



CDEC FINAL RECOMMENDATION

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

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that ingenol mebutate not be listed.

Reasons for the Recommendation:

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 actinic keratosis (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.

Background:

Ingenol mebutate is indicated for the topical treatment of non-hyperkeratotic, non-hypertrophic 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.

Summary of CDEC Considerations

CDEC considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of ingenol mebutate, a critique of the manufacturer's pharmaco-economic evaluation, and patient group-submitted information about outcomes and issues that are important to individuals with AK.

Patient Input Information

The following is a summary of key information provided by two patient groups that responded to the CDR call for patient input and collaborated to produce a joint submission:

Common Drug Review

- Current treatment options have negative side effects that cause discomfort and diminish the quality of life of some individuals undergoing treatment for AK. These side effects can make it difficult to complete the treatment protocols.
- The short treatment duration of ingenol mebutate is a benefit, particularly for those who find it difficult to manage the side effects of longer therapies, and 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.

Clinical Trials

The systematic review included four 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 the trunk and extremities. PEP005-016 (N = 269) and PEP005-025 (N = 278) evaluated the efficacy and safety of ingenol mebutate 0.015% for the treatment of AK on the face and scalp. In all of the included trials, patients were required to have four to eight clinically visible and discrete lesions within a contiguous area of 25 cm².

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Complete clearance — defined as clearance of all clinically visible AK lesions in the target treatment area.
- Per cent reduction — defined as the percentage change from baseline in the total number of AK lesions.
- Skindex-16 Dermatology Survey — measures the effect of skin disease on a patient's quality of life using three domains: symptoms, emotions, and functioning.
- Treatment Satisfaction Questionnaire for Medication (TSQM) — measures patient satisfaction with treatment using four domains: effectiveness, side effects, convenience, and global satisfaction.
- Local skin response — measures the severity of adverse skin events in the following categories: erythema, flaking or scaling, crusting, swelling, vesiculation or pustulation, and erosion or ulceration.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The primary efficacy outcome in all of the included studies was the proportion of patients achieving complete clearance of all clinically visible AK lesions in the target treatment area at day 57.

Efficacy

- The proportion of patients achieving complete clearance of all clinically visible AK lesions in the target treatment area at day 57 was reported as follows:
 - Trunk and extremities studies: 27.8% with ingenol mebutate and 4.7% with vehicle in PEP005-014 (risk difference 23.1% [95% CI: 14.5% to 31.8%]); 42.0% with ingenol mebutate and 4.9% with vehicle in PEP005-028 (risk difference 37.2% [95% CI: 26.6% to 47.7%]).

Common Drug Review

CDEC Meeting — October 16, 2013; CDEC Reconsideration — January 15, 2014

Notice of Final Recommendation — January 22, 2014

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- Face and scalp studies: 37.0% with ingenol mebutate and 2.2% with vehicle in PEP005-016 (risk difference 34.8% [95% CI: 26.3% to 43.3%]); 47.2% with ingenol mebutate and 5.1% with vehicle in PEP005-025 (risk difference 42.0% [95% CI: 33.0% to 51.1%]).
- In all of the included trials, the proportion of patients achieving partial clearance of AK lesions at day 57 was reported as follows:
 - Trunk and extremities studies: 44.4% with ingenol mebutate and 7.0% with vehicle in PEP005-014 (risk difference 37.5% [95% CI: 27.7% to 47.2%]); 55.0% with ingenol mebutate and 6.8% with vehicle in PEP005-028 (risk difference 48.2% [95% CI: 37.3% to 59.1%]).
 - Face and scalp studies: 60.0% with ingenol mebutate and 6.7% with vehicle in PEP005-016 (risk difference 53.3% [95% CI: 44.0% to 62.6%]); 67.6% with ingenol mebutate and 8.1% with vehicle in PEP005-025 (risk difference 59.5% [95% CI: 50.6% to 68.5%]).
- Across the included trials, the median per cent reduction in the number of AK lesions from baseline to day 57 was reported as follows:
 - Trunk and extremities studies: 69% with ingenol mebutate and 0% in vehicle in PEP005-014; 75% with ingenol mebutate and 0% with vehicle in PEP005-028.
 - Face and scalp studies: 83% with ingenol mebutate and 0% with vehicle in PEP005-016; 87% with ingenol mebutate and 0% with vehicle in PEP005-025.
- In PEP005-016 and PEP005-025 (face and scalp studies) and PEP005-028 (trunk and extremities study), there was a statistically significant improvement in the ingenol mebutate groups compared with the vehicle groups in the emotions and functioning domains of the Skindex-16 Dermatological Survey at day 57. In all of the included trials, there was a decline in the symptoms domain score at day 8 in the ingenol mebutate groups, while there was an improvement in the vehicle group, suggesting that patients in the ingenol mebutate groups were more bothered by their symptoms compared with the vehicle group at day 8. These differences in the symptoms domain score at day 8 between treatment groups were statistically significant in all trials. Subsequent to day 8, there were improvements in both treatment groups in the symptoms domain score, with statistically significantly greater improvements in the ingenol mebutate groups compared with the vehicle groups at day 29 and day 57.
- In all of the included trials, the mean TSQM scores at day 57 were statistically significantly greater for ingenol mebutate compared with vehicle for the effectiveness domain (69.5 to 77.4 versus 36.1 to 45.6) and global satisfaction domain (71.3 to 77.8 versus 34.3 to 39.2). The mean TSQM scores for the side effects domain were statistically significantly higher in the vehicle groups than the ingenol mebutate groups (99.2 to 100 versus 93.3 to 95.2).

