Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Angela Timoney FRPharmS
NHS SCOTLAND

ingenol mebutate, 150 & 500micrograms/g, gel (Picato®) SMC No. (851/13)

LEO Laboratories

08 February 2013

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

ingenol mebutate (Picato®) is accepted for use within NHS Scotland.

Indication under review: Cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.

In four randomised, double-blind, phase III studies, a significantly greater proportion of adults with actinic keratosis (AK) achieved complete clearance when treated with ingenol mebutate gel compared with vehicle control.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

Cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.

Dosing Information

The 150micrograms/g gel is for intended for application to the face and scalp: one tube (containing 70micrograms ingenol mebutate in 0.47g of gel) should be applied once daily to the affected area for 3 consecutive days.

The 500micrograms/g gel is intended for application to the trunk and extremities: one tube (containing 235micrograms ingenol mebutate in 0.47g of gel) should be applied once daily to the affected area for 2 consecutive days.

The content of one tube covers a treatment area of 25cm^2 (e.g. 5cm x 5cm). The content of the tube should be applied to one treatment area of 25cm^2. The tube is for single use only and should be discarded after use. Washing and touching the treated area should be avoided for a period of six hours after application. After this period, the treatment area may be washed using mild soap and water.

Product availability date

January 2013

Summary of evidence on comparative efficacy

Ingenol mebutate is a new topical agent for the treatment of AK. It has a novel mode of action that is not fully understood, but is believed to involve a dual effect on AK lesions: induction of local lesion cell death, and a pro-inflammatory response characterised by infiltration of immuno-competent cells.

Evidence for the use of ingenol mebutate in the treatment of AK is from four similarly designed randomised, double-blinded, vehicle-controlled, parallel-group phase III studies. Two of the studies investigated the efficacy and safety of ingenol mebutate when applied to lesions on the face or scalp (PEP005-016, PEP005-025) and two when applied to the trunk or extremities (PEP005-014, PEP005-028). Observational extension studies gathered evidence of safety, durability of response and recurrence rate over one year of follow-up.[1-3]

The four pivotal studies recruited adults with four to eight discrete, clinically typical (eg non-hypertrophic, non-hyperkeratotic) and visible AK lesions within a 25cm^2 contiguous area on the anatomical location of interest. Patients were randomised in a ratio of 1:1 to receive either ingenol mebutate gel or vehicle control, applied once daily to the 25cm^2 area. In the two studies of AK on the face or scalp, ingenol 150micrograms/g gel or vehicle was applied for three consecutive days. In the two studies of AK on the trunk or extremities, ingenol mebutate 500micrograms/g gel or vehicle was applied for two consecutive days. Patients were followed up for eight weeks. The primary outcome measure for both studies was complete clearance of all clinically visible lesions within the target area on day 57 analysed in the intention-to-treat (ITT) population with imputation using last observation carried forward. A significantly greater proportion of patients treated with ingenol mebutate achieved complete clearance compared with vehicle in all four studies.[1] The results for the primary outcome for each individual study, and pooled analyses by anatomical location are presented in the table below:

Anatomical Location	Study	Complete Clearance		
		Ingenol mebutate (n, %)	Vehicle (n, %)	p-value of difference
Face & Scalp	PEP005-016	50/135 (37%)	3/134 (2.2%)	<0.001
	PEP005-025	67/142 (47%)	7/136 (5.1%)	<0.001
	Pooled	117/277 (42%)	10/270 (3.7%)	<0.001
Trunk & Extremities	PEP005-014	35/126 (28%)	6/129 (4.7%)	<0.0001
	PEP005-028	42/100 (42%)	5/103 (4.9%)	<0.001
	Pooled	77/226 (34%)	11/232 (4.7%)	<0.001

Table: Primary outcome results for the pivotal studies and pooled analyses by anatomical location.[1]

