



Ingenol mebutate: a novel treatment for actinic keratosis

Practice points

- Ingenol mebutate gel (Picato[®] gel, LEO Pharma, Ballerup, Denmark) is a novel topical self-applied treatment for nonhyperkeratotic, nonhypertrophic actinic keratoses in adults.
- Picato gel (0.05%) is applied to trunk and extremity lesions for 2 consecutive days, and at lower strength (0.015%) applied to face and scalp lesions for 3 consecutive days.
- The mechanism of action is rapid induction of cell necrosis followed by neutrophil-mediated antibody-dependent cellular cytotoxicity.
- Ingenol mebutate is transported via P-glycoprotein, through the epidermis to the subcutis, with no detectable systemic absorption.
- Efficacy is broadly similar to alternative field-directed topical treatments, but the treatment regime offers potentially greater effectiveness.
- Local skin reactions (erythema, irritation, pruritus and pain) shortly follow completion of applications, reducing by week 2 and resolving by week 4.
- There is no evidence of drug interactions, and the mode of treatment minimizes the probability.

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A novel, topically applied, short course therapy for actinic keratoses (AK) is now widely licensed following first approval in the USA in 2012. The active agent, ingenol mebutate, is a naturally occurring diterpenoid found in the plant *Euphorbia peplus*. AK, the most common premalignant dermatological pathology, is increasing in prevalence with increased UV radiation exposure and aging populations, and has the potential to progress to malignant disease. Various treatment modalities exist for AK and the choice for the clinician and patient is now extended with this novel treatment, which requires topical application for only 2 or 3 days, and has cosmetic and tissue-sparing advantages. Ingenol mebutate gel is used as a field-directed therapy, thereby potentially reducing perilesional subclinical AK.

Keywords: actinic keratosis • field-directed therapy • ingenol 3-angelate • ingenol mebutate • PEP0005 • solar keratosis

In this review, we aim to inform clinicians who treat actinic keratoses (AK) of the details of the novel topical therapy containing ingenol mebutate. We provide the background to the evaluation of this new drug with emphasis on recent clinical trials, safety data and its history and mechanism of action.

Actinic keratoses: a burgeoning problem

Actinic keratoses (AK), also known as solar keratoses, represent the most frequent dermatological premalignant presentation. Clinically, AK presents as rough erythematous plaques or papules with a superficial scale, typically on areas of chronic sun expo-

sure. Diagnosis can be confirmed histologically, which demonstrates proliferation of atypical keratinocytes confined to the deeper epidermis and is invariably surrounded by features of solar elastosis.

The pathophysiology of AK is principally dependent on the cumulative effect of UV radiation from sun exposure on the skin. UVB can directly cause DNA and RNA damage and mutation of regulatory genes including p53 [1,2]. This can disrupt protective apoptotic mechanisms, intracellular signaling and cytokine regulation [3]. Additional risk factors in AK development include genetic instability, melanin deficiency and fair skin, age, immunosuppression, history of nonmelanoma skin cancer and male sex.

The worldwide prevalence of AK is reportedly 11–25% [1,4] and continues to rise in line with increased UV exposure and aging populations. The prevalence among males over 70 years of age was 34% in the north west of England [5]. The higher solar UV exposure of European male seafarers resulted in a 1.80-fold risk of AK [6]. A recent solar UV index study in Chile showed a marked correlation of accumulated solar UV index with the incidence of skin cancer [7].

A continuum of cancerous change

AK can be regarded as an early step on a continuum of change to squamous cell carcinoma (SCC) [2,8]. Wide variation exists in estimates of the probability and timing of lesions progressing to SCC [9]. Lifetime progression to SCC in patients with AK has been estimated at between 6 and 10%, rising to 40% in immunocompromised patients; however, further studies are needed to more accurately determine the risk of progression and to gain insight into the characteristics of those lesions that progress [10,11].

A study of AK on the face and ears of a high-risk group showed that 65% of SCCs diagnosed in the study cohort initially presented as AK [12]. In order to diminish the risk of malignant transformation, early diagnosis and evaluation for treatment of actinically damaged sites is indicated [13]. AK frequently regress but are likely to recur or form perilesionally [12–14].

Treatment of AK

A variety of treatments for AK exist and the selection should be tailored to the individual patient. In choosing the appropriate treatment, the factors to consider include the location and extent of actinic damage, any patient comorbidities, and the likelihood of sustaining the treatment, which may be affected by the location of services and patient frailty. Treatment options can be divided into field-directed or lesion-directed therapies, or a combination of both [15]. A treatment algorithm for AK has been proposed that indicates

treatments for both multiple lesions and solitary AK lesions [16].