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one adverse event was reported as follows:
 - Trunk and extremities studies: 32.0% with ingenol mebutate and 28.7% with vehicle in PEP005-014; 35.0% with ingenol mebutate and 25.2% with vehicle in PEP005-028.
 - Face and scalp studies: 47.0% with ingenol mebutate and 23.0% with vehicle in PEP005-016; 28.2% with ingenol mebutate and 21.3% with vehicle in PEP005-025.
- The most commonly reported adverse events with ingenol mebutate were in the category of infections and infestations (trunk and extremities studies: 8.8% with ingenol mebutate and 9.3% with vehicle in PEP005-014, 4.0% with ingenol mebutate and 2.9% with vehicle in PEP005-028; face and scalp studies: 10.6% with ingenol mebutate and 5.9% with vehicle in PEP005-016, 4.2% with ingenol mebutate and 2.9% with vehicle in PEP005-025), and

Common Drug Review

general disorder and administration site conditions (trunk and extremities studies: 4.0% with ingenol mebutate and 0% with vehicle in PEP005-014, 24.0% with ingenol mebutate and 5.8% with vehicle in PEP005-028; face and scalp studies: 24.2% with ingenol mebutate and 3.0% with vehicle in PEP005-016, 14.1% with ingenol mebutate and 2.2% with vehicle in PEP005-025).

- The proportion of patients who experienced at least one serious adverse event was reported as follows:
 - Trunk and extremities studies: 0.8% with ingenol mebutate and 2.3% with vehicle in PEP005-014; 2.0% with ingenol mebutate and 1.9% with vehicle in PEP005-028.
 - Face and scalp studies: 1.5% with ingenol mebutate and 1.5% with vehicle in PEP005-016; 0.7% with ingenol mebutate and 0% with vehicle in PEP005-025.
- Withdrawals due to adverse events were reported as follows:
 - Trunk and extremities studies: 1.6% with ingenol mebutate and 0.8% with vehicle in PEP005-014; 0% with ingenol mebutate and 1.0% with vehicle in PEP005-028.
 - Face and scalp studies: 1.6% with ingenol mebutate and 0.8% with vehicle in PEP005-016; 0% with ingenol mebutate and 1.0% with vehicle in PEP005-025.
- In all of the 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 trunk and extremities studies; day 4 for face and scalp studies) before returning to approximately baseline values at day 29.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing drug costs of ingenol mebutate with imiquimod 5% or 5-FU in patients who had previously failed or were intolerant to 5-FU for the treatment of AK. The manufacturer used data from PEP005-016 and PEP005-025 for ingenol mebutate 0.015% and PEP005-014 and PEP005-028 for ingenol mebutate 0.05% to determine the proportion of patients likely to respond to treatment, and the rate of recurrence of AK lesions. There was a lack of data to support second-line therapy with ingenol mebutate, and there is an absence of robust evidence to support the assumption that ingenol mebutate is equivalent to 5-FU and/or imiquimod 5%. The cost per two to three-day course of treatment for both strengths of ingenol mebutate (\$383) is less than that of imiquimod 5% (\$529, twice weekly for 16 weeks), but more expensive than 5-FU (\$34, twice daily for 2 to 4 weeks).

Other Discussion Points:

CDEC noted the following:

- Approximately 20% of patients in all of the included trials had previously received treatment with 5-FU; however, the prior treatment was not necessarily in the same area as the treatment area in the included studies.
- The need to perform retreatment of an AK lesion, due to recurrence or incomplete clearance, would not necessarily prompt a change in the treatment regimen.
- There is no clear or readily applicable definition of what it means to fail or be intolerant to 5-FU; therefore, the size of the patient population who might be included in the listing request is uncertain.

Common Drug Review

CDEC Meeting — October 16, 2013; CDEC Reconsideration — January 15, 2014

Notice of Final Recommendation — January 22, 2014

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Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- There are no trials directly comparing ingenol mebutate with 5-FU or imiquimod 5% for the initial treatment of AK or for the treatment of recurrent AK.
- There are no data demonstrating that treatment of AK with ingenol mebutate reduces the occurrence of squamous cell carcinoma.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

Regrets:

October 16, 2013: None

January 15, 2014: 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 not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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Common Drug Review

CDEC Meeting — October 16, 2013; CDEC Reconsideration — January 15, 2014

Notice of Final Recommendation — January 22, 2014

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