The main secondary endpoint in the pivotal studies was partial clearance, defined as at least a 75% reduction in the number of AK lesions within the target area when assessed at day 57 compared with baseline. In the pooled analysis of studies on the face or scalp, PEP005-016 and PEP005-025, partial clearance was achieved by 64% and 7.4% of patients in the ingenol mebutate and vehicle groups respectively, $p<0.001$. In the pooled analysis of the studies on the trunk and/or extremities, PEP005-014 and PEP005-028, partial clearance was achieved by 49% and 6.9% of patients in the ingenol mebutate and vehicle groups respectively, $p<0.001$.[1]

Quality of life was assessed using the validated Skindex-16 questionnaire which measured sixteen items grouped into three domains (emotions, function, and symptoms) rated on a 7-point scale, with higher scores relating to a lower quality of life. In the studies of AK lesions of the face or scalp, ingenol mebutate was associated with significantly greater improvements in score for the three domains at day 57 compared with vehicle. There were mixed results in the trunk and/or extremities studies: PEP005-014 found no significant difference between the groups at day 57, but PEP005-028 did.[3]

Lesion recurrence, defined as any newly identified AK lesion in the selected treatment area, whether previously treated or not, was assessed in a phase III, observational, extension study in which patients with complete clearance at day 57 from studies of the face or scalp, PEP005-016 and PEP005-025 (ingenol mebutate [n=108], vehicle [n=9]) were followed-up over 1 year. At 12 months, in the pooled analysis the recurrence rate in the ingenol mebutate group was 54%. The Kaplan-Meier estimate of the median time to recurrence was 365 days in the ingenol mebutate group.[2,3]

Two one-year observational extension studies following up patients with complete clearance of trunk and/or extremity lesions were pooled to characterise the recurrence rate associated with ingenol mebutate treatment. One study recruited patients from PEP005-028 and the other from an open-label phase study not previously described, PEP005-020 (ingenol mebutate [n=76], vehicle [n=5]) . In the pooled analysis, the recurrence rate at 12 months was 56% in the ingenol mebutate group. The Kaplan-Meier estimate of the median time to new or recurrent lesion was 274 days.[2,3]

Summary of evidence on comparative safety

No comparative safety data are available. Refer to the summary of product characteristics for details of adverse effects.

When lesions of the face or scalp were treated, adverse events were reported in 37% (102/274) of ingenol mebutate and 22% (60/271) of vehicle patients. The most common adverse events were administration-site reactions: pruritus (8.0% versus 1.1%), pain (14% versus 0.4%), and irritation (1.8% versus 0%) in the ingenol mebutate and vehicle groups respectively. Local skin reactions peaked at day 4 in the ingenol mebutate group and tended to resolve by day 14.[1]

A similar profile was noted when treating trunk and/or extremities' lesions: 33% (75/225) of ingenol mebutate and 27% (63/232) of vehicle patients reported adverse events. Administration-site reactions incidence were: pruritis (8.4% versus 0%), pain (2.2% versus 0%), and irritation (3.6% versus 0.4%) in the ingenol mebutate and vehicle groups respectively. Local reactions peaked between days 3 and 8 in the ingenol mebutate group and tended to resolve by day 29.[1]

No adverse events related to treatment were identified during the one-year follow-up studies.[2]

Summary of clinical effectiveness issues

Ingenol mebutate treatment was associated with significantly superior rates of complete clearance of AK lesions from a field area of 25cm^2 on the trunk, extremities, face, or scalp compared with vehicle control. In the pooled analyses, the proportion of patients achieving complete clearance was 34% and 42% on the trunk/extremities and face/scalp, respectively.[1] Approximately half of patients (44% to 46% depending upon anatomical location) who achieved complete clearance with ingenol mebutate remained clear after 1 year.[2,3] There is no evidence to support re-treating with ingenol mebutate in patients who either do not achieve clearance or experience recurrence.

