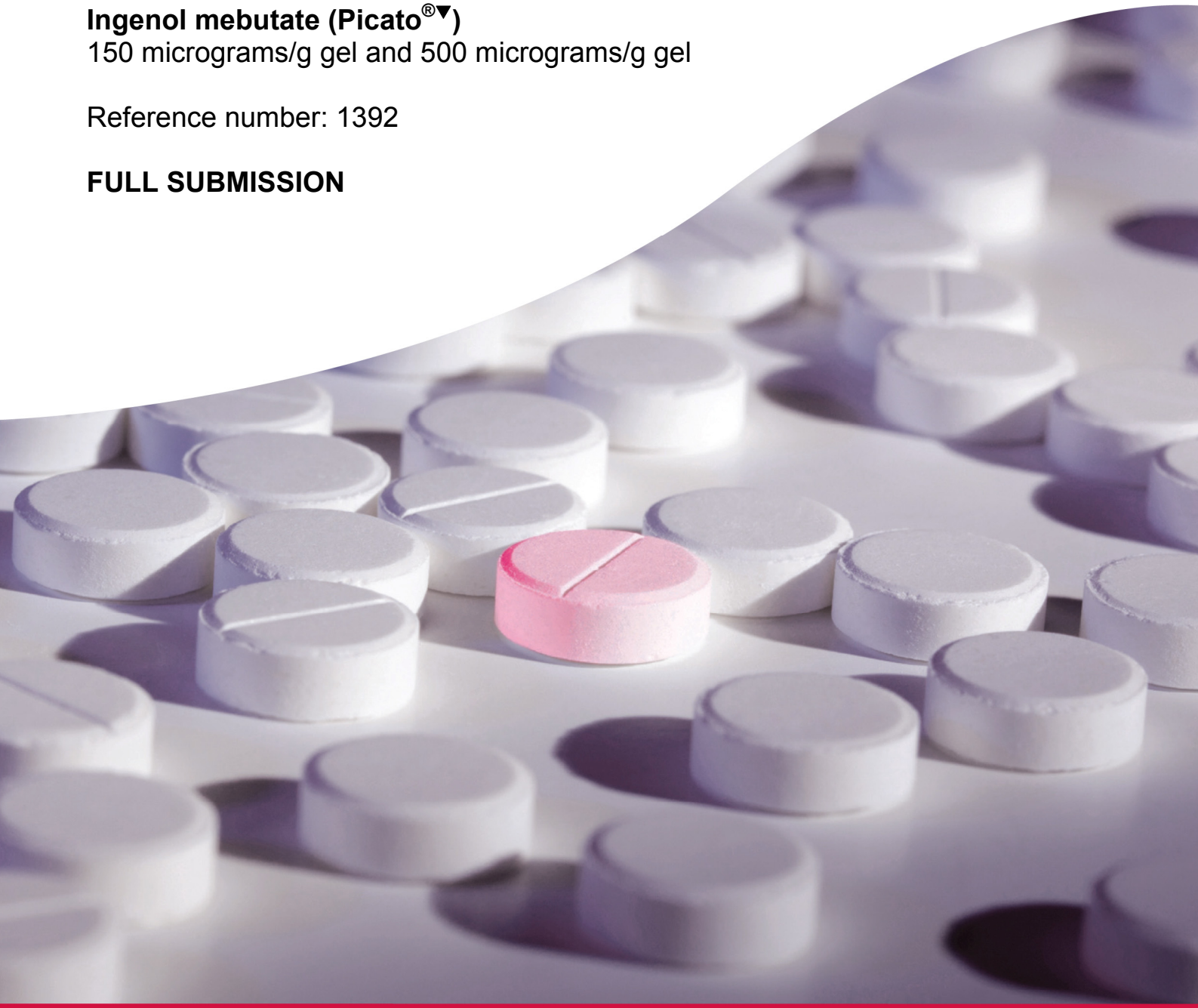
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Ingenol mebutate (Picato®▼)
150 micrograms/g gel and 500 micrograms/g gel