The concept of field change, first described in 1953 and more recently demonstrated at the molecular level, involves patches of genetically altered stem cell clones developing into individual fields that progress into contiguous pastures of precancerous cells [2,17]. This underpins the logic of therapy being also field directed as opposed to being simply lesion directed. Further support for this approach comes from the observation that 82% of SCCs arise within, contiguous with, or in close proximity to a region of AK. Also, it is observed that if AK lesions are treated, the risk of adjacent skin developing SCC is reduced [18].

Lesion-directed therapies, such as cryotherapy, curettage and electrodesiccation, and surgery, are well established, often simple and can provide low-cost treatment of focal lesions. However, they do not address the issue of perilesional, subclinical AK.

Field-directed treatments include dermabrasion, chemical peels, laser resurfacing, photodynamic therapy and the topical self-applied treatments imiquimod, 5-fluorouracil (5-FU), diclofenac in hyaluronic acid and ingenol mebutate.

In contrast with alternative self-applied topical treatments that require treatment over a period of weeks, ingenol mebutate only requires a treatment period of 2 or 3 days.

There is evidence that this rapid action of ingenol mebutate is due to a dual mechanism of action combining cytotoxic and immunomodulatory effects in which rapid lesion necrosis and antibody-dependent cellular cytotoxicity (ADCC) mediated by neutrophils occurs [19]. Further elucidation of the mechanisms by which ingenol mebutate mediates cytotoxicity, involving multiple cell organelles, has been reported [20].

Ingenol mebutate

Ingenol mebutate (formerly PEP005), produced by LEO Pharma and marketed as Picato® (LEO Pharma, Ballerup, Denmark), is a gel for patient-applied topical field-directed treatment of AK.

Overview of the market

Nonmelanoma skin cancer and AK present a large and growing problem in western dermatology and generate a high proportion of clinic visits. Estimates in the USA in 2004, of the direct and intangible costs through impact on quality of life, of AK were US\$1.2 and US\$5.8 billion respectively [21,22].

Patient compliance in AK care programs is frequently low due to discomfort, limited treatment efficacy and long courses of therapy associated with correspondingly long duration of treatment-related adverse effects [8].

Multiple treatment options exist, however, comparison of treatments is limited by the lack of head-to-head trials of efficacy or side-effect profiles. A recent indirect network meta-analysis of eight interventions for AK was performed, ranking agents, which included ingenol mebutate gel, on the criterion of 'participant complete clearance'. This varied between studies but correlated with the complete clearance of target lesions or of all lesions.

Interventions were ranked 5-fluorouracil (5-FU) > photodynamic therapy (PDT) \approx imiquimod \approx ingenol mebutate > cryotherapy > diclofenac in hyaluronic acid > placebo on this particular criterion. 5-FU was identified as the treatment of choice, based on this criterion alone, but it was acknowledged that "the choice of therapy should be based on the outcome sought, as well as on other factors such as tolerability, cost or cosmetic results" [23].

NICE evaluation of treatment cost estimated a course of ingenol mebutate to be less expensive than 3.75% imiquimod, similar to diclofenac in hyaluronic acid, similar to 0.5% 5-FU and salicylic acid, and more expensive than 5% 5-FU.

A recent global study of physician treatment perceptions in AK found that most physicians treating AK prefer short duration treatment options with fast-resolving local skin responses (LSRs) [24].

Introduction to the compound

This application of ingenol mebutate arose from an investigation of traditional plant-based remedies [25]. *Euphorbia peplus*, also known variously as petty spurge, milkweed or radium weed, has a sticky white irritating latex sap that has been used for centuries in traditional medicine as a treatment for skin lesions, including AK [25]. This sap has been shown to be effective against human nonmelanoma skin cancer in a Phase I/II clinical study in which 48 skin cancer lesions were treated topically once daily for 3 days [25]. *E. peplus* sap contains ingenol mebutate at $\approx 200 \mu\text{g ml}^{-1}$ as an active compound, thereby confirming community experience and prompting further research [25].

Chemistry

Ingenol mebutate is a diterpenoid with the structure shown in Figure 1, with molecular formula $\text{C}_{25}\text{H}_{34}\text{O}_6$ and molecular weight of 430 Da, which makes it, in pharmacological terms, a small molecule. The compound is extracted from *E. peplus*.

