

## ORIGINAL ARTICLE

# Evaluation of the treatment costs and duration of topical treatments for multiple actinic keratosis based on the area of the cancerization field and not on the number of lesions

P. Calzavara-Pinton,<sup>1,\*</sup> N. Tanova,<sup>2</sup> P. Hamon<sup>3</sup>

<sup>1</sup>Dermatology Department, University of Brescia, Brescia, Italy

<sup>2</sup>Amaris, London, UK

<sup>3</sup>Galderma, Paris, France

\*Correspondence: P. Calzavara-Pinton. E-mail: piergiacomo.calzavarapinton@unibs.it

## Abstract

**Background** The cost of topical treatments for actinic keratosis (AK) has historically been evaluated in relation to the number of lesions requiring treatment or simply by the price of a single tube/sachet of the drug used.

**Objective** To demonstrate a new method of costing topical treatments in AK, which takes into account the actual cancerization area treated.

**Methods** In order to evaluate the actual cost of each treatment, the official approval status of the drug was used to estimate the amount of cream needed per one cm<sup>2</sup>. This value was then applied to the hypothetical cancerization area sizes to demonstrate the impact of the size treated on the actual cost of treatment. The price considered was the ex-factory price in Italy.

**Results** Areas which could be treated with a single tube/sachet of Metvix<sup>®</sup>, Picato<sup>®</sup>, Aldara<sup>®</sup>, Solaraze<sup>®</sup> and Zyclara<sup>®</sup> were 200, 25, 25, 33.3 and 200 cm<sup>2</sup>, respectively. For the treatment of smaller areas (<100 cm<sup>2</sup>), treatment with Metvix<sup>®</sup> was the most costly topical option in Italy. However, for the treatment of cancerization areas larger than 100 cm<sup>2</sup>, Metvix<sup>®</sup> was the least expensive treatment option. Treatment with Metvix<sup>®</sup> was least long, requiring a single day of treatment for an area of up to 200 cm<sup>2</sup>, compared with up to 224 days of treatment with Aldara<sup>®</sup> for the treatment of a similar size.

**Conclusion** Changing treatment costing strategy in the management of multiple AKs towards costing per cancerization area instead of costing per lesion is a much more accurate representation of the 'real world cost' for AK.

Received: 3 July 2018; Accepted: 19 September 2018

## Conflict of interests

Prof. Piergiacomo Calzavara-Pinton has received honoraria from Galderma, Leo, Meda and Almirall. Neda Tanova has received honoraria from Galderma. Pol-Antoine Hamon was employed by Galderma during this research programme

## Funding sources

This research programme was funded by Galderma.

## Introduction

Actinic keratosis (AK) is a skin condition characterized by chronic cutaneous lesions, caused by exposure to ultraviolet light.<sup>1</sup> Their presence is considered a risk factor for skin malignancies. AK occurs on sun-exposed areas of the body, such as the head, neck and forearms<sup>2</sup> and primarily affects the elderly population. In Europe, the overall prevalence of AK is estimated to range between 6% and 26%, with a higher prevalence in southern countries.<sup>3</sup>

Actinic keratosis lesions are precancerous and may evolve into invasive squamous cell carcinoma (iSCC). While historically the risk of progression was believed to be dependent on the clinical classification of lesions (measured by the Olsen *et al.* score), recent research suggests that it does not accurately assess their underlying histology,<sup>3</sup> and therefore is not indicative of the risk of progression towards iSCC.<sup>4</sup> Currently, the goal of AK therapy is to treat all lesions, irrespective of their thickness. However, there is a recent paradigm shift in the treatment of multiple

lesions ( $\geq 5$ ) in an anatomical area, where lesion-targeted therapy is no longer believed appropriate due to possible field cancerization. There is a growing consensus that in such cases the treatment should aim at treating every AK lesion as well as the surrounding photo-damaged skin.<sup>5–7</sup> Evidence for this is also the recently developed field-directed ‘actinic keratosis area and severity index’ (AKASI) which allows for the quantitative evaluation of AK severity across the entire affected area of the head.<sup>8</sup>