Reference number: 1392

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Ingenol mebutate (Picato®▼)
150 micrograms/g gel and 500 micrograms/g gel

This assessment report is based on evidence submitted by Leo Laboratories Ltd on 3 December 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Ingenol mebutate (Picato®▼) is indicated for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (AK) in adults.
Dosing	For AK on the face or scalp, one tube of 150 micrograms/g gel should be applied once daily to the affected area for three consecutive days. For AK on the trunk and extremities, one tube of 500 micrograms/g gel should be applied once daily to the affected area for two consecutive days. The content of one tube should be used for one treatment area of 25 cm^2, allowing it to dry for 15 minutes. Refer to the Summary of Product Characteristics for further administration details[2,3].
Marketing authorisation date	15 November 2012[2,3].

2.0 DECISION CONTEXT

2.1 Background

Actinic keratoses (AKs) are skin lesions considered to be precursors to squamous cell carcinoma (SCC)[4]. They present as dry, rough, yellow-brown scaly plaques which may become thickened and horny[5]. AKs occur most commonly on areas of increased sun exposure (for example the face, scalp, hands and forearms), and occur more frequently in individuals with fairer skin types, suggesting that most result from chronic exposure to ultraviolet radiation[4,6]. Prevalence of AKs increases with age and is higher in men than women[7,8]. A 1996 study conducted in South Wales estimated the prevalence of AK in individuals aged 60 or over to be 33% in men, 16% in women and 23% for both sexes combined[7] (refer to Section 5 for discussion of the number of patients eligible for treatment with ingenol mebutate).

The risk of progression of an AK lesion to malignancy is low and lesions may undergo spontaneous regression without treatment; rates of spontaneous regression over one year have been reported as 15–25%[6,7,9]. Most individuals present with multiple lesions, and the risk of malignant transformation of at least one lesion over a ten-year period has been estimated as 10%[6]. In addition to prevention of progression to SCC, treatment may also aim to provide relief of symptoms or disfigurement resulting from the presence of lesions[6]. Clinical opinion appears to be divided on whether all AK cases require treatment; some guidelines recommend no therapy as a reasonable option for mild lesions[6], others argue that it is impossible to predict which lesions will become malignant and therefore all cases should be treated[10]. Treatment strategies include palliative treatment with an emollient, topical treatment (options available in the UK include fluorouracil cream, imiquimod 5% cream, fluorouracil and salicylic acid solution and 3% diclofenac gel), surgical excision, cryotherapy or photodynamic therapy[6]. Ingenol mebutate has a dual mechanism of action: induction of local lesion cell death and promotion of an inflammatory response characterised by infiltration of immunocompetent cells[11].

2.2 Comparators

The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were:

- Diclofenac 3% gel (Solaraze®)
- Fluorouracil 5% cream (Efudix®)

2.3 Guidance and related advice

- Primary Care Dermatology Society. Clinical guidance: actinic keratoses (2012)[5].
- Primary Care Dermatology Society. Actinic (solar) keratosis primary care treatment pathway (2012)[12].
- European Dermatology Forum. Guidelines for the management of actinic keratoses (2011)[10].
- British Association of Dermatologists. Guidelines for the management of actinic keratoses (2007)[6].
- National Institute for Health and Clinical Excellence (NICE). Interventional Procedure Guidance 155. Photodynamic therapy for non-melanoma skin tumours (including premalignant and primary non-metastatic skin lesions) (2006)[13].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company has submitted evidence from eight clinical trials assessing the use of ingenol mebutate to treat AK: two pivotal phase III trials in patients with AKs on the face or scalp; two pivotal phase III trials in patients with AKs on the trunk or extremities; one uncontrolled, single arm open label phase IIIb trial; and three follow-up studies from the phase III/IIIb trials. The uncontrolled trial was not significant in drawing additional conclusions regarding the efficacy of ingenol mebutate[11] and therefore this trial will not be discussed further. In order to estimate the relative efficacy of ingenol mebutate, diclofenac and fluorouracil, the company also conducted a systematic review of the published literature to identify randomised controlled trials (RCTs), from which a mixed treatment comparison (MTC) was conducted.