A 14-step synthetic route has been devised, from the readily available careen, via ingenol [26]. An aspect of the synthetic approach is that it facilitates the preparation of analogs. Analogs are of interest both with regard to potential pharmacological improvements and

also as they can shed light onto the structure activity relationship of ingenol mebutate [27].

A motivation for studying analogs of ingenol mebutate is to improve its chemical stability. For ingenol mebutate to remain chemically stable, it requires both anhydrous conditions and the control of pH to avoid base-catalyzed and other rearrangements [27]. The current necessary use of an anhydrous gel based on isopropanol, gives rise to some LSRs from the vehicle gel, as shown in the trials data [28,29]. The gel has a low pH, significantly lower than that of the skin, in order to maximize the chemical stability of ingenol mebutate (which is optimal at pH 3.2); citrate buffering keeps the pH of the gel from rising above 4 [30].

The ester function was found to have importance with regard to biological activity [15,27]. Four novel ingenol derivatives with other ester groups showed potential advantages over ingenol mebutate [27]. Analogs of ingenol mebutate may give rise to improvements in both chemical stability and clinical effectiveness.

Ingenol mebutate has been shown to activate PKC, like the structurally related phorbol ester tumor promoter, TPA. The pattern of activation is different from that of TPA. Unlike TPA, ingenol mebutate was found not to promote tumors induced by the initiator DMBA; this is ascribed to its ester chain being much shorter than that of TPA [30–36].

Pharmacodynamics

No reports of human *in vivo* pharmacodynamics studies have been published. Data are available from studies conducted *in vitro*, in human and animal cell lines, and in animal models. Currently AK animal models do not exist, so experience is limited to non-AK tumor models.

Ingenol mebutate has been shown, in a murine model, to act as a substrate for, and be transported by P-gp a transmembrane protein which facilitates transport through the epidermis into the deep dermis where it damages the vasculature of the tumor, as an essential part of its antitumor effect [37].

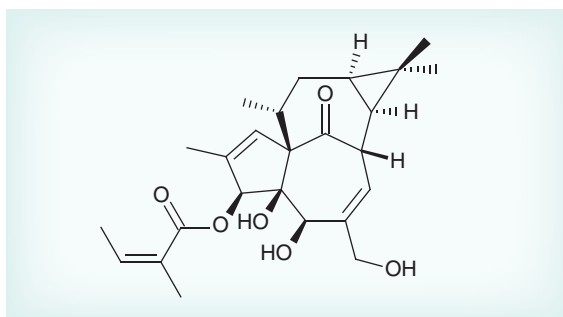


Figure 1. Structure of ingenol mebutate. This compound is also known as ingenol 3-angelate or PEP005, and is the active ingredient in the gel Picato® (LEO Pharma, Ballerup, Denmark).

In vitro experiments, using a relatively high concentration of ingenol mebutate (230 $\mu\text{mol/l}$) with B16 mouse melanoma cells and Lewis lung cancer cells, demonstrated rapid onset of cell death, which was complete within 6 h. Electron microscopy showed loss of mitochondrial membrane potential followed by mitochondrial swelling, clumping of chromatin and cell membrane rupture without nuclear membrane distribution, consistent with cell death via primary necrosis [38].

The mechanism via which cell necrosis is induced is not fully established; however, it is hypothesized that ingenol mebutate may dissolve in the plasma membrane, forming endocytic vesicles, which results in increased intracellular calcium ion concentrations, leading to mitochondrial membrane disruption and subsequent cell death [38].

In vivo studies of murine SCC and melanoma tumors grown in mice, demonstrated marked erythema following topical application of ingenol mebutate when compared with vehicle isopropanol gel. Inflammation subsided by 5–10 days, the skin appearing clinically normal at 3 weeks [39]. Following topical application of ingenol mebutate gel, histological examination of lesions demonstrated marked neutrophilic infiltrate with small vessel dilatation at 6 h and with scattered macrophages visible at 24 h [39].

Investigations using immunodeficient mice have given insights into the mechanism of the immune response [39]. First, neutrophil-depleted anti-Ly-6G Ab mice, and B-cell-defective SCID mice, treated with ingenol mebutate, showed increased tumor recurrence, but no significant change was noted in macrophage-depleted and NK-depleted mice or T-cell-impaired mice [38,39]. Second, in real-time PCR studies, ingenol mebutate was seen to induce chemotactic factors, including MIP-2/IL-8, TNF- α and IL-1b, which stimulate the adherence of neutrophils to the microvasculature, transmigration, and extravasation to the treatment site. Third, studies of the anti-tumor effect of neutrophils stimulated by ingenol mebutate, revealed that direct degranulation was not induced, but there was a significant elevation in superoxide anion products, consistent with oxidative burst [39].