Therefore, for multiple lesions, the real cost of topical treatments depends on the size of the cancerization area which requires treatment, rather than on the number of AKs. There is, however, a disconnection between the real cost incurred when treating the full cancerization area and the cost attached to different topical options in past economic evaluations. Previous cost-effectiveness studies focused on cost per lesion or cost per pack of medication instead of examining the area of cancerization and quantity of treatment used. Aguilar *et al.*<sup>9</sup> estimated the quantity of MAL cream by evaluating the weight consumed to treat lesions; a cost per tube was applied. Similarly, Annemans *et al.*<sup>10</sup> calculated the total cost of care and the cost per lesion in AK patients, by multiplying each item with its unit cost. This method of costing per lesion/per pack in AK is consistent in the literature.<sup>9–12</sup>

The main objective of this study was to estimate the true cost of topical treatments for the management of AK with multiple lesions in Italy by looking at the quantity of topical drug needed as a function of the cancerization area.

## Materials and methods

Treatment options for AK include destructive therapies [e.g., surgery, cryotherapy, dermabrasion, photodynamic therapy (PDT)], topical medications [e.g., topical fluorouracil (5-fluorouracil, 5-FU), imiquimod, ingenol mebutate, diclofenac], and chemical peels (e.g., trichloroacetic acid). The focus of this study was on topical treatments for the management of multiple AK lesions in Italy.

Topical treatments indicated for the treatment of AK currently available in Italy are similar to those available in other European countries and include the following:

- Metvix<sup>®</sup>: 16% methyl aminolevulinic photodynamic therapy (MAL PDT), which requires illumination of a red light source or daylight. Currently available as 1 tube (2 g) package.<sup>13</sup>
- Picato<sup>®</sup>: 0.015% ingenol mebutate (IngMeb) is currently available as a box of 2 tubes (47 mg each).<sup>14</sup>
- Aldara<sup>®</sup>: 5% imiquimod (IMQ), currently available as a box of 12 sachets. Each sachet of Aldara<sup>®</sup> contains 12.5 mg of IMQ in 250 mg cream.<sup>15</sup>
- Zyclara<sup>®</sup>: 3.75% IMQ, currently available as a box of 28 sachets. Each sachet of Zyclara<sup>®</sup> contains 9.375 mg of IMQ in 250 mg cream.<sup>16</sup>

- Solaraze<sup>®</sup>: 3% diclofenac sodium currently available in a tube of 60 g.<sup>17</sup>

Table 1 outlines the relevant data and assumptions. In order to evaluate the actual cost of each treatment, the official approval status of the drug was used to estimate the amount of cream needed per one cm<sup>2</sup>. If the summary of product characteristics (SmPC) did not provide guidance on the maximum area covered per application, it was assumed that 250 mg/25 cm<sup>2</sup> topical treatments were applied on the cancerization area.

The cost of treatment was calculated based on the total area treated (i.e., the area of the cancerization field), and the quantity of treatment used to effectively treat this area. To understand how much cream was needed to cover the cancerization area of a certain size, it was essential to calculate what surface a tube/sachet of cream could cover and check if any restrictions based on the SmPC were in place. Therefore, to understand the cost incurred with each of these treatments, the corresponding SmPCs were reviewed for relevant posology information related to: (i) the maximum treatment area allowed in a single session and (ii) the maximum allowed quantity per application.

According to the SmPC, Metvix<sup>®</sup> did not have any restrictions on the surface which could be treated during one session. Metvix<sup>®</sup> was approved for application in 1 mm thick layer, with a maximum of 2000 mg per single application. If the maximum amount was used during PDT, large quantities of product would be needed. The usual amount of cream needed, however, is assumed to be lower and, therefore, a consistent assumption of 250 mg of cream needed for the treatment of an area of 25 cm<sup>2</sup> was applied.