3.1 Clinical evidence comparing ingenol mebutate and vehicle gel

Four multicentre, randomised, parallel-group, double-blind studies were conducted: two trials were carried out on patients with AKs on the face or scalp and two trials were conducted on patients with AKs on the trunk or extremities. The studies have been analysed as four individual trials[1] and as two pooled studies[14]; data presented in this report focuses on the pooled results. Eligibility criteria for all four trials included an age of ≥ 18 years and the presence of four to eight clinically typical, visible and discrete AKs within a 25 cm^2 contiguous area. Approximately half of the treated population had a history of skin cancer and the majority of patients had either Fitzpatrick skin type I (always burns, never tans) or II (burns easily, tans minimally). The mean age of participants was 65.1 years[14].

Patients with AKs on the face or scalp (n = 547) were randomly assigned to receive either ingenol mebutate 150 micrograms/g gel (n = 277) or vehicle gel (n = 270), to be self-applied to a 25 cm^2 area once daily for three consecutive days. Patients with AKs on the trunk or extremities (n = 458) received either ingenol mebutate 500 micrograms/g gel (n = 226) or vehicle gel (n = 232), to be self-applied to a 25 cm^2 contiguous area once daily for two consecutive days. The primary end point was complete clearance (CC, defined as no clinically visible AK lesions in the selected treatment area) measured on day 57 following treatment. Partial clearance (PC, defined as a reduction of 75% or more from baseline in the number of AKs in the target area) on day 57 was a secondary end point[14].

In the pooled face and scalp studies, 42.2% of patients in the ingenol mebutate arms had CC at day 57 versus 3.7% in the placebo arms ($p < 0.001$). In the pooled trunk and extremities studies, CC at day 57 was achieved for 34.1% of patients in the ingenol mebutate arms versus 4.7% in the placebo arms ($p < 0.001$). PC results for the pooled data were also statistically significant, supporting the primary endpoint. Analysis of the individual results from each of the four trials (summarised in Appendix 1, Table 1A[1]) was consistent with the pooled analysis[14].

Patient-reported outcomes were measured as exploratory endpoints, using the Treatment Satisfaction Questionnaire for Medication (TSQM) and Skindex-16 Dermatological Survey[1]. At study day 57, the TSQM results showed statistically significantly higher mean patient satisfaction with ingenol mebutate treatment compared to placebo treatment. Skindex-16 data showed a statistically significantly greater improvement for ingenol mebutate treatment versus placebo at day 57 for all studies, with the exception of PEP005-014 (results indicated improvement in patient concern regarding their skin condition in both treatment groups, but there were no statistically significant differences between groups)[11].

Three observational follow up studies (one of the face and scalp and two of the trunk and extremities) were carried out to evaluate recurrence of AKs within the selected target area and long term safety of ingenol mebutate therapy. These studies are summarised in Appendix 1, Table 2A. An observational follow-up trial of the face and scalp studies was carried out at month 12, on patients whose lesions had completely cleared at day 57 (108 received ingenol mebutate, 9 received placebo). One or more lesions developed or recurred in the treatment field within 12 months for 53.9% of patients receiving ingenol mebutate and for 72.2% of placebo-treated patients[1]. An observational follow-up trial of the trunk and extremities studies was also carried out at month 12, on patients whose lesions had completely cleared at day 57 (38 received ingenol mebutate, 5 received placebo). One or more lesions developed or recurred in the treatment field within 12 months for 50% of patients receiving ingenol mebutate and for 80% of placebo-treated patients [1,14]. A further follow-up study was carried out on 38 patients, who had achieved CC in the uncontrolled single arm study of ingenol mebutate, targeting trunk and extremities. At month 12 one or more lesions had developed or recurred for 62.5% of these patients.