Evidence supporting cell death via neutrophil-mediated ADCC has been demonstrated in murine models. In ADCC, effector cells, in this case neutrophils, bind to the Fc region of anti-tumor antibodies, which are in turn bound to tumor cells, and this leads to tumor cell lysis. Following application of ingenol mebutate, murine antitumor antibody levels were significantly elevated. In addition, sera adoptively transferred from mice treated with ingenol mebutate was demonstrated to significantly reduce tumor cell viability in com-

parison with sera from untreated mice or from naive mice [39].

From these studies the mechanism of action of ingenol mebutate in AK, although not fully elucidated, appears to be a dual mechanism, of local lesion cell necrosis and neutrophil-mediated ADCC.

In higher concentrations ingenol mebutate has been shown to induce cellular necrosis, but in lower concentrations it has been shown to potently affect PKC isoforms and thereby intracellular signaling. Like the chemically related phorbol ester TPA, ingenol mebutate has been shown to be a potent activator of PKC isoforms. PKC δ activation appears to have a principal role, but that role is not yet fully elucidated. Studies of PKC modulation, by ingenol mebutate, of kinases have shown antiproliferative and proapoptotic effects in several human cancer cell lines; this supports the targeting of PKC isoforms with ingenol mebutate in cancer therapy [40].

In a wider context, it is known that PKC δ has a role in apoptosis and cell death while in other circumstances it favors cell survival, the precise role depending on the type of cell, the extent of phosphorylation and the presence of cofactors and other molecules [41].

It has been recently shown that ingenol mebutate binds to and activates RasGRP1 and RasGRP3 resulting in elevation of Ras-GTP [42]. It was suggested that some of the anti-cancer effects of ingenol mebutate may stem from the activation of RasGRPs [42].

Ingenol mebutate is now approved for use as a field-directed topical treatment of AK and significant progress has been made in studies of its potential use in hematological malignancies [35,43]. Characterization of the effect ingenol mebutate in a panel of human solid tumor cell lines has been carried out and studies on the wider oncological applications of ingenol mebutate are continuing [40].

Thus, a series of studies, using a variety of cell lines and animals, have shown the likely factors involved in the pharmacodynamics of ingenol mebutate leading to the currently accepted view of a dual mechanism of rapid cellular necrosis followed by neutrophil-mediated ADCC.

Pharmacokinetics & metabolism

The pharmacokinetics investigation of the systemic absorption of ingenol mebutate gel 0.05% was evaluated in a randomized vehicle-controlled double blind study, in which 1 g was applied to a contiguous 100 cm^2 area of multiple AKs on the dorsal forearms of 16 patients in two consecutive daily applications [15,44,45]. This clinical trial showed that there was no detectable systemic absorption of the parent drug or its two principal metabolites (both acyl isomers of ingenol

mebutate), when the limit of detection was 0.1 ng/ml [15,44,45].

In vitro studies using [³H]-ingenol mebutate showed that metabolism of the drug by human hepatocytes is extensive [45]. Other *in vitro* studies showed that ingenol mebutate neither induces human CYP450 enzymes CYP1A2, 2C9 and 3A4a, nor inhibits CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 [45].

Clinical efficacy

An account of the principal outcomes of clinical trials is given in this section. A search of the ClinicalTrials.gov [46] website on 18 October 2013 showed 32 trials completed and three active. Four of these trials are the main Phase III pivotal trials, which feed into a further three Phase III extension studies, and these seven trials form the main focus of this section.

Phase I studies

Phase I studies on healthy volunteers are listed in Table 1.

A Phase I trial has been completed to evaluate the local tolerability on the finger after exposure to ingenol

mebutate 0.05 and 0.015% gel, followed by hand washing in healthy subjects, for 2 or 3 consecutive days. This was an interventional, randomized, open-label, parallel assignment safety study measuring LSRs up to day 8 with an estimated enrollment of 100 (NCT01302925). The results of this trial are not yet published.

Three separate clinical pharmacology studies were carried out to evaluate the phototoxic, photosensitizing, and sensitizing or allergenic potential of ingenol mebutate gel. Their results gave no areas of concern and suggested a favorable topical safety profile [48].

Phase II studies

A randomized, double blind, vehicle-controlled Phase IIa trial of the safety and efficacy of the treatment of 58 patients with AK was carried out [28]. This dose-escalation study showed that ingenol mebutate gel at a range of concentrations up to 0.05% was well tolerated, and the highest concentration, 0.05%, was the most efficacious [28]. A separate Phase IIa dose-escalation study was also carried out and gave comparable results [49,50].