Similarly to Metvix<sup>®</sup>, the SmPC of Zyclara<sup>®</sup> restricts the quantity of cream which could be used per application. The leaflet indicates a maximum of two sachets (250 mg) per day for the full face or bald scalp, which corresponds to a maximum area treated of about 150–200 cm<sup>2</sup> per sachet. For the purpose of the analysis, the total area which could be treated with two sachets per day was assumed to be 400 cm<sup>2</sup> (2 × 200 cm<sup>2</sup>).

Picato<sup>®</sup> and Aldara<sup>®</sup>, on the other hand, had restrictions related to the size of the area which could be treated. According to the corresponding SmPC, the content of one tube of Picato<sup>®</sup> covers an area of 25 cm<sup>2</sup> for the treatment of AK. The Italian health ministry allows the use of two tubes simultaneously if the two treated areas are not adjacent. Similarly, a single sachet of Aldara<sup>®</sup> is sufficient to cover a wart area of 20 cm<sup>2</sup>. As the SmPC did not provide specific guidance to the size of the AK area which could be treated with a single sachet of 250 mg cream, the assumption that the treatment of 25 cm<sup>2</sup> area requires 250 mg of cream was applied.

Finally, the SmPC of Solaraze<sup>®</sup> did not provide specific restrictions related to the maximum area which could be treated per day. However, it provided guidance which allows for its

**Table 1** Characteristics of topical treatments available in Italy

	Metvix <sup>®13</sup>	Picato <sup>®14</sup>	Aldara <sup>®15</sup>	Solaraze <sup>®17</sup>	Zyclara <sup>®16</sup>
<b>Product characteristics</b>					
DCI	16% MAL PDT	0.015% IngMeb	IMQ 5%. Each sachet contains 12.5 mg of IMQ in 250 mg cream	3% Diclofenac Sodium	IMQ 3.75%. Each sachet contains 9.375 mg of IMQ in 250 mg cream
Quantity per unit	1 tube (2 g)	box (2 tubs)	1 box = 12 sachets	60 g	1 box = 28 sachets
Therapeutic strategy	One session of PDT repeated after 3 months if needed	1 tube a day, 2 days (1 tube = 0.47 g delivering 0.25 g)	Up to 1 sachet per application. 3 times per week × 4 weeks. Repeat treatment if needed after a 4-week treatment-free period	0.5 g twice per day for each 25 cm <sup>2</sup> (maximal daily dose 8 g) up to 90 days	Up to 2 sachets per day for 2 weeks followed by 2 weeks rest and other 2 weeks of treatment
<b>Maximum area treated and quantity of cream required</b>					
Max. area treated in 1 session	No maximum	25 cm <sup>2</sup>	25 cm <sup>2</sup>	200 cm <sup>2</sup>	face or scalp (~300–400 cm <sup>2</sup> )
Max. quantity per application	2000 mg	250 mg	250 mg	4000 mg b.i.d. (8 g/day)	500 mg
Area treated per application with 1 tube/sachet	200.00 cm <sup>2</sup> *	25 cm <sup>2</sup>	25 cm <sup>2</sup>	60 g/90 days/2 per day = 0.33 g per day and area of 33.3 cm <sup>2</sup>	200 cm <sup>2</sup>
Num. of tubes per treatment course assuming max. allowed area covered	N/A No maximum area	1 tube	1 sachet	12 tubes to cover 200 cm <sup>2</sup> in 90 days	56 sachets for full course of 2 weeks + 2 weeks
<b>Price of topical therapies, per pack</b>					
List price (EUR)	387.27	106.68	61.93	71.86	101.68
Ex-factory (EUR)	133.65†	64.63	33.02	43.54	61.29

\*Assuming 250 mg of the topical treatment are applied to treat cancerization area of 25 cm<sup>2</sup>.