3.2 Comparative efficacy of ingenol mebutate, diclofenac and fluorouracil

In the absence of a direct comparison of ingenol mebutate and other AK treatments, the company conducted a systematic review of the published literature to identify suitable RCTs for inclusion in an MTC[1]. Trials identified were the four studies discussed in section 3.1 (treated as two RCTs in the MTC[1]), five trials of diclofenac gel[15–19] and one trial of fluorouracil cream[20]; results and design of these are summarised in Table 3A, Appendix 1. Although imiquimod was not a requested comparator, three RCTs using imiquimod[20–22] were also included in the MTC in order to connect the treatments of relevance. The majority of studies identified were placebo controlled. The primary measure of efficacy used in the MTC was CC, the definition of which varied between the included studies. The time to follow-up in the trials ranged from four weeks to six months. Both a random-effects and a fixed-effects MTC were conducted; the company report that the random-effects model provided the best fit for the data and these results have been used in the cost-effectiveness model supplied. The results of the random-effects and fixed-effects MTC are displayed in Table 1.

Table 1. Mixed treatment comparison results: mean log odds ratios and probabilities of complete clearance[1]

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3.3 Comparative safety

Safety evidence is presented from the pivotal phase III studies described in Section 3.1, comparing ingenol mebutate and vehicle gel. Safety endpoints in these studies included adverse events and local skin responses (LSRs)[14]. Most patients treated with ingenol mebutate (> 95%) experienced mild to moderate LSRs, most commonly erythema and flaking/scaling. Typically, LSRs occurred within one day of treatment initiation, peaked in intensity up to one week after treatment and resolved within two weeks for face or scalp applications and within four weeks for the trunk or extremities[11]. Across all four studies, the most common application site reactions reported by ingenol mebutate-treated patients were pain (13.9%: 2.2%), pruritus (8.0%: 8.4%) and irritation (1.8%: 3.6%)[1,14].

As part of the follow-up trials (see Section 3.1 and Appendix 1, Table 2A), patients with CC at day 57 (184 treated with ingenol mebutate and 14 treated with placebo) were monitored for adverse events for an additional 12 months. There were no differences to the safety profile of ingenol mebutate observed in the phase III studies[11].

Safety data pooled from 13 trials, including the pivotal phase III studies, showed that serious adverse events (SAEs) occurred in 4.2% of patients in the ingenol mebutate arms and 3.6% of patients in the vehicle gel arms[11]. Basal cell carcinoma occurred in 1.5% of ingenol mebutate-treated patients and in 1.1% of vehicle gel-treated patients. SCC occurred in 0.9% of patients in the active gel group and in 0.8% of the vehicle gel group. Three patients treated with the 500 micrograms/g gel had treatment-related SAEs: one developed Bowen's disease and two developed SCC; all three SAEs resolved after excision[11].

No data directly comparing the safety profiles for ingenol mebutate with any active comparator was included in the company submission.

3.4 AWTTC critique

- Ingenol mebutate offers a shorter duration of AK treatment compared to the 4–12 week duration for existing topical treatments. The company suggest this may increase adherence to AK treatment in clinical practice. Adherence within the pivotal trials of ingenol mebutate was 98%[14] (adherence is likely to be lower in clinical practice than in a clinical trial) and the resolution of LSRs relatively rapid[11]. The evidence on rates of adherence to other topical AK treatments is limited, but suggests adherence is lower than the rates reported for ingenol mebutate[23,24].
- In the pivotal ingenol mebutate trials approximately half the patients had a history of skin cancer and more than 75% had received cryotherapy. However the typical levels of disease and treatment experience of patients in clinical practice are not known.
- Whilst diagnosis of AK by clinical examination is routine practice and there is reasonably good concordance between clinical diagnosis of clearance and histological clearance, histology is considered to be the confirmatory diagnosis[25]. Conclusive evidence of histological clearance was not shown in the included trials of ingenol mebutate. However, other studies of the biological effects of ingenol mebutate show the clearance of AK lesions[11].
- No data on re-treatment with ingenol mebutate have been provided. The company have initiated a study to evaluate repeat use of ingenol mebutate for multiple AKs on the face or scalp; this is due to report in May 2014[11].
- The follow-up studies only analysed patients who successfully responded to treatment, and excluded patients with residual AKs who may have been at a higher risk of SCC[11]. However, CHMP acknowledge that even if these patients had been included in the studies, a conclusion on the risk of SCC would not

have been possible due to the low rates of SCC occurrence and the confounding background rate of AK to SCC conversion in the absence of treatment. The company have committed to carry out a 3 year study comparing the incidence of SCC after treatment with ingenol mebutate[11].