A Phase IIb study was conducted to further assess ingenol mebutate gel at 0.025 and 0.05% concentra-

Table 1. Summary of Phase I and II trials.

Focus of investigation	ClinicalTrials.gov identifier	Phase
Sensitization potential and skin irritation on normal skin	NCT00357916	I
Photoirritation potential	NCT00850811	I
Photoallergic potential on normal skin	NCT00850681	I
Systemic absorption from forearm application	NCT00544258	I
Contiguous vs individual area application	NCT00659893	I
Safety of single application to nonhead area	AGN204332-004 [†]	I
Local tolerability after finger exposure	NCT01302925	I
Safety for treatment of AK	NCT00375739	II
Maximum tolerated dose, clinical safety, systemic absorption	NCT00239135	II
Pharmacokinetics in maximum use setting on forearm	NCT00852137	II
Safety and toleration for AK on hand dorsum	NCT00544297	II
Optimal tolerated regimen for AK on face or face and scalp	NCT00427050	II
Safety and efficacy of three concentrations on face and scalp	NCT00700063	II
Safety, efficacy and dosing regimen	NCT00107965	II
Safety and resolution of nodular BCC	NCT00108121	II
Safety and resolution of superficial BCC	NCT00108134	II
Safety and resolution of cutaneous SCC <i>in situ</i>	NCT00329121	II
Maximum tolerated dose for superficial BCC on the trunk	NCT00432185	II
Safety and efficacy seborrhoeic keratosis on body	NCT01214564	II
Safety and efficacy photo-damaged skin on the face	NCT01214577	II

See [46] for specific ClinicalTrials.gov websites.
[†]See [47].
 AK: Actinic keratosis; BCC: Basal cell carcinoma; SCC: Squamous cell carcinoma.

tions in respect of their relative safety and efficacy as field-directed treatments for nonfacial lesions [49]. This was a randomized, double-blind, double-dummy, vehicle-controlled, sequential, multicentered dose ranging study. This study evaluated the safety, tolerability and efficacy of ingenol mebutate gel at 0.025%, applied once daily for 3 consecutive days, and ingenol mebutate gel at 0.05%, applied once daily for 2 or 3 consecutive days, to a 25 cm² contiguous treatment area [49]. The results of this study were consistent with ingenol mebutate gel at 0.025 and 0.05% concentrations being an efficacious field-directed short course treatment for AK on nonfacial sites, offering the potential of improved patient compliance when compared with alternative field-directed topical treatments for AK, which have significantly longer treatment schedules [49].

Phase III studies

Phase III studies are listed in Table 2.

The treatment of AK with ingenol mebutate gel was the subject of a series of four double-blind, vehicle (placebo)-controlled interventional studies [29]. The mean age of all the patients in the four studies was 65.1 years, with the majority having Fitzpatrick skin type I or II, and all identified themselves as white. The demographics of the treatment and placebo groups were not significantly different. These Phase III pivotal trials also acted as feeder trials for three Phase III extension studies.

Two of these studies (PEP005-016 and PEP005-025) addressed the treatment of AK on head area locations (face or scalp) [29]. The other two studies (PEP005-014 and PEP005-028) were of AK on nonhead area locations (trunk or extremities) [29]. In each of these four multicenter studies, patients were selected who were aged at least 18 and had, in a 25 cm² contiguous area in the relevant part of the body, four to eight discrete visible AKs that were clinically typical [29]. All patients applied the gels themselves and were randomly assigned

to have either the placebo gel (vehicle) or the ingenol mebutate gel. In both of the head area studies, patients were given either ingenol mebutate gel 0.015% or vehicle gel for application once daily for 3 consecutive days. In both of the nonhead area studies patients were given either ingenol mebutate gel 0.05% or vehicle gel for application once daily for 2 consecutive days.

The primary outcome measure, or primary end point, of these four trials was for the complete clearance of AK lesions at day 57, with the complete clearance rate being defined as the proportion of patients with no clinically visible AK lesions in the selected treatment area. The secondary outcome measure, or secondary efficacy end point, was for patients with partial clearance of AK at day 57, with patients with partial clearance defined as $\geq 75\%$ reduction in the number of AK lesions identified at baseline in the treatment area. An additional secondary end point was added: the percentage change in the total number of AKs at day 57 compared with the total number of AKs at baseline.