†Discounted hospital price was applied as Metvix<sup>®</sup> is used on outpatient basis only.

Description: Product characteristics of the topical treatments available in Italy, according to their SmPCs, including restrictions on maximum area allowed to be treated or maximum quantity of cream to be applied.

**Table 2** Realistic surface area treated per unit with full course of treatment

	Metvix <sup>®</sup>	Picato <sup>®</sup>	Aldara <sup>®</sup>	Solaraze <sup>®</sup>	Zyclara <sup>®</sup>
	Realistic surface treated per unit (cm <sup>2</sup> ) in small area < 100 cm <sup>2</sup> (25 cm <sup>2</sup> /250 mg)				
	200 mg	25 mg	25 mg	33.3 mg	500 mg
–	25 cm <sup>2</sup>	1 tube	1 tube	1.50 tubes	1 box
–	50 cm <sup>2</sup>	1 tube	2 tubes	3 tubes	1 box
Cheek or nose or temple	100 cm <sup>2</sup>	1 tube	4 tubes	6 tubes	1 box
Half face or half scalp or forehead	200 cm <sup>2</sup>	1 tube	8 tubes	12 tubes	1 box
Face or scalp	400 cm <sup>2</sup>	2 tubes	16 tubes	24 tubes	2 boxes
Face and scalp	800 cm <sup>2</sup>	4 tubes	32 tubes	48 tubes	4 boxes

Description: Number of tubes/sachets needed to cover areas of different sizes.

estimation. According to the SmPC, a maximum daily dose of 8000 mg (8 g) is indicated and should not be exceeded. The suggested treatment duration is 60–90 days and the cream needs to be applied twice a day during this period. It was assumed that to achieve full efficacy, the 90-day period of treatment will be required. In addition, the SmPC states that ‘normally, 0.5 g (the size of a pea) of the gel is used on a 5 cm × 5 cm lesion site’.

Therefore, one tube of 60 g allows for the use of 666.7 mg per day during the 90-day treatment period, or 333.3 mg per application. If we apply the same assumption that the treatment of a 25 cm<sup>2</sup> area requires 250 mg of cream, one tube of Solaraze<sup>®</sup> is enough for the treatment of a cancerization area of 33.3 cm<sup>2</sup>.

To estimate the cost per area treated with each topical option, the ex-factory discounted price was used. This is the price paid

**Table 3** Total cost per area treated with full course of treatment, Euro

		Metvix®	Picato®	Aldara®	Solaraze®	Zyclara®
<b>Product price (EUR)</b>		<b>133.65</b>	<b>64.63</b>	<b>33.02</b>	<b>43.54</b>	<b>61.29</b>
–	25 cm <sup>2</sup>	133.65	64.63	33.02	65.31	61.29
–	50 cm <sup>2</sup>	133.65	129.26	66.04	130.62	61.29
Cheek or nose or temple	100 cm <sup>2</sup>	133.65	258.52	132.08	261.24	61.29
Half face or half scalp or forehead	200 cm <sup>2</sup>	133.65	517.04	264.16	522.48	61.29
Face or scalp	400 cm <sup>2</sup>	267.30	1034.08	528.32	1044.96	122.58
Face and scalp	800 cm <sup>2</sup>	534.60	2068.16	1056.64	2089.92	245.16

Description: Total drug cost (in Euro) of treating areas of different sizes.

by the Italian NHS to companies if their drug is used outside of the hospital setting; it is published in the official journal of the Italian government, the Gazzetta Ufficiale. As this is the price covered by the Italian NHS, it was assumed to be more appropriate than the list price, which would only be relevant for the private setting. The ex-factory prices applied in the current analysis are listed in Table 1. As Metvix® is used on an outpatient basis and is, therefore, not reimbursed by the NHS for use outside of the hospital setting, its discounted price paid by the hospitals was applied in the analysis.

