



Common Drug Review

Pharmacoeconomic Review Report

February 2014

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
AK	actinic keratosis
AMSTAR	assessing methodological quality of systematic reviews
CDR	Common Drug Review
CMA	cost-minimization analysis
HTA	health technology assessment
PBAC	Pharmaceutical Benefits Advisory Committee
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

SUMMARY

Ingenol mebutate gel (Picato) is a topical cream that the manufacturer is requesting to use as a second-line treatment in patients with actinic keratosis (AK) who have failed or are intolerant to 5-fluorouracil (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 being incurred by public plans.

¹These 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.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

Ingenol mebutate gel (Picato) is a topical cream for which the manufacturer is requesting listing as a second-line treatment in patients with actinic keratosis (AK) who have failed or are intolerant to 5-fluorouracil (5-FU). Ingenol mebutate gel is available in two strengths for different administration sites:

- 0.015% for lesions on the face and scalp
- 0.05% for lesions on the trunk or extremities.

The recommended treatment course for ingenol mebutate 0.015% is once daily for three days, while the recommended treatment course for ingenol mebutate 0.05% is once daily for two days. Ingenol mebutate is flat-priced at \$383.00 per pack for both the 0.015% and 0.05% strengths. Each pack lasts for one treatment course.

1.1 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.

TABLE 1: COST COMPARISON TABLE FOR INGENOL MEBUTATE GEL

Drug/ Comparator	Strength	Dosage Form	Price (\$)	Recommended Treatment Course	Cost per Treatment Course, Range (\$)
Ingenol Mebutate (Picato)	0.015% gel	3 x 0.47 g single use tubes	383.0000 ^a	Apply once daily for <u>2</u> days to the face and/or scalp	383.00 ^b
	0.05% gel	2 x 0.47 g single use tubes	383.0000 ^a	Apply once daily for <u>2</u> days to the trunk and/or extremities	383.00 ^b
Imiquimod (Aldara) ^c	5% cream	250 mg Packs of 12 or 24	14.7067 ^d	Apply twice weekly for 16 weeks	24 doses: 352.96 ^e 36 doses: 529.44 ^e
Fluorouracil (Efudex)	5% cream	40 g tube	33.5120 ^d	Apply twice daily for 2 to 4 weeks	33.51 ^f

^aManufacturer's submitted price.

^bAs per monograph, each single-dose unit covers a maximum of 25 cm², excess cream should be discarded.

^cImiquimod is not approved by Health Canada for use on the trunk or extremities.

^dPrice from the Nova Scotia formulary was used as it provided the mode and median prices for Aldara and mode for Efudex, based on July 2013 pricing.

^eAssumes two packs are required for one course of treatment.

^fAssumes one 40 g tube is sufficient to cover 25 cm² for an entire treatment course.

Note: Zyclara (imiquimod 3.75% and imiquimod 2.5%) was not considered an appropriate cost comparator given it is not reimbursed, and the clinical expert consulted for this review indicated it was not commonly used in clinical practice.

2. SUMMARY OF PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-minimization analysis (CMA),¹ considering only the direct cost of drugs related to treatment of AK. The objective of the CMA was to compare the cost of ingenol mebutate compared with imiquimod 5% or 5-FU in patients who had previously failed or were intolerant to 5-FU. Four treatment sequences were assessed in the model for the two strengths and indications (Table 2).

TABLE 2: TREATMENT SEQUENCES IN THE MANUFACTURER'S CMA MODEL

Treatment Sequence	Initial Treatment Success		Initial Treatment Failure	
	Initial Treatment	Recurrence	Second Treatment	Third Treatment
IMG 0.015% (3 days)	5-FU (face and scalp)	5-FU	IMG 0.015%	IMG 0.015%
IMG 0.05% (2 days)	5-FU (trunk and extremities)	5-FU	IMG 0.05%	IMG 0.05%
Imiquimod 5% (16 weeks)	5-FU (face and scalp)	5-FU	Imiquimod 5%	Imiquimod 5%
5-FU	5-FU (face and scalp OR trunk and extremities)	5-FU	5-FU	5-FU

5-FU = 5-fluorouracil; IMG = ingenol mebutate gel.

