CDEC RECORD OF ADVICE

INGENOL MEBUTATE
(Picato — LEO Pharma Inc.)
Indication: Actinic Keratosis

This document summarizes the Canadian Drug Expert Committee (CDEC) response to the Common Drug Review (CDR)-participating drug plan's request for advice regarding the ingenol mebutate (Picato) *CDEC Final Recommendation* (January 22, 2014) and should be read in conjunction with the *CDEC Final Recommendation* document (January 22, 2014).

Background:
Ingenol mebutate is indicated for the topical treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (AK) in adults. It 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. Ingenol mebutate is applied once daily for two consecutive days for AK lesions on the trunk and extremities and once daily for three consecutive days for AK lesions on the face and scalp.

Submission History:
Ingenol mebutate was reviewed by CDEC for the treatment of AK and received a "do not list" recommendation for the following reasons:

1. 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 AK.
2. 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.

The Common Drug Review (CDR)-participating drug plans submitted a request for advice to ask CDEC for additional clarity on the following:

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 AK in adults. The manufacturer's requested listing criteria was 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?

Summary of CDEC Considerations:
CDEC considered the following to address the request for advice:

- the *CDEC Final Recommendation* for ingenol mebutate (January 22, 2014)
- the CDEC brief for the 2013 CDR review of ingenol mebutate
- an updated cost comparison table for ingenol mebutate, 5-FU, and imiquimod
- a summary of North American guidelines for the treatment of AK
- a summary of two manufacturer-provided studies regarding adherence and persistence with topical treatments for AK.

Summary of 2013 CDR Systematic Review
The 2013 systematic review included four manufacturer-sponsored, 57-day, vehicle-controlled, double-blind RCTs. PEP005-014 (N = 255) and PEP005-028 (N = 203) evaluated the efficacy of ingenol mebutate, 0.05% for the treatment of AK 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% for the treatment of AK on the head (face and scalp). In both non-head and head trials, the proportion of patients achieving complete and partial clearance at day 57 was statistically significantly higher in the ingenol mebutate groups compared with vehicle groups. In all included trials, the composite mean local skin response scores in the ingenol mebutate groups 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 local skin reaction scores in the vehicle groups were relatively stable at all time points.

No RCTs comparing ingenol mebutate with 5-FU or imiquimod were identified. However, a Cochrane systematic review of treatments for AK conducted by Gupta et al. (2012) was summarized and critically appraised by CDR. The systematic review included numerous treatments and dosages that were not specifically relevant to the CDR review and were not consistent with the Health Canada recommended dosing regimens. In addition, there was significant between-trial heterogeneity and no RCTs comparing 5-FU or imiquimod with ingenol mebutate.

Updated Cost Information
CDR prepared an updated cost comparison for ingenol mebutate, 5-FU, and imiquimod. The revised cost comparison included the newly available generic imiquimod product. The cost per course of treatment with ingenol mebutate ($383) is similar to that of imiquimod depending on the dose and price ($265 to $436), but considerably higher than that of 5-FU ($32 to $37).

Summary of AK Treatment Guidelines
The National Comprehensive Cancer Network in the United States has developed guidance on the treatment of AK; however, they did not address the use of ingenol mebutate in their recommendations. The manufacturer provided unpublished draft guidelines on the diagnosis and management of non-melanoma skin cancer that were developed by the Non-Melanoma Skin Cancer Guidelines Committee; a team of 10 Canadian dermatologists and dermatologic surgeons in 2014. The draft Canadian guidelines recommend that [redacted]

Summary of Treatment Adherence Data

The manufacturer provided two studies that aimed to understand adherence to, and persistence with, AK topical therapies. One was a manufacturer-funded, community-based, cross-sectional study of adult patients with AK across the United Kingdom. The other was a manufacturer-conducted, prospective cohort study consisting of an online questionnaire-based survey conducted with patients who had AK, living in the United Kingdom, France, and Germany who had been prescribed self-administered topical therapy by an AK-treating physician. Neither of the two studies included results specific to ingenol mebutate. The cross-sectional study found that the duration of treatment was a significant factor influencing non-adherence and non-persistence, with higher rates of both when the treatment duration exceeded four weeks. The prospective cohort study found that patients receiving longer durations of topical therapies (≥ 2 weeks) for AK may experience difficulties 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.