The results of the two studies involving head area AKs were pooled with 547 patients being ultimately included. On day 57 this pooled ingenol mebutate group had 42.2% of patients showing complete clearance and 63.9% showing partial clearance (defined as 75% reduction) with a median reduction in AK number of 83%. The corresponding placebo group, who applied the vehicle gel, showed much lower clearance rates of 3.7% complete clearance ($p < 0.001$), 7.4% partial clearance ($p < 0.001$) and a median clearance of 0%. From the results of these two studies of treatment of AK in head areas, it was calculated that the number needed to treat, for complete clearance in one patient, was 2.6, and, for partial clearance, the number needed to treat was 1.8. The 108 patients in the head area studies, who had been shown to be clear of AK at day 57, were further monitored for a further 12 months and a mean of 87.2% of the number of lesions at baseline in the treatment area sustained their clearance [29,51].

Table 2. Phase III trial results.

Rates of clearance and lesion reduction	Ingenol mebutate 0.015%	Vehicle
Head areas (face & scalp) studies PEP005-016 & PEP005-025, o.d. for 3 days		
Complete clearance	42.2% of 277 patients	3.7% of 270 patients
Partial clearance	63.9% of 277 patients	7.4% of 270 patients
Median lesion count reduction	83% of 273 lesions	0% of 269 lesions
Nonhead areas (trunk & extremities) studies PEP005-005 & PEP005-028, o.d. for 2 days		
Complete clearance	34.1% of 277 patients	4.7% of 270 patients
Partial clearance	49.1% of 277 patients	6.9% of 270 patients
Median lesion count reduction	75% of 220 lesions	0% of 229 lesions
Outcomes at day 57 for the four Phase III trials [29]. $p < 0.001$ ingenol mebutate versus vehicle for complete and partial clearance. o.d.: Once daily.		

The results of the two studies involving nonhead area AKs were pooled, with 458 patients being ultimately included. On day 57 this pooled ingenol mebutate group had 34.1% of patients showing complete clearance and 49.1% showing partial clearance (defined as 75% reduction) with a median reduction in AK number of 75%. The corresponding placebo group, who applied the vehicle gel, again showed much lower clearance rates of 4.7% complete clearance ($p < 0.001$), 6.9% partial clearance ($p < 0.001$) and a median clearance of 0%. From the results from these two studies of treatment of AK in nonhead areas, it was calculated that the number needed to treat, for complete clearance in one patient was 3.4, and, for partial clearance, the number needed to treat was 2.4. The 38 patients in the nonhead area studies, who had been shown to be clear of AK at day 57, were further monitored for a further 12 months and a mean of 85.1% of the number of lesions at baseline in the treatment area sustained their clearance of lesions [29,51].

These results show that both complete and partial clearance rates of AKs on both head and nonhead areas were significantly higher ($p < 0.001$) in those patients who had undergone these short courses of treatment with ingenol mebutate gel than in the comparator placebo groups.

A separate Phase III field study (NCT01541553) was completed in July 2013 involving the application of ingenol mebutate gel 0.015% as a field-directed treatment 3 weeks after lesion-directed treatment using cryotherapy to AK. A 25 cm² contiguous area of the head on the face or scalp was treated and the results after 12 months were compared with cryotherapy followed by treatment with placebo vehicle gel; the results of this trial are not yet published [52,53]. The use of cryotherapy for lesion-directed treatment is well established and relatively convenient and this, combined with the short treatment period required with ingenol mebutate gel, facilitates convenience and treatment adherence.

In the future combination of lesion and field-directed treatments may increasingly be used and Phase III trials of ingenol mebutate in combination treatments of AK with lesion directed cryotherapy are awaited with interest [52,53]. Direct head-to-head trials comparing alternative treatments strategies for AK may improve the evidence base on which clinicians select and recommend treatments.

Postmarketing surveillance

Postmarketing surveillance is at an early stage. Ingenol mebutate became available on the market in the USA in March 2012 and has subsequently been launched worldwide (Table 3). In the UK, as a new substance, it is under close surveillance and is on the Black Trian-

gle List. Similarly it is on the EMA's 'list of medicinal products under additional monitoring'.

The use of modern pharmacovigilance systems should ensure that the Phase IV aspects of ingenol mebutate will be fully covered and reported in due course.

Safety & tolerability

Ingenol mebutate is a broad-range activator of classical and novel PKC isoenzymes [31–36,54]. Its proapoptotic and immunostimulatory effects in several types of malignant cells have been reviewed and the risk of severe systemic toxicity in potential systemic applications considered [54]. In the approved treatments of AK with ingenol mebutate a review of the preclinical, Phase II and Phase III studies concluded that these had demonstrated significant efficacy and an excellent safety profile [55]. It is suggested that use of ingenol mebutate may show increased levels of compliance compared with other field-directed therapies as it has a much shorter treatment schedule and is relatively well tolerated [49].

