who contributed personal experience using ingenol mebutate for AK reported that the drug was better tolerated and more effective than other treatments they had used.

#### **4.6 Studies of Adherence to Topical Treatments for Actinic Keratosis Provided by the Manufacturer**

The manufacturer provided two studies that aimed to understand adherence to, and persistence with, AK topical therapies.<sup>21,22</sup> Adherence refers to the extent of conformity to the recommendations about day-to-day treatment by the provider with respect to timing, dosage, and frequency, while persistence refers to the act of continuing the treatment for the prescribed duration.

One manufacturer-funded study was a community-based, cross-sectional study of 305 adult patients ( $\geq 18$  years) with AK across the UK.<sup>21</sup> Patients were eligible if they were currently using or had previously (within the last 12 months) used one of the following topical treatments for AK: diclofenac sodium 3%, 5-FU 5%, imiquimod 5%, or 5-FU 5 mg/g plus salicylic acid 100 mg/g solution. Patients were excluded if they had previously received cryotherapy or excision surgery for AK lesions.

Of the 305 enrolled patients, 203 (66.6%) were male, 297 (97.4%) were white, and 172 (56.4%) were older than 65 years. In terms of lesion distribution, 152 (50%) patients had lesions on the face or scalp only; 46 (15%) had lesions on other body areas but not the face or scalp; and 107 (35%) had lesions on both the body and face or scalp. At the time of recruitment, 131 (43%) patients were using topical therapy and 120 (40%) patients had ceased therapy within the last six months.

A total of 269 (88%) patients were self-reported to be one of non-adherent, non-persistent, or both non-adherent and non-persistent to their topical therapy for AK. Non-adherence was statistically significantly more likely to occur with treatment durations of greater than four weeks (adjusted odds ratio [OR] 2.2; 95% CI, 1.3 to 3.6). With regard to non-persistence, 43 (14%) patients were non-persistent with a three- to four-week treatment period; 64 (21%) patients were non-persistent with a four- to eight-week treatment period; and 61 (20%) patients were non-persistent with a six- to 12-week treatment period. The study concluded that the duration of treatment is a significant factor influencing non-adherence and non-persistence, with higher rates of both when the treatment duration exceeded four weeks.

A prospective cohort study conducted by the manufacturer consisted of an online questionnaire-based survey conducted with 224 patients with AK living in the UK, France, and Germany who had been prescribed self-administered topical therapy by an AK-treating physician.<sup>22</sup> A baseline questionnaire and

up to six follow-up questionnaires were administered to patients at fortnightly intervals, allowing for follow-up during a full treatment cycle.

Of the 224 enrolled patients, 130 (58%) were male, 204 (91%) were white, and 147 (66%) were at least 60 years old. Of the treatments prescribed at baseline, 128 (57%) patients were prescribed diclofenac sodium; 51 (23%) patients were prescribed imiquimod 5%; 37 (17%) patients were prescribed fluorouracil; five (2%) patients were prescribed fluorouracil plus salicylic acid; two (1%) patients were prescribed imiquimod 3.75%, and one patient received an unspecified treatment.

Of the 224 patients, 162 (72%) reported that they remained on the treatment prescribed at baseline until the end of the survey, while 62 (28%) patients ceased baseline treatment and 24 patients switched to another topical treatment during the study. A total of 50 (22%) patients were non-persistent, 41 (18%) were persistent, 70 (31%) were over-persistent, and persistence could not be determined for 63 (28%) patients. A total of 167 (75%) patients adhered to their prescribed treatment regimen, and a multivariate regression analysis found that age statistically significantly affected adherence at all time points, with subjects aged 18 to 59 years being less likely to be adherent compared with subjects  $\geq 60$  years (OR 0.25 to 0.42;  $P < 0.05$ ). The authors of this study concluded that these results suggest that in the real-world settings, patients receiving longer durations of topical therapies ( $\geq 2$  weeks) for AK may experience issues leading to treatment switches, premature discontinuations, and over-persistence of treatment.