The estimated cost per cm<sup>2</sup> treated allowed for a better understanding of the true cost of treatment in relation to the size of the area treated. To illustrate this, six hypothetical sizes were evaluated and the cost of treating each one of them with the available treatment options was estimated.

**Results**

The analysis estimated the number of tubes/sachets needed for the treatment of the cancerization area of a certain size and then estimated the total costs, based on the ex-factory price.

Outlined in Table 2 is the number of tubes/sachets that cover a specific surface area, broken down by treatment option. For example, 100 cm<sup>2</sup> is estimated to approximate the treatment of a full cheek. An area of this size would require only one tube of Metvix®, or one box of 28 sachets of Zyclara®, but treating it with Solaraze® would require six tubes instead. Similarly, half a face or half a scalp would require treatment of about 200 cm<sup>2</sup>. An area of this size could still be treated with a single tube of

Metvix®; however, treatments like Picato®, Aldara® and Solaraze® would require much larger quantities of cream, resulting in 8 boxes, 8 boxes and 12 tubes, respectively.

As demonstrated in Table 2, two tubes of Metvix® would be sufficient to treat a cancerization field of 400 cm<sup>2</sup>. In contrast to Metvix®, one tube of Picato® would cover a cancerization area of up to 25 cm<sup>2</sup>, meaning that sixteen boxes of Picato® would be needed to treat a 400 cm<sup>2</sup> cancerization area. The same holds true for Aldara®, where sixteen boxes of 12 sachets would be required to treat an area of 400 cm<sup>2</sup>. Finally, 24 tubes of Solaraze® would be needed to cover a cancerization area of the same size in 90 days, while six tubes would be needed to cover only a small part of the face such as the nose, cheek or temple (approximately 100 cm<sup>2</sup>).

Overall, Zyclara® and Metvix® required a single pack to treat a cancerization area as large as 200 cm<sup>2</sup>, while the number of packs needed, increased linearly for all other treatments for areas larger than 25 cm<sup>2</sup>.

Table 3 reports the total cost of treating different parts of the head, taking into account the ex-factory price and the number of packages needed to cover an area of a certain size. It is evident from Table 2 and Table 3 that one tube of Metvix® and one box of Zyclara® cover a much larger surface than any of the other treatment options. While Metvix® has the highest cost per pack, at 100 cm<sup>2</sup> cancerization area, Metvix® becomes the cheaper option, compared with Picato® and Solaraze®. When treating an area of 200 cm<sup>2</sup>, Metvix® becomes the cheapest option retaining a price of €134 in comparison to Picato®: €517, Aldara®: €264 and Solaraze® now being the most expensive option at €522.

**Table 4** Treatment duration by cancerization filed size and maximum allowed treatment are per cycle, days

		Metvix®	Picato®	Aldara®	Solaraze®	Zyclara®
<b>Treatment area per treatment cycle</b>		<b>200 cm<sup>2</sup></b>	<b>25 cm<sup>2</sup> × 2</b>	<b>25 cm<sup>2</sup></b>	<b>200 cm<sup>2</sup></b>	<b>200 cm<sup>2</sup></b>
–	25 cm <sup>2</sup>	1	3	28	90	45
–	50 cm <sup>2</sup>	1	3	56	90	45
Cheek or nose or temple	100 cm <sup>2</sup>	1	6	112	90	45
Half face or half scalp or forehead	200 cm <sup>2</sup>	1	12	224	90	45
Face or scalp	400 cm <sup>2</sup>	2	24	448	180	90
Face and scalp	800 cm <sup>2</sup>	4	48	896	360	180

Description: Estimated treatment duration (in days) depending on the size of the area treated.

The trend persisted with larger cancerization areas, reaching €2090 for the treatment of 800 cm<sup>2</sup> with Solaraze<sup>®</sup>, compared to only €535 with Metvix<sup>®</sup>. Similarly to Metvix<sup>®</sup>, Zyclara<sup>®</sup> retains a low price of larger treatments areas and would be the cheapest treatment option for cancerization areas higher than 25 cm<sup>2</sup>.