- The patients in the pivotal phase III studies, conducted in Australia and the USA were white, had Fitzpatrick skin types I and II, a mean age of 65 years and reflect the type of patients with AK lesions in Wales[1].
- Results of the MTC should be interpreted with caution due to the inherent limitations in the method and differences in study patient populations, such as the prior experience of skin cancer and previous treatments for AK. The company report that the RCT providing efficacy data for fluorouracil had a "high risk of bias" because the study was not blinded and patient numbers in both the fluorouracil arm (n = 24).and imiquimod arm (n = 26) were small[1].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis of ingenol mebutate gel (Picato®▼) compared to diclofenac 3% gel (Solaraze®) and fluorouracil 5% cream (Efudix®) for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults[1].

The analysis is based on a decision analytic model. The model considers a hypothetical cohort of patients with clinically confirmed AK lesions covering an area of 25 cm^2. The patients enter the model on the initiation of first line therapy with either ingenol mebutate (two or three days), or diclofenac 3% gel (8 or 12 weeks), or fluorouracil 5% cream (four weeks). It is assumed that treatment will be administered in primary care; however, based on expert opinion, a proportion of patients (90% for fluorouracil, 10% for other treatments) will be referred to secondary care for assessment by a dermatologist. The model assumes that all patients complete a course of treatment. Six months after the initiation of first-line therapy, it is assumed that a patient will have either responded to treatment and achieved CC of AK lesions ("success") or failed treatment and have not achieved CC ("non-success"). PC (defined as a reduction of 75% or more in the number of clinically visible AK lesions) was not considered a relevant treatment outcome for inclusion in the model.

Patients were assumed to remain in "success" or "non-success" health states for the subsequent 6 months of the model. The base case analysis assumes a 12 month time horizon with no recurrence. A scenario analysis assuming recurrence occurs over a 24 month time horizon is provided.

In the absence of direct comparative studies for ingenol mebutate, efficacy estimates used in the model were derived from indirect comparisons of published studies using network meta-analyses. Supplementary analyses using Bucher methods of indirect comparison have also been provided. In the base case analysis, adverse events are excluded. Utility values associated with health states were derived from the literature and assumptions, and resource use is informed by expert opinion. The model does not consider the impact of treatment on progression of AK to SCC and associated survival.

4.1.2 Results

Results of the base case analyses are summarised in Table 2. The following treatment regimens were considered: ingenol mebutate 150 mcg/g once daily for 3 days (face or scalp) and 500 mcg/g once daily for 2 days (trunk or extremities); diclofenac twice daily for 8 and 12 weeks; fluorouracil twice daily for 4 weeks.

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Table 2. Company-reported results of the base case analyses
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A wide range of sensitivity and scenario analyses, which consider the assumptions on referral rates to secondary care and account for adverse events and AK recurrence have been conducted by the company. [Commercial in confidence data removed]

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Table 3. Selected univariate sensitivity and scenario analyses
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4.1.3 AWTTC critique

Due to a lack of direct comparative studies for ingenol mebutate versus diclofenac and fluorouracil, efficacy parameter estimates used in the model were derived from adjusted indirect comparisons: the included trials differed in design, and time of assessment of treatment outcomes. The resultant probabilities of treatment effect (complete clearance) are associated with uncertainty reflected in wide credible intervals. Expert opinion is used to inform assumptions on referral rates to secondary care, and duration of impact of adverse events. The base case model excludes recurrence of AK, which seems implausible given the reported recurrence rates of > 50% at 12 months in the longer-term follow up of ingenol mebutate trials. The scenario analyses including recurrence would therefore seem more plausible, but there are no data available on the effectiveness of re-treatment. Results of cost-utility analyses presented in this submission are, therefore, subject to considerable uncertainty. The reliability of the supplementary cost minimisation analyses depends on the extent to which therapeutic equivalence has been demonstrated. In these analyses, ingenol mebutate is marginally more costly than diclofenac, but cost saving compared with fluorouracil.