Limitations of these studies include the use of patient-reported measures to determine adherence and persistence, and the absence of results specific to ingenol mebutate. In addition, the studies were not conducted in Canada.

## **5. COST INFORMATION**

Ingenol mebutate gel (Picato) is a topical cream the manufacturer requested 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 per treatment course. The manufacturer submitted a cost-minimization analysis compared with 5-FU for the trunk and extremity indication, and compared with 5-FU and imiquimod 5% for the face and scalp indication. As denoted by the CDR recommendation, 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 the dose and price (range: \$265 to \$436), but considerably higher than that of 5-FU (\$32 to \$37). Whether ingenol mebutate will generate savings or incur additional costs if listed by public plans depends on how ingenol mebutate will be utilized (patient population), and the accepted price relative to the comparator treatments. Use in AK patients who have failed 5-FU treatment may generate modest savings when compared with imiquimod 5%. However, first-line use for AK is likely to result in substantially higher costs incurred by public plans.



### 5.1 Cost Comparison Table

The comparator treatments presented in the table below have been deemed the appropriate comparators by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

**TABLE 8: COST COMPARISON TABLE FOR INGENOL MEBUTATE GEL**

Drug/Comparator	Strength	Dosage Form	Price, Range (\$)	Recommended Treatment Course	Cost per Treatment Course, Range (\$)
Ingenol mebutate (Picato)	0.015% gel	3 x 0.47 g single-use tubes	383.0000 <sup>a</sup>	Apply once daily for <u>3</u> days to the face and/or scalp	383.00 <sup>b</sup>
	0.05% gel	2 x 0.47 g single-use tubes	383.0000 <sup>a</sup>	Apply once daily for <u>2</u> days to the trunk and/or extremities	383.00 <sup>b</sup>
Imiquimod (Aldara) <sup>c</sup>	5% cream	250 mg Packs of 12 or 24	12.118 <sup>d</sup> (11.98 to 16.9652)	Apply twice weekly for 16 weeks	24 doses: <b>290.83</b> (287.52 to 407.16) 36 doses: <b>436.25<sup>e</sup></b> (431.28 to 610.75)
Imiquimod (generic) <sup>c</sup>	5% cream	250 mg Packs of 12 or 24	11.03 <sup>d</sup> (11.03 to 12.3536)	Apply twice weekly for 16 weeks	24 doses: <b>264.72</b> (264.72 to 296.49) 36 doses: <b>397.08<sup>e</sup></b> (397.08 to 444.73)
Fluorouracil (Efudex)	5% cream	40 g tube	33.90 <sup>d</sup> (32.00 to 37.272)	Apply twice daily for 2 to 4 weeks	<b>33.90<sup>f</sup></b> (32.00 to 37.272)

<sup>a</sup> Manufacturer's submitted price.

<sup>b</sup> As per monograph, each single-dose unit covers a maximum of 25 cm<sup>2</sup>; excess cream should be discarded.

<sup>c</sup> Imiquimod is not approved by Health Canada for use on the trunk or extremities.

<sup>d</sup> Price from the Alberta formulary was used as it provided the mode prices for imiquimod, and mode and median prices of Efudex, based on June 2014 pricing.

<sup>e</sup> Assumes two packs are required for one course of treatment.

<sup>f</sup> Assumes one 40 g tube is sufficient to cover 25 cm<sup>2</sup> for an entire treatment course.

- The dose range for imiquimod 5% is based on clinical expert opinion, which is supported by IMS Pharmastat Claims data (~24 doses), and the product monograph recommended dosing, which includes wastage (36 doses).
- Zyclara (imiquimod 3.75% and imiquimod 2.5%) was not considered an appropriate cost comparator as it is not currently reimbursed by any of the Canadian provincial public drug formularies.
- Not all the provinces that reimburse imiquimod do so for this indication.