The primary outcome measure in all four pivotal studies, the percentage of patients with complete clearance of AK lesions in the treatment area, is a clinically relevant endpoint for patients with AK. AK is associated with a small risk of progression to squamous cell cancer. The rate of malignant transformation is less than 1 in 1,000 per year, and the risk has been estimated as 10% over 10 years in people with an average of 7.7 lesions.[4]

In general, the studies were well conducted with little risk of bias identified although there may have been a risk of un-blinding due to a higher rate of local adverse events with ingenol mebutate,

As there were no active-comparator studies, the company presented a Bayesian network meta-analysis (NMA) in which ingenol mebutate was indirectly compared with diclofenac 3% gel (8-week and 12-week courses), 5-fluorouracil 5% cream and 5-fluorouracil 0.5%/salicylic acid 10% cutaneous solution. The network was comprised of 11 studies in adults with AK and compared one outcome, complete clearance of lesions. In the analysis using a random-effects model, wide 95% credible intervals led to the conclusion that none of the treatments were statistically significantly different to one-another.

The validity (internal and external) of the NMA added to the uncertainty in interpreting the results. For a number of factors that could be considered relative treatment effect modifiers, either there are known differences between the studies (e.g. time of outcome assessment post completion of treatment, anatomical location and number of AK lesions at baseline), or there are un-quantified sources of clinical heterogeneity between the studies due to inconsistent reporting (eg Fitzpatrick skin type, thickness, or lesion type). Another limitation of the indirect comparison is the unknown generalisability of the results, again due to inconsistent reporting of the constituent studies. The proposed indication under review is the treatment of non-hyperkeratotic and non-hypertrophic AK lesions in adults. Some of the studies did not consider or report lesion thickness/type as part of the inclusion/exclusion criteria.

Ingenol mebutate has a short treatment duration (either two or three days) that is likely to be convenient to the patient, promoting a high degree of patient adherence as other licensed topical medicines for AK have recommended treatment courses of at least four weeks. Between 97 and 99% of patients treated with ingenol mebutate in the pivotal studies completed the treatment. With local

skin reactions from ingenol mebutate application peaking in the first few days following commencement, the short duration of treatment may encourage patients to persevere with the course.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis using a one-year time horizon comparing ingenol mebutate with a range of comparator topical treatments: diclofenac (8 weeks and 12 weeks), 5-fluorouracil, 5-fluorouracil/salicylic acid and cryotherapy. The submitting company stated that the main comparator was diclofenac as this is the most commonly prescribed therapy for AK lesions in primary care in Scotland. The economic analysis considered the use of the 150mcg/g gel (for use on the face or scalp) and the 500mcg/g gel (for use on the trunk or extremities) separately.

A decision tree model was used in the analysis. Patients entered the model on initiation of first-line therapy, where they received either ingenol mebutate gel or one of the comparator treatments. Six months after initiation of first-line therapy it was assumed that patients either responded to treatment and achieved complete clearance (CC) or failed treatment and did not achieve CC. Patients were assumed to remain in these health states for the remainder of the model. The impact of recurrence was considered in a scenario analysis where the time horizon was extended to 2 years.

The source of clinical data used in the model was the NMA indirect comparison. For the efficacy data relating to ingenol mebutate the pivotal placebo-controlled studies were included in the NMA. The utility values for CC (1.00) and AK (0.986) health states were obtained from published studies. Quality of life loss from adverse events was not included in the base case, but considered as a scenario analysis. It was estimated that all patients with AK were initially seen in primary care but a proportion would be referred to a dermatologist. It was also assumed that following the dermatology appointment patients would require a follow-up GP visit.

