Committee to Evaluate Drugs (CED)

Recommendations and Reasons

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Ingenol mebutate

Product: ingenol mebutate (Picato®) topical gel

Class of Drugs: skin and mucous membrane agent

Reason for Use: actinic keratosis

Manufacturer: Leo Pharma Inc.

Date of Review: February 5, 2014

CED Recommendation

The CED recommended that ingenol mebutate (Picato®) not be funded. The effectiveness of ingenol mebutate compared with less costly treatment alternatives is unknown. Furthermore, there is a lack of compelling evidence to demonstrate that patients who have failed or are intolerant to alternative therapies would benefit from ingenol mebutate.

Executive Officer Decision*

Based on the CED's recommendation, the Executive Officer decided not to fund ingenol mebutate (Picato®).

Funding Status*

Not funded by the Ontario Public Drug Programs.

** This information is current as of the posting date of the document. For the most up-to-date information on Executive Officer decision and funding status, see: www.health.gov.on.ca/en/pro/programs/drugs/status_single_source_subm.aspx.*

Ontario

Highlights of Recommendation:

- Ingenol mebutate topical gel has been shown in randomized controlled studies to be effective in clearing actinic keratosis (AK) lesions when compared with vehicle control (a placebo gel).
- There are no clinical studies directly comparing ingenol mebutate to alternative topical treatments for AK. The effectiveness of ingenol mebutate relative to less expensive treatment options such as 5-fluorouracil cream is unknown.
- Ingenol mebutate costs $383 per treatment course. By comparison, 5-fluorouracil cream costs $34 per treatment course. There are no data to support that ingenol mebutate is cost-effective.

Background:

Actinic keratosis (AK) is a skin condition that develops as a result of long-term exposure to ultraviolet (UV) light. AK presents as thickened, scaly lesions that are found on the face, scalp, back of the hands, and other areas of the skin that are often in the sun. A small percentage of AK lesions can eventually become skin cancer.

The choice of treatment is guided by the patient's clinical presentation. If only a few isolated AK lesions are present, procedures such as cryotherapy (freezing), surgical excision (cutting), or curettage (scraping) are usually used to remove the lesions. If there are multiple AK lesions on a skin area, therapies that treat the entire affected area may be more appropriate. These consist of topical drug treatments including 5-fluorouracil, imiquimod, and ingenol mebutate.

Detailed Discussions:

- For this evaluation, the CED considered:
    - Findings from the Common Drug Review (CDR) and the recommendation of the Canadian Drug Expert Committee (CDEC);
    - Information in the manufacturer's submission;
    - Two patient group submissions.
- The CED reviewed four vehicle-controlled, double-blind randomized trials. PEP005-014 and PEP005-028 evaluated the efficacy of ingenol mebutate 0.05% for the treatment of AK on the trunk and extremities, and PEP005-016 and PEP005-025 evaluated the efficacy and safety of ingenol mebutate 0.015% for the treatment of AK on the face and scalp.
- The primary efficacy outcome in the four studies was the proportion of patients achieving complete clearance of all clinically visible AK lesions in the target treatment area at day 57. The studies found that statistically greater proportions of patients treated with ingenol mebutate achieved the primary outcome compared to patients treated with vehicle, with absolute risk differences ranging from 23.1% to 42.0%.
- The proportion of patients achieving partial clearance of AK lesions at day 57 was statistically greater in the ingenol mebutate groups compared to vehicle groups, with absolute risk differences ranging from 37.5% to 59.5%.

- The median percent reduction in the number of AK lesions from baseline to day 57 was 0% in the vehicle groups in all studies and 69%, 75%, 83% and 87% in the ingenol mebutate groups in PEP005-014, PEP005-028, PEP005-016 and PEP005-025, respectively.
- In all of the included trials, the mean Treatment Satisfaction Questionnaire for Medication (TSQM) scores at day 57 were statistically significantly greater for ingenol mebutate groups compared to vehicle groups for the effectiveness domain and global satisfaction domain. The mean TSQM scores for the side effects domain were statistically significantly higher in the vehicle groups compared to ingenol mebutate groups.
- The most commonly reported adverse events associated with ingenol mebutate were related to the administration site (e.g., pain, pruritus, irritation).
- There are no randomized controlled trials comparing ingenol mebutate to other topical treatments for AK. The effectiveness of ingenol mebutate relative to less expensive treatment options such as 5-fluorouracil cream is unknown.
- The manufacturer requested that ingenol mebutate be funded for patients who are intolerant or have failed 5-fluorouracil cream. The CED noted that there are insufficient data to determine the benefits of ingenol mebutate in these patients. Only 20% of patients in the available randomized controlled trials had previously received treatment with 5-fluorouracil cream and prior treatments were not necessarily in the same area. It was further noted that the need to perform retreatment of an AK lesion, due to recurrence or incomplete clearance, would not necessarily require a change in the treatment regimen.
- Ingenol mebutate costs $383 per treatment course. Ingenol mebutate treatment is significantly more expensive than 5-fluorouracil cream, which cost $34 for an average treatment course. There are no data to support that ingenol mebutate is cost-effective.
- The CED considered input from two patient groups. The patient submissions outlined the impact of AK on patients' quality of life and the side effects of current therapies. Patients who have used ingenol mebutate reported that the side effects were short-term and more tolerable and indicated a preference for the shorter duration of treatment with this drug.
- Overall, four randomized controlled trials demonstrated that statistically greater proportions of patients achieved complete or partial clearance of AK lesions with ingenol mebutate compared to vehicle. There are no randomized controlled studies directly comparing ingenol mebutate to 5-fluorouracil cream and a lack of compelling evidence to show that patients who have failed or are intolerant to alternative therapies would benefit from ingenol mebutate. The cost of ingenol mebutate is substantially higher than 5-fluorouracil cream and there is no evidence that the drug is cost-effective.

Committee to Evaluate Drugs (CED)

The Committee to Evaluate Drugs (CED) is comprised of practicing physicians, pharmacists, health economists, and patient representatives. In conducting its review, the CED considers data contained in the drug manufacturer's submission, input provided by patient groups, findings from the national Common Drug Review and the pan-Canadian Oncology Drug Review, and other scientific information as necessary.

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