## 6. CONCLUSIONS

Appropriate comparators for ingenol mebutate in the treatment of AK include 5-FU and imiquimod. The CDR-conducted systematic review identified four vehicle-controlled trials that showed superiority of ingenol mebutate over vehicle gel in the treatment of clustered AK lesions on the face and scalp, and on the trunk and extremities. In addition, the superiority of ingenol mebutate over vehicle was demonstrated in both 5-FU naive and 5-FU experienced patients in both the head and non-head studies, although it was uncertain whether 5-FU experienced patients had used the treatment in the same treatment area. The systematic review of ingenol mebutate conducted by CDR did not identify any trials comparing ingenol mebutate with 5-FU or imiquimod; thus, there is no direct evidence of the comparative benefit of ingenol mebutate compared with either 5-FU or imiquimod, in the total AK population, or for the patient population for whom the manufacturer requested reimbursement (patients who failed or were intolerant to 5-FU). A systematic review conducted by Gupta et al. of treatments for AK that pooled results from multiple studies is of limited value in assessing comparative treatment benefits due to inconsistencies with Health Canada dosing regimens and between-trial heterogeneity. Given the limitations of the available clinical trial data, whether the cost-effectiveness of ingenol mebutate may be improved relative to other active comparators in a subpopulation of patients (e.g., those who failed or are intolerant to 5-FU) could not be determined.

A literature search for North American evidence-based guidelines for the management of AK, which may provide insight into the role for ingenol mebutate, identified one 2014 US guideline that recommended various treatments, including 5-FU and imiquimod, for the treatment of AK, but did not mention ingenol mebutate. Unpublished draft Canadian guidelines for the management of NMSC, provided in the manufacturer's submission to CDR, recommend [REDACTED]

Ingenol mebutate has a shorter Health Canada–recommended treatment duration (two to three days, depending on site of application) than both 5-FU (two to four weeks) and imiquimod (16 weeks), which may affect adherence to treatment regimens. Responses to the CDR call for patient input suggested that patients with AK find it difficult to complete treatment cycles due to uncomfortable side effects. Patients felt that the short treatment duration of ingenol mebutate may improve adherence compared with other active treatments, but comparative studies are lacking.