Source: Adapted from Manufacturer's pharmacoeconomic submission,¹ Table 1, page 6.

The manufacturer submitted a decision tree using data from pivotal phase III vehicle-controlled studies of ingenol mebutate 0.015% (Study PEP005-016² and Study PEP005-025)³ and ingenol mebutate 0.05% (Study PEP005-014⁴ and Study PEP005-028)⁵ to determine the proportion of patients likely to respond to treatment, and the rate of recurrence. Results from the four studies were pooled.

The primary outcomes of all four studies was complete clearance (no lesions remaining), although a secondary end point of partial clearance (> = 75% of lesions) was also assessed. Treatment response for imiquimod 5% and 5-FU were assumed to be equal to the ingenol mebutate population. The likelihood of recurrence for imiquimod 5% was assumed to be identical to ingenol mebutate 0.015%. The likelihood of recurrence for 5-FU was assumed to correspond to the average of ingenol mebutate 0.015% and ingenol mebutate 0.05%. This was done to account for the differences in administration site.

The manufacturer identified one meta-analysis of treatments for AK (Gupta et al.)⁶ to support the argument that ingenol mebutate was equivalent to other AK treatments. The manufacturer assumed a cycle length of 6 months, after which patients were assessed, and a time horizon of 24 months. A 5% discount rate was applied to costs after Year 1.

The manufacturer's results report the cost of the complete treatment sequence (assumed to be four cycles over 24 months); thus all cost analyses include initial and recurrent treatment with 5-FU. The results of the CMA for complete and partial clearance of lesions on the face and scalp indicated that ingenol mebutate 0.015% had an incremental cost of between \$170 and \$313 compared with 5-FU and a saving of less than \$1 when compared with imiquimod 5% in the same patient population (Table 3). The results of the CMA for complete and partial clearance of lesions on the trunk and extremities

indicated that ingenol mebutate 0.015% had an incremental cost of between \$264 and \$375 compared with 5-FU (Table 3).

TABLE 3: SUMMARY OF INCREMENTAL TOTAL DRUG COSTS AS REPORTED BY THE MANUFACTURER

Treatment, Compared With IMG	Incremental Total Drug Cost (Versus IMG)	
	Complete Clearance	Partial Clearance
Face and Scalp		
Imiquimod 5%: 2 x week (16 weeks)	(\$0.32)	(\$0.17)
5-FU: 2 x daily (4 weeks)	\$313.30	\$169.60
Trunk and extremities		
5-FU: 2 x daily (4 weeks)	\$374.98	\$264.21

5-FU = 5-fluorouracil; IMG = ingenol mebutate gel.

Source: Adapted from Manufacturer’s Pharmacoeconomic Submission,¹ Table 14, page 22.

All four studies measured quality of life and patient satisfaction compared with vehicle; however, these results were not presented.

3. INTERPRETATIONS AND KEY LIMITATIONS

The following limitations with the manufacturer’s submission were noted:

- Lack of data to support second-line therapy.** In the clinical studies, only a small proportion of patients received ingenol mebutate after having received 5-FU. Although the results of a subgroup analysis for this population are generally similar to the overall patient population, the results appear to indicate that ingenol mebutate works better as a first-line topical agent. However, the population is small and thus the robustness of these results is uncertain. The majority of the clinical data are for use as a first-line treatment, in line with the Health Canada indication.
- No robust evidence that ingenol mebutate gel is equivalent to 5-FU and/or imiquimod 5%.** As indicated in Appendix 7 of the clinical report, the systematic review by Gupta et al. (2012)⁶ does not adequately assess the indirect treatment comparison of ingenol mebutate gel 0.015% versus 5-FU or imiquimod 5% in patients with AK on the face or scalp; or ingenol mebutate gel 0.05% versus 5-FU in patients on the trunk or extremities. Although the systematic review met all assessing methodological quality of systematic reviews (AMSTAR) criteria and is considered to be of high methodological quality, it was limited by the heterogeneity and low methodological quality of the included studies.
- Model cycle time may not be appropriate.** The manufacturer stated that clinical experts consulted indicated that patients would be reassessed between four and six months after treatment, but use a six-month cycle as opposed to a four-month cycle. The clinical expert consulted by the Common Drug Review (CDR) indicated that assessment at four months was more likely to be appropriate. During the two-year period, the use of a four-month cycle substantially increases the incremental cost of ingenol mebutate compared with 5-FU compared with using a six-month cycle. Therefore, the use of a six-month cycle by the manufacturer has likely underestimated the actual treatment costs.