The submitting company estimated the following results for ingenol mebutate 150mcg/g gel:

Ingenol mebutate 150mcg/g gel (3 days) vs	**Incremental cost**	**Incremental Quality-adjusted life-years (QALYs)**	**Incremental cost per QALY**
Diclofenac (8 weeks)	£0.20	0.0045	£44
Diclofenac (12 weeks)	£0.20	0.0054	£36
5-FU (4 weeks)	-£62.88	-0.0024	£26,525*
5-FU/salicylic acid (12 weeks)	£0.20	0.0042	£47
Cryotherapy	-£47.80	0.0036	Dominant

*ingenol mebutate less expensive but less effective

For the analysis based on the 500mcg/g strength, the following results were estimated:

Ingenol mebutate 500mcg/g gel (2 days) vs	Incremental cost	Incremental QALYs	Incremental cost per QALY
Diclofenac (8 weeks)	£0.20	0.0018	£114
Diclofenac (12 weeks)	£0.20	0.0027	£74
5-FU (4 weeks)	-£62.88	-0.0051	£12,150*
5-FU/salicylic acid (12 weeks)	£0.20	0.0015	£134
Cryotherapy	-£47.80	0.0009	dominant

*ingenol mebutate less expensive but less effective

The following weaknesses were noted:

- Scottish prescribing data indicates that diclofenac is the most widely prescribed treatment in primary care. However, the results of the economic analysis showed that ingenol mebutate may not be cost-effective when compared with 5-fluorouracil, which is also widely used in practice.
- There were some weaknesses with the NMA. In particular, the differences between the active comparator treatments were not statistically significant.
- The rate of recurrence was not included in the NMA due to the lack of data on recurrence for all the treatments in the model. Therefore, some assumptions had to be made to estimate the recurrence rates for diclofenac and 5-fluorouracil/salicylic acid.

Given the weakness regarding the inclusion of non-significant differences in outcomes, the submitting company provided additional analysis to show the results under the conditions of a cost-minimisation analysis (i.e. no differences in outcomes between treatments). This showed that ingenol mebutate would be associated with an additional cost of £0.20 compared to both diclofenac regimens and 5-FU/salicylic acid, but would be give cost-savings of £62.16 and £47.80 against 5-FU (4 weeks) and cryotherapy respectively. The company also provided evidence from a Bucher method indirect comparison to indicate that ingenol mebutate would be associated with statistically significant improvements in efficacy compared to diclofenac 5-FU/salicylic acid, and hence that the assumption of equal outcomes under the cost-minimisation analysis may be conservative against these comparators.

Additional analyses using the cost-minimisation approach were also provided to include allowance for recurrence rates. This increased the additional costs associated with ingenol mebutate to £4.32 against the diclofenac regimens and to £8.44 against 5-FU/salicylic acid but increased the savings versus 5-FU (4 weeks) and cryotherapy to £81.63 and £99.73 respectively. It should be noted however that the cost-minimisation analysis scenarios all assumed equal adherence to therapy, which may not be realistic given the shorter treatment duration with ingenol mebutate which could be expected to translate into better compliance.

Given these additional analyses, the economic case has been demonstrated.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Melanoma Action and Support Scotland – MASScot
- Skin Conditions Campaign Scotland

Additional information: guidelines and protocols

The Primary Care Dermatology Society published an updated Primary Care Treatment Pathway of actinic (solar) keratosis in 2012. All patients are encouraged to use sun screen and protection and to use emollients for symptom control. For non-hyperkeratotic, non-hypertrophic AK lesions (which would be considered Grade I lesions on the Olsen scale), treatment with diclofenac 3% gel was strongly recommended, with relative recommendations made for 5-fluorouracil 5% cream, imiquimod, 5-fluorouracil 0.5%/salicylic acid 10% cutaneous solution and cryotherapy.[5]

In a patient pathway published in 2010 under NHS Scotland's "18 weeks: Better Care Without Delay" and developed in consultation with the Scottish Dermatological Society, primary care management of AK was outlined. For keratoses that are non-tender and non-infiltrated, the following treatment options were recommended:

- No treatment or diclofenac 3% gel for small non-tender AKs
- Cryotherapy or 5-fluorouracil for more extensive, thicker AKs
- Curettage for solitary cutaneous horns, with specimens sent for histopathology testing.[6]