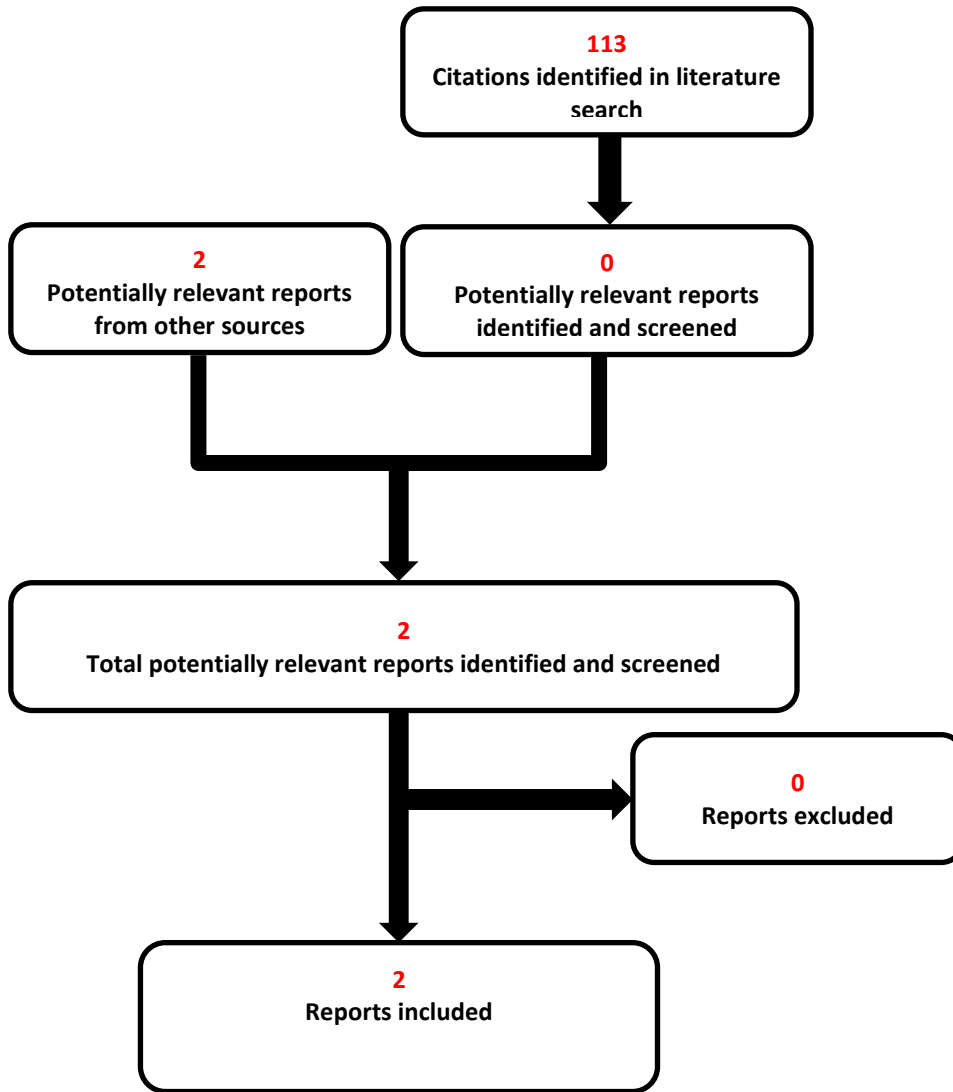
## APPENDIX 1: METHODOLOGY

### Literature Search Methods

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via 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 actinic keratosis.

Methodological filters were applied to limit retrieval to guidelines. Retrieval was limited by publication year (2009-current), but not by language. The initial search was completed on July 14, 2014. Grey literature (literature that is not commercially published) was identified by searching relevant websites from the Clinical Practice Guidelines section of the Grey Matters checklist (<http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters>). Google and other Internet search engines were used to search for additional web-based material.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF GUIDELINES



## REFERENCES

1. Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratosis. *N Engl J Med* [Internet]. 2012 Mar 15 [cited 2014 Jul 3];366(11):1010-9. Available from: <http://www.nejm.org/doi/full/10.1056/NEJMoa1111170>
2. Lebwohl M, Shumack S, Stein GL, Melgaard A, Larsson T, Tyring SK. Long-term follow-up study of ingenol mebutate gel for the treatment of actinic keratoses. *JAMA Dermatol*. 2013 Jun;149(6):666-70.
3. Gupta AK, Paquet M, Villanueva E, Brintnell W. Interventions for actinic keratoses. *Cochrane Database Syst Rev*. 2012;12:CD004415.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 -. NCT00828568, a randomized, double-blind, parallel-group, vehicle-controlled therapeutic equivalence study of two imiquimod cream 5% treatments for patients with actinic keratosis; 2013 [cited 2014 Jul 29]. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT00828568>
11. 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.
12. 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.
13. 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.
14. 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.

15. 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.
16. 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.
17. 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.
18. 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.
19. National Comprehensive Cancer Care Network. Basal cell and squamous cell skin cancers [Internet]. Version 2.2014. Fort Washington (PA): NCCN; 2014. [cited 2014 Sep 3]. (NCCN clinical practice guidelines in oncology). Available from: [http://www.nccn.org/professionals/physician\\_gls/pdf/nmsc.pdf](http://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf) Registration required.
20. Non-melanoma skin cancer in Canada [**CONFIDENTIAL** draft 2 guideline].2013 Nov. Submitted on behalf of LEO Pharm Inc. on June 6, 2014.
21. Shergill B, Zokaie S, Carr AJ. Non-adherence to topical treatments for actinic keratosis. *Patient Preference Adherence* [Internet]. 2013 [cited 2014 Sep 3];8:35-41. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3872140>
22. Erntoft S, Norlin J, Pollard C, Diepgen TL. Patient adherence and non-persistence behavior in real life actinic keratosis topical treatment in the UK, France and Germany. Poster presented at: International Society for Pharmacoeconomics and Outcomes Research; 2014 May 31-Jun 4; Montreal.