In addition to the cost of treatment, the analysis further calculated the duration of treatment with each topical option, based on the maximum area size to be treated per cycle. The estimated treatment duration by area size, taking into account the maximum allowed area size to be treated, is reported in Table 4. The analysis estimated that Metvix<sup>®</sup> requires the least number of days for treatment, compared with all other topical options in Italy. For a cancerization area of up to 200 cm<sup>2</sup> Metvix<sup>®</sup> requires a single day of treatment, compared to 12, 45, 90 and 224 days for Picato<sup>®</sup>, Zyclara<sup>®</sup>, Solaraze<sup>®</sup> and Aldara<sup>®</sup>, respectively.

## Discussion

This study demonstrates that the price of treatment depends on the cancerization field and, therefore, the quantity of treatment used per area should be considered. We evaluated the cost of the available topical treatments for multiple AKs in Italy, while considering the size of the cancerization area, in line with the price per dose needed to cover the cancerization area.

Based on the information provided in the SmPCs of the evaluated treatment options, the area which could be treated with a single pack of Metvix<sup>®</sup>, Picato<sup>®</sup>, Aldara<sup>®</sup>, Solaraze<sup>®</sup> and Zyclara<sup>®</sup> was estimated at 200, 25, 25, 33.3 and 200 cm<sup>2</sup>, respectively. For the treatment of smaller areas (below 100 cm<sup>2</sup>), treatment with Metvix<sup>®</sup> was the most costly topical option in Italy. However, for the treatment of cancerization areas larger than 100 cm<sup>2</sup> Metvix<sup>®</sup> was the second cheapest treatment option, preceded only by Zyclara<sup>®</sup>. As the European Medicines Agency (EMA) is responsible for the regulations for the use of drugs in the Europe Union, these calculation can be easily replicated for other European countries as far as the local costs are applied.

In addition to being one of the least expensive options, the duration of treatment with Metvix<sup>®</sup> was also significantly shorter, compared with the rest of the treatments. The estimated length of treatment is an important factor by itself and is indicative of the duration of discomfort and the need for topical medications with impairment on social and working activities. In the literature, treatment duration was reported to be associated with significantly reduced adherence and persistence during treatment,<sup>18</sup> and the development of treatment options with shorter treatment duration has been recommended by experts.<sup>19</sup> In addition, other factors including efficacy, level of pain, and adverse events also have an impact on the choice of treatment by dermatologists, however, this information has been well documented in published RCT studies. Therefore, the current analysis focused solely on the two factors that have not previously been discussed: the calculation of cost of the drug per treated area and the length of treatment.

## Conclusion

The current study demonstrated that changing treatment costing strategies in the management of multiple AKs towards costing per cancerization area instead of costing per lesion, is a much more accurate representation of the 'real world cost' for actinic keratosis. This conclusion is expected to have implication on the reimbursing decisions, in addition to the corresponding efficacy of the treatments. Currently, the reimbursement status of topical treatments in Italy is not consistent. Treatments like Picato<sup>®</sup>, Solaraze<sup>®</sup> and Zyclara<sup>®</sup> are fully reimbursed by the National Health System, while the reimbursement of Metvix<sup>®</sup> is restricted to hospitals. The current analysis suggests that the use of Metvix<sup>®</sup> for patients with multiple AK lesions and cancerization field larger than 100 cm<sup>2</sup> is a cost-saving solution and full reimbursement for this population could be of interest to the Italian NHS.