Strengths of the economic evidence include:

- In the absence of direct comparative data, the company has undertaken a systematic literature review and a network meta-analysis to estimate model parameters.
- A wide range of sensitivity and scenario analyses, including probabilistic sensitivity analyses, has been conducted to explore the impact of uncertainty associated with several key parameters.

Limitations of the economic evidence include:

- The model does not consider the potential for AK to progress to SCC.
- Effectiveness estimates derived from the network meta-analyses are imprecise and subject to uncertainty, as reflected in the wide credible intervals around point estimates of probabilities of complete clearance of AK. The included studies differed in design, time of assessment and reported treatment outcomes.
- Utility estimates are derived from the literature and exceed population norms for the patient group that is modelled. The approach to weighting health states assumes that benefit from treatment, resulting in an improved utility value, is only achieved four weeks after cessation of treatment. As treatment duration with ingenol mebutate is for only two to three days, and for the comparators ranges from 4 to 12 weeks, this assumption implies no benefit for the comparators until 8 to 16 weeks after treatment initiation, which may bias the model in favour of ingenol mebutate.
- Recurrence of AK is not considered in the base case analyses, which seems implausible given the high rates of recurrence (> 50%) observed by 12 months in the longer term follow-up of trials. The scenario analyses that include recurrence would therefore seem the most plausible analyses, although it is unclear whether they adequately reflect the time to recurrence; this may bias the modelled QALY gains. Median time to recurrence of AK following ingenol mebutate treatment was observed to be between > 183 days and 365 days in the long term follow up studies. Furthermore, it is assumed that re-treatment would be with the same product, and there are no data available to inform on the effectiveness of re-treatment.
- The reliability of the supplementary cost minimisation analyses depends on the extent to which ingenol mebutate has been demonstrated to be therapeutically equivalent to the comparators. Few details are provided for the supplementary pairwise indirect treatment comparison versus diclofenac, which reports ingenol mebutate to have statistically superior efficacy at 12 weeks.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches have not identified any published economic evidence on the cost-effectiveness of ingenol mebutate for the treatment of patients with non-hyperkeratotic, non-hypertrophic actinic keratosis.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on a 1993 study conducted in South Wales[7], the prevalence of AK is assumed to be 23%. Applying this to 2011 population statistics for Wales[26], the company estimates that there are approximately 177,300 people over 60 years old with AK in Wales. Assuming that 15% of these patients will be diagnosed and of these 90% will receive a treatment for AK (company estimates, no further detail provided), the estimated number of treated patients is 23,936. According to a company forecast of market uptake for ingenol mebutate of 5%, 14%, 23%, 30% and 35% in each of the next five years, the number of people expected to be prescribed ingenol mebutate in Wales would increase from 1,197 in year one to 8,378 in year five.

5.1.2 Results of company budget impact analysis

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Table 4. Company-reported costs associated with use of ingenol mebutate gel for the treatment of patients with non-hyperkeratotic, non-hypertrophic actinic keratosis

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5.1.3 AWTTC critique of the budget impact analysis

- Due to a lack of epidemiological data for AK in the population covered in this submission, a range of assumptions have been made by the company to estimate the number of patients eligible for treatment with ingenol mebutate.
- The company based their estimations on the total number of patients with AK in Wales, while ingenol mebutate is indicated for a subpopulation of patients with non-hyperkeratotic, non-hypertrophic actinic keratosis. The number of patients eligible for treatment with ingenol mebutate may therefore be overestimated, and is subject to uncertainty.

5.2. Comparative unit costs

A comparison of costs for topical medicines licensed for the treatment of hyperkaratotic actinic keratosis is problematic, as usage will depend on the surface area and number of lesions to be treated. Table 5 provides examples of acquisition costs of products for the treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adult patients; however, the Summaries of Product Characteristics[2,3,27–29] should be consulted for full treatment details and appropriate uses.