- **Adherence and persistence.** The manufacturer's analysis did not consider the potential for greater adherence and persistence rates with ingenol mebutate when compared with either comparator due to the substantially shorter treatment duration with ingenol mebutate. The benefits from the shorter treatment duration cannot be seen in the submitted analysis. The only available data related to persistence and adherence are from a patient survey from the UK, in which persistence and adherence rates for ingenol mebutate (~70%) were higher compared with 5-FU (45% to 52%). However, by not taking the improved adherence and persistence into account, the manufacturer may have underestimated the total cost of treatment with ingenol mebutate compared with the comparator treatments.
- **Inappropriate pricing of imiquimod 5%.** It would have been more appropriate to use prices from plans that participate within the CDR process as opposed to using Régie de l'assurance maladie du Québec (RAMQ) pricing in the cost comparison. The submission also presents the results using the cost of exactly 32 doses, although the manufacturer only supplies the imiquimod 5% in packs of 24 and 12. It is thus likely to have wastage (assuming all 32 doses are prescribed). This needed to be taken into account when determining the cost of this comparator, which may increase or decrease the cost of imiquimod 5%, depending on the prescribing habits of clinicians.

4. ISSUES FOR CONSIDERATION

- **Potential for use of ingenol mebutate as first-line therapy.** Based on clinical experience, the Health Canada indication, and available clinical evidence, ingenol mebutate may be used as a first-line topical therapy. If ingenol mebutate is used as a first-line topical agent, this would incur substantially higher treatment costs for public plans than the current first-line topical agent (5-FU).
- **The price of ingenol mebutate.** Given the potential use of ingenol mebutate as a first-line treatment in clinical practice, a price reduction analysis was undertaken versus the current first-line therapy, 5-FU (Appendix 1: Price Reduction Analysis). This analysis indicates that a price reduction of more than 90% is likely required for ingenol mebutate to become cost-saving if used as a first-line therapy.
- **Other issues.** Australia's Pharmaceutical Benefits Advisory Committee (PBAC) rejected an application for ingenol mebutate to be listed on its Pharmaceutical Benefits Scheme (PBS) on the basis of uncertainty in the clinical claim and cost-effectiveness, and that "utilization is uncertain, and is likely to be high and substantially underestimated in the submission." This decision and others are summarized in Appendix 2: Review of Other HTA Agency Reports.

5. CONCLUSIONS

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),² 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 being incurred by public plans.

²These 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.

APPENDIX 1: PRICE REDUCTION ANALYSIS

Because it is possible that ingenol mebutate will be used instead of 5-FU as a first-line therapy for AK, CDR calculated the price reduction that would be required to produce a price of ingenol mebutate that would be equivalent to 5-FU. The calculation considered only drug costs. As shown in Table 4 below, the price of ingenol mebutate would need to be reduced by 91% (from \$383.00 to \$33.51) to be equivalent to the price of 5-FU, based on the median price of 5-FU (see Table 1). At this reduced price, there would be no net savings for public plans. Therefore, if it were to be used as a first-line therapy, the price of ingenol mebutate would need to be reduced by more than 91% to generate any cost savings.