Response to the Request for Advice:

1. **Question from the Drug Plans:**
   Can CDEC provide further clarity with regard to the comparative effectiveness and role of ingenol mebutate relative to appropriate comparators?

   CDEC Response:
   Given the absence of direct or indirect comparative data, CDEC is unable to provide additional clarity regarding the comparative effectiveness of ingenol mebutate relative to 5-FU and imiquimod. The systematic review of ingenol mebutate conducted by CDR did not identify any trials comparing ingenol mebutate with 5-FU or imiquimod; therefore, 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 (i.e., patients who failed or were intolerant to 5-FU). The Cochrane systematic review of treatments for AK that pooled results from multiple studies (Gupta et al. 2012) is of limited value in assessing comparative treatment benefits due to inconsistencies with Health Canada dosing regimens and between-trial heterogeneity.

2. **Question from the Drug Plans:**
   Ingenol mebutate is indicated for the topical treatment of non-hyperkeratotic, non-hypertrophic AK in adults. The manufacturer's requested listing criteria was 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?

   CDEC Response:
   As noted above, ingenol mebutate is indicated for the "topical treatment of non-hyperkeratotic, non-hypertrophic AK in adults" and the manufacturer requested a listing recommendation "for patients who have failed or are intolerant to 5-FU." As part of the deliberative process, CDEC considers both the full Health Canada-approved indication as well as the manufacturer's listing criteria.

Consideration of the Full Indication

CDEC considered the full indication for ingenol mebutate and concluded that there was insufficient evidence from RCTs to assess the comparative clinical benefit of ingenol mebutate relative to other less costly treatments for AK. This is based on the absence of any comparative data provided in the manufacturer's submission or identified in CDR's literature review. An updated literature search conducted by CDR as part of the request for advice failed to identify any direct or indirect comparisons on which to evaluate the comparative clinical benefit of ingenol mebutate relative to 5-FU or imiquimod.

Consideration of the Manufacturer's Requested Listing Criteria

With respect to the manufacturer's request for listing after failure of or intolerance to 5-FU, CDEC noted that there are two main issues that would preclude such listing criteria:

- There were insufficient data in the included RCTs to suggest that the same AK lesions that fail to respond to 5-FU, or recur following treatment with 5-FU, should be treated with ingenol mebutate. Studies PEP005-014, PEP005-028, PEP005-016, and PEP005-025 were not designed to evaluate the efficacy of ingenol mebutate in the treatment of recurrent AK lesions. Approximately 20% of patients in these trials had previously received treatment with topical 5-FU; however, it was not specified if this prior treatment was targeting the same treatment area as was being observed in the clinical trials (i.e., it is uncertain if the AK lesions being treated in the RCTs were new or recurrent lesions).
- CDEC noted that patient groups and the clinical expert indicated that some patients undergoing treatment for AK may be unable to complete a full course of treatment with 5-FU due to intolerance. However, the included clinical trials provided no evidence to evaluate the efficacy of ingenol mebutate in patients with intolerance to 5-FU. In addition, there is no clear or readily applicable definition of what it means to fail or be intolerant to 5-FU.

The request for advice also asked CDEC to confirm whether there was consideration given to a listing recommendation for ingenol mebutate in a subset of patients if its cost-effectiveness could be improved relative to other clinical treatments. CDEC considered the use of ingenol mebutate in specific subpopulations, particularly for patients who have had an inadequate response or intolerance to 5-FU and determined that there is insufficient evidence to conclude that ingenol mebutate would be an efficacious and cost-effective treatment option for those patients. 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 based on the information provided in the manufacturer's submission.

October 15, 2014 Meeting

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets:

None.

Conflicts of Interest:
None

About This Document:
CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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