Table 5. Examples of drug acquisition costs for topical treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adult patients

Drug	Regimen	Initial treatment duration	Cost per package
Picato®▼ Ingenol mebutate gel 150 mcg/g or 500 mcg/g	Face/scalp: 1 × 150 mcg/g tube daily	3 days	3 × 150mcg/g tubes or 2 × 500mcg/g tubes = £65.00
	Body: 1 × 500mcg/g tube daily	2 days	
Aldara® imiquimod 5% cream	Three times per week	4 weeks	12 × 250 mg = £48.50
Solaraze® diclofenac sodium 3%, sodium hyaluronate 2.5% gel	Twice daily	60–90 days	1 × 50 g = £38.30 1 × 100 g = £76.60
Efudix® fluorouracil 5% cream	Once or twice daily	4 weeks	1 × 40 g = £32.83

All costs are based on MIMS[30] list prices as of 17 January 2013, with the exception of ingenol mebutate (company-provided price).
This table does not imply therapeutic equivalence of drugs or the stated doses.
See relevant Summaries of Product Characteristics for full details of appropriate use of the above products[2,3,27–29].

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, ingenol mebutate (Picato®▼) for the indication under consideration may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company submission did not identify any ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 4 January 2013
Date range of evidence search: No date limits were applied to database searches.

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Appendix 1. Additional clinical information

Table 1A. Summary of results for four pivotal phase III trials of ingenol mebutate versus vehicle gel[1]

	Face or scalp						Trunk or extremities					
Trial number	**PEP005-016**			**PEP005-025**			**PEP005-014**			**PEP005-028**		
	Ingenol mebutate gel, 150 mcg/g (n = 135)	**Vehicle gel (n = 134)**	**p value**	**Ingenol mebutate gel, 150 mcg/g (n = 142)**	**Vehicle gel (n=136)**	**p value**	**Ingenol mebutate gel, 500 mcg/g (n = 126)**	**Vehicle gel (n = 129)**	**p value**	**Ingenol mebutate gel, 500mcg/g (n=100)**	**Vehicle gel (n=103)**	**p value**
CC, n (%) [95% CI]	50 (37.0) [28.9, 45.8]	3 (2.2) [0.5, 6.4]	< 0.001	67 (47.2) [38.8, 55.7]	7 (5.1) [2.1, 10.3]	< 0.001	35 (27.8) [20.2, 36.4]	6 (4.7) [1.7, 9.9]	< 0.001	42 (42.0) [32.2, 52.3]	5 (4.9) [1.6, 11.0]	< 0.001
PC, n (%) [95% CI]	81 (60.0) [51.2, 68.3]	9 (6.7) [3.1, 12.4]	< 0.001	96 (67.6) [59.2, 75.2]	11 (8.1) [4.1, 14.0]	< 0.001	56 (44.4) [35.6, 53.6]	9 (7.0) [3.2, 12.8]	< 0.001	55 (55.0) [44.7, 65.0]	7 (6.8) [2.8, 13.5]	< 0.001
CI: confidence interval; CC: complete clearance; PC: partial clearance; mcg/g: micrograms/gram.												

Table 2A. Observational follow-up studies[1,14]

	Face or scalp		Trunk or extremities		
Trial number	**PEP005-30**		**PEP005-32**		**PEP005-31**
Previous phase III/IIIb trial number*	**PEP005-16 and PEP005-25**		**PEP005-28**		**PEP005-20 (uncontrolled trial)**
Treatments (number of patients treated)	**Ingenol mebutate (n = 108)**	**Vehicle gel (n = 9)**	**Ingenol mebutate (n = 38)**	**Vehicle gel (n = 5)**	**Ingenol mebutate (n = 38)**
% of patients with lesion recurrence	53.9	72.2	50	80	62.5
* patients with complete clearance of actinic keratoses at day 57 from phase III/IIIb trials were included in observational follow-up trials.					

Table 3A. Summary of trials included in the MTC
[Commercial in confidence data removed]