TABLE 4: CDR ANALYSIS FOR PRICE REDUCTION SCENARIOS FOR IMG FOR THE TREATMENT OF AK COMPARED WITH 5-FU

Scenario	Current Price	% Reduction Needed	Reduced Price	Savings ^b (min. to max.)	Max. Savings ^b
Price reduction needed to equal 5-FU	\$383.00	91.3%	\$33.51 ^a	\$0	None

5-FU = 5-fluorouracil; AK = actinic keratosis; IMG = ingenol mebutate gel.

^a Median cost of 5-FU (Nova Scotia). The price of 5-FU ranges from \$32 to \$36 according to publicly available prices from drug formularies.

^b Savings per patient per year.

APPENDIX 2: REVIEW OF OTHER HTA AGENCY REPORTS

Australia's PBAC rejected the submission for the use of ingenol mebutate for the "field treatment of solar keratosis³ of the face and scalp in patients where topical fluorouracil 5% is clinically inappropriate ... on the basis that the clinical claim that treatment of solar keratosis with ingenol reduces the risk of squamous cell carcinoma was not quantified, that the cost-effectiveness in the PBS setting is unknown, and that the utilisation is uncertain, and is likely to be high and substantially underestimated in the submission."

The manufacturer undertook an indirect comparison of ingenol mebutate and imiquimod 5% based on five trials; PEP005-015, PEP005-016, and PEP005-025 (ingenol), and Jorizzo 2007 and Korman 2005 (imiquimod). The PBAC noted that the results of the indirect comparison showed that the relative risk of the primary outcome measure of complete clearance with ingenol was not significantly different than that of imiquimod.⁷

As of March 2013, an evidence summary by the National Institute for Health and Care Excellence (NICE) indicated that ingenol mebutate gel was not considered appropriate for a NICE technology appraisal and is not currently planned into any other work program.⁸ These evidence summaries provide summaries of key evidence for selected medicines that are considered to be of significance to the National Health Service (NHS). The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS. However, it is important to note that this summary is not NICE guidance.

The Scottish Medicines Consortium (SMC) accepted the application for ingenol mebutate for cutaneous treatment of non-hyperkeratotic, non-hypertrophic AK in adults because the balance of costs and benefits meant that the SMC considered it offered value for money.⁹

³Solar keratosis is another term for actinic keratosis

REFERENCES

1. Pharmacoeconomic evaluation. In: CDR submission binder: Picato® (ingenol mebutate) topical gel 0.015% and 0.05% [CONFIDENTIAL manufacturer's submission]. Thornhill (ON): LEO Pharma Inc; 2013 May.
2. 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.
3. 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.
4. 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.
5. 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 (REGION-Ib) [CONFIDENTIAL internal manufacturer's report]. Bowen Hills, QLD (Australia): Peplin Operations Pty Ltd; 2010 Sep 8.
6. Gupta AK, Paquet M, Villanueva E, Brintnell W. Interventions for actinic keratoses. *Cochrane Database Syst Rev.* 2012;12:CD004415.
7. Australian Government. Department of Health and Ageing. Ingenol, gel, 0.15 mg per g (0.015%), 70 mcg ingenol mebutate in 0.47 g single use tubes, 3, Picato® [Internet]. Canberra: Commonwealth of Australia; 2012. [cited 2013 Jul 18]. Available from: <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-11/ingenol>
8. National Institute for Health and Care Excellence. ESNM14: actinic keratosis: ingenol lmebutate gel [Internet]. London: The Institute; 2013. [cited 2013 Jul 18]. Available from: <http://publications.nice.org.uk/esnm14-actinic-keratosis-ingenol-mebutate-gel-esnm14/relevance-to-nice-guidance-programmes>
9. Scottish Medicines Consortium. Ingenol mebutate, 150 & 500 micrograms/g, gel Picato®. LEO Laboratories. SMC no. (851/13) [Internet]. Glasgow: NHS Scotland; 2013 Mar 11. [cited 2013 Jul 29]. Available from: http://www.scottishmedicines.org.uk/files/advice/ingenol_mebutate_gel_Picato_FINAL_FEBRUARY_2013_amended_04.03.13_for_website.pdf