In 2007, the British Association of Dermatologists published "Guidelines for the management of actinic keratoses". The guidelines concluded that there was insufficient comparative data to make a justified single recommendation on treatment choice, rather treatment should be individualised with the following factors considered: clinical presentation, the efficacy, morbidity, availability and cost of relevant treatments and patient choice.[4]

Additional information: comparators

Treatments for AK include topical therapies such as application of emollients and sun-block. Medicines specifically licensed for the treatment of AK include: fluorouracil 5% cream, diclofenac 3% gel, imiquimod 5% cream, and fluorouracil 0.5%/salicylic acid 10% cutaneous solution. The indications for each product varies by type of lesion to be treated (e.g. Olsen grade) and number or surface area to be treated.

Other treatment modalities include: cryosurgery, curettage/excisional surgery, laser, chemical peel, dermabrasion, and photo-dynamic therapy (using photosensitising agents such as methyl aminolevulinate cream, 5-aminolaevulinic acid gel).

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Ingenol mebutate gel	**Face or scalp: 150micrograms/g gel applied to lesions once daily for three days. Trunk or extremities: 500micrograms/g gel applied to lesions once daily for two days.**	**65**
Methyl aminolevulinate cream	Applied topically to lesions as part of photodynamic therapy. Can be repeated after 12 weeks if insufficient response.	199 to 398*
5-aminolaevulinic acid gel	Applied topically to lesions as part of photodynamic therapy. Can be repeated after 12 weeks if insufficient response.	184 to 368*
Imiquimod 5% cream	Applied to lesions three times a week for four weeks. Can be repeated after four week treatment-free period if lesions persist.	49 to 97
Diclofenac 3% gel	Applied topically to lesions twice daily for 60 to 90 days.	77
Fluorouracil 0.5% & salicylic acid 10% cutaneous solution	Applied to lesions once daily for up to 12 weeks.	77
Fluorouracil 5% cream	Applied topically to lesions once or twice daily for up to 28 days.	33

Doses are for general comparison and do not imply therapeutic equivalence. Costs based on treating surface area of 5x5cm. Costs from eVadis on 14 November 2012, except ingenol mebutate (from company submission) and * from www.mims.co.uk [Accessed 19 December 2012].

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 37,392 in all years with an estimated uptake rate of 5% in year 1 and 25% in year 5. The gross impact on the medicines budget was estimated to be £122k in year 1 and £608k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to result in savings of £18k in year 1 and £88k in year 5.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1) Lebwohl M, Swanson N, Anderson LL et al. Ingenol mebutate gel for actinic keratosis. New Eng J Med 2012; 366: 1010-9 (plus online supplement)

2) Stein Gold L, Larsson T, Melgaard A. Long-term follow-up studies of ingenol mebutate gel for the treatment of actinic keratosis. American Academy of Dermatology Annual Meeting 2012 Poster Presentation #5620. 2012. [online] Available from www.aad.org/Posters/view/default.aspx

3) European Medicines Agency. Assessment Report – Picato EMA/650464/2012. [online] Available from www.ema.europa.eu [Last updated 29 November 2012].

4) De Berker D, McGregor JM & Hughes BR. Guidelines for the management of actinic keratoses. Br J Dermatol (2007); 156: 222-30.

5) Keohane S, Kownacki S, Moncrieff G et al. PCDS Guidelines – Actinic (solar) keratosis: primary care treatment pathway. September 2012. [online] Available from http://www.pcds.org.uk/ee/images/uploads/general/Actinic_(Solar)_Keratosis_Primary_Care_Treatment_Pathway.pdf

6) Dermatology referral and management pathway: solar (actinic) keratoses and Bowen's disease. [online] Available from http://www.18weeks.scot.nhs.uk/patient-pathways/dermatology [Accessed 15 October 2012]

This assessment is based on data submitted by the applicant company up to and including 11 January 2013.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.