The safety end points were recorded in the clinical trials covering general adverse events (AEs), and scarring and pigmentation in the area of treatment, and other LSRs including erythema, scaling or flaking, crusting, swelling, postulation or vesiculation, and ulceration or erosion. For these last six categories the responses were graded quantitatively using a defined scale recording increasing severity in the range of 0 (not present) to 4 (severe), with reporting consistency aided by the use of photographic guides. Thus, the combined score for all the six categories ranged from a minimum of 0 to a maximum of 24 [29]. In the head area treatment studies, those using ingenol mebutate gel 0.015% showed a mean (\pm standard deviation) maximum combined LSR score of 9.1 (± 4.1) out of a possible 24, whereas the placebo users scored 1.8 (± 1.6) on the same scale [15,29,56]. These results show evidence of wide interpatient variability which is stressed as an important clinical feature. In the nohead area studies, those using ingenol mebutate gel 0.05% showed a mean maximum combined LSR score of 6.8 (± 3.5), again out of a possible 24, whereas the placebo users scored 1.6 (± 1.5) on the same scale [15,29,56].

Across the four Phase III trials for each of these six LSR categories, the majority of patients had a maximum score of 1 to 3, corresponding to a mild-to-moderate classification [15,29]. Thus, in the treatment of patients with AK, topical ingenol mebutate was in general well tolerated and mild-to-moderate severity reactions predominated [15,29,56]. The development of LSRs showed that in the head area treatment studies there was a rapid response to ingenol mebutate 0.015%, which began at the first day following completion of the 3 day treatment period and the response increased rapidly up to

Table 3. Licensing status for ingenol mebutate gel.

Jurisdiction	Approval status
USA	Approved January 2012
Brazil	Approved July 2012
Australia	Approved November 2012
EU	Approved November 2012
Canada	Approved January 2013
Switzerland	Approved June 2013
New Zealand	Pending

day 4 and then quickly declined to day 15 and thereafter, by day 29, was judged to be normal. In the equivalent nonhead area treatment studies, the LSR, following the 2 day treatment with 0.05% ingenol mebutate, was observed to maximize between day 3 and day 8 with a gradual return to day 29 when the reaction had largely finished [15,29,56].

There were no serious AEs relating to the study treatments in any of the four groups [29]. Ingenol mebutate topical treatment did not give rise to any systemic AEs in any of the four Phase III trials [51]. In all of the four Phase III study groups both scarring and changes of pigmentation were minimal [29]. Of those receiving ingenol mebutate in all the four groups, the most commonly reported adverse reactions were application-site conditions, comprising 19% of patients (52 out of 274 patients) with application sites on the head in comparison with 2.6% (seven out of 271 patients) who received only the vehicle gel, and, for those in the non-head area of application groups, 12% of patients (27 out of 225 patients), in comparison with 6% (six out of 232 patients) who received only the vehicle gel [29]. At the administration sites on the head, of those receiving the 0.015% ingenol mebutate gel daily over 3 days, the most common conditions reported were pain, in 13.9% of patients (38 patients out of 274), pruritus, in 8.0% of patients (22 patients out of 274), and irritation, in 1.8% of patients (five patients out of 274), in comparison with the corresponding placebo groups where 0.4% (one patient out of 271) reported pain, 1.1% (three patients out of 271) reported pruritus, and no patients reported irritation (zero patients out of 271) [29]. At the administration sites in the nonhead areas, of those receiving the 0.05% ingenol mebutate gel daily over 2 days, the most common conditions reported were pain, in 2.2% of patients (five patients out of 225), pruritus in 8.4% of patients (19 patients out of 225) and irritation in 3.6% of patients (eight patients out of 225). These are in comparison with the placebo groups where none (zero patients out of 232) reported pain, none (zero patients out of 232) reported pruritus and 0.4% of patients reported irritation (one patient out of 232) [29].

As existing topical treatments of AK give rise to local reactions in the area of application, it was expected that this would occur for ingenol mebutate. This was confirmed in these four trials where 69.7% scored 3 or higher on the 0 to 4 LSR scale, compared with 2.2% of those who received only the vehicle placebo, showing a very clear response, consistent with inflammation being a part of the mechanism of action of this drug [1]. Of the ingenol mebutate patients treated in these four studies, a minority scored 3 or higher on the 0 to 4 LSR scale for any of the six categories scored, other than for erythema.

Although, as expected, topical treatment with ingenol mebutate gel gave rise to local reactions consistent with an inflammatory response, it was noteworthy that these LSRs resolved quickly [29]. On the face, where cosmesis is most important, the maximum reaction was recorded at the day 4 point and then normalized quickly, with little visible evidence by day 15 [29]. It has been noted that the effectiveness of ingenol mebutate gel is likely to be enhanced by a higher adherence to treatment, as the short periods required, daily for 2 or 3 days, minimize the demands on patient compliance [29]. It is anticipated that these treatment protocols involving ingenol mebutate gel may retain a higher ratio of compliance in general use, to compliance in supervised trials, than alternative treatments that have longer treatment periods.

LSRs, together with eye disorders, represent important identified risks [57]. Ongoing safety concerns are being addressed, including potential overdose after treatment at multiple locations, and similarly additional information is being sought in regard to retreatment with ingenol mebutate gel and also in respect of patients who are immunocompromised or immunosuppressed [57].

For patients who cannot tolerate side effects ensuing from protracted courses of current topical treatments, ingenol mebutate treatment will be of particular value. Furthermore, for patients with AK on sites where poor healing may be predicted, such as the lower leg, ingenol mebutate treatment is likely to provide a very useful treatment.

AKs have increasing prevalence in later life and often patients are dependent on relatives or carers to assist them with their treatment; we consider that ingenol mebutate will enable a greater compliance with the prescribed treatment generally, but particularly in such cases.

Regulatory affairs

Ingenol mebutate gel is currently approved in the USA, EU, Australia, Canada and Brazil with the indication being for the topical treatment of AK.

Ingenol mebutate gel (0.015 and 0.05%), as Picato gel, was approved in January 2012 in the USA for the topical treatment of AK [45]. Approval in the EU followed in November 2012 with the indication 'for the cutaneous treatment of nonhyperkeratotic, nonhypertrophic actinic keratosis in adults' [30,58].

Australia, where ingenol mebutate was initially developed as a pharmaceutical, approved its use in November 2012 [57]. Approval followed in Canada [59], Switzerland [60] and Brazil. In New Zealand the Medicines Classification Committee has recommended that ingenol mebutate should be added to the New Zealand Schedule as a prescription medicine [61,62].

We anticipate that, with increasing use of ingenol mebutate gel there will be a corresponding increase in the comprehensive medicine information relating to it, in particular with data relating to its application over greater areas, its use in combined treatments, and in results from clinical trials comparing ingenol mebutate with alternative treatments.

The prescribing information emphasizes the need to avoid eye contact.

Conclusion

Ingenol mebutate gel has been shown to be a safe and effective as a field-directed treatment for AK in adults. It is comparable in efficacy to alternative topical treatments and has significant practical advantages in having a short treatment period of only 2 or 3 days, with a relatively short period of treatment-related side effects. No head-to-head trials are currently available to afford direct comparison between ingenol mebutate gel and alternative treatments.

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The indication for use of ingenol mebutate could be extended beyond its current limitation to include the treatment of skin cancers, particularly basal cell carcinoma, either as an independent treatment or combined with lesion-directed treatments.

There is no evidence of major safety concerns with ingenol mebutate gel treatment. The AEs reported were dominated by LSRs at the site of application that affected most patients (more than 95%) but these typically resolved quickly within 2–4 weeks, with facial treatments resolving the most quickly.

Ingenol mebutate gel therefore has a place in the range of available treatments for AK and offers efficacy, combined with good cosmetic outcomes, easy cost-effective application and a particularly short treatment regimen.

Information resources

Head-to-head clinical trials data, involving ingenol mebutate with other field-directed topical treatments of AK, are not yet available, but a meta-analysis following up a Cochrane review [63] has been produced [23]. Progression of AK to SCC has been studied [2,64], as has the role of ingenol mebutate in cancer more widely [31–33,43,65–67]. The management of AK has been addressed [68–71].

Full details, including prescribing details, are available from the LEO Pharma website and via the NICE, EMA and FDA websites. Details of the clinical trials can be found at the US NIH [46] website and an account of the key evidence is to be found at [29,51].

Several reviews or general papers relevant to both ingenol mebutate and AK are available [44,47,56,68,72–83]. The origin of field-directed therapy is of interest [84].

Financial & competing interests disclosure

JT Lear has accepted honoraria for speaking at meetings by Leo, Galderma, Almirall, Astellas and GSK. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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