## References

- Dréno B, Amici J, Basset-Seguín N, Cribier B, Claudel J, Richard M. Management of actinic keratosis: a practical report and treatment algorithm from AKTeam™ expert clinicians. *J Eur Acad Dermatol Venereol* 2014; **28**: 1141–1149.
- Dodds A, Chia A, Shumack S. Actinic keratosis: rationale and management. *Dermatol Ther (Heidelb)* 2014; **4**: 11–31.
- Schmitz L, Kahl P, Majores M, Bierhoff E, Stockfleth E, Dirschka T. Actinic keratosis: correlation between clinical and histological classification systems. *J Eur Acad Dermatol Venereol* 2016; **30**: 1303–1307.
- Fernandez Figueras M. From actinic keratosis to squamous cell carcinoma: pathophysiology revisited. *J Eur Acad Dermatol Venereol* 2017; **31**: 5–7.
- Calzavara-Pinton P, Haedersdal M, Barber K *et al.* Structured expert consensus on actinic keratosis: treatment algorithm focusing on daylight PDT. *J Cutan Med Surg* 2017; **21**: 35–165.
- De Berker D, McGregor J, Hughes B. Guidelines for the management of actinic keratoses. *Br J Dermatol* 2007; **156**: 222–230.
- Stockfleth E, Ferrandiz C, Grob JJ, Leigh I, Pehamberger H, Kerl H. Development of a treatment algorithm for actinic keratoses: a European Consensus. *Eur J Dermatol* 2008; **18**: 651–659.
- Dirschka T, Pellacani G, Micali G *et al.* A proposed scoring system for assessing the severity of actinic keratosis on the head: actinic keratosis area and severity index. *J Eur Acad Dermatol Venereol* 2017; **31**: 1295–1302.
- Aguilar M, De Troya M, Martín L, Benítez N, González M. A cost analysis of photodynamic therapy with methyl aminolevulinate and imiquimod compared with conventional surgery for the treatment of superficial basal cell carcinoma and Bowen's disease of the lower extremities. *J Eur Acad Dermatol Venereol* 2010; **24**: 1431–1436.
- Annemans L, Caekelbergh K, Roelants R *et al.* Real-life practice study of the clinical outcome and cost-effectiveness of photodynamic therapy using methyl aminolevulinate (MAL-PDT) in the management of actinic keratosis and basal cell carcinoma. *Eur J Dermatol* 2008; **18**: 539–546.
- Soini EJ, Hallinen T, Sokka A-L, Saarinen K. Cost-utility of first-line actinic keratosis treatments in Finland. *Adv Ther* 2015; **32**: 455–476.
- Caekelbergh K, Annemans L, Lambert J, Roelants R. Economic evaluation of methyl aminolevulinate-based photodynamic therapy in the management of actinic keratosis and basal cell carcinoma. *Br J Dermatol* 2006; **155**: 784–790.
- Ltd GU. Metvix™ 160 mg/g cream Summary of Product Characteristics. URL <https://www.medicines.org.uk/emc/product/6777/smpc> (last accessed 2018 12 April).

- 14 S.p.A LP. Picato™ Summary of Product Characteristics. URL [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/002275/WC500135327.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002275/WC500135327.pdf) (last accessed 2018 12 April).
- 15 S.p.A. MP. Aldara™ 5% cream Summary of Product Characteristics URL [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000179/WC500023122.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000179/WC500023122.pdf) (last accessed 2018 12 April).
- 16 S.p.A. MP. Zyclara™ 3.75% cream Summary of Product Characteristics URL [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/002387/WC500132261.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002387/WC500132261.pdf) (last accessed 2018 12 April).
- 17 SA A. Solaraze™ Summary of Product Characteristics. URL <https://www.medicines.org.uk/emc/product/6385/smpc> (last accessed 2018 12 April)
- 18 Shergill B, Zokaie S, Carr AJ. Non-adherence to topical treatments for actinic keratosis. *Patient Prefer Adherence* 2013; **8**: 35–41.
- 19 Stockfleth E, Peris K, Guillen C *et al.* A consensus approach to improving patient adherence and persistence with topical treatment for actinic keratosis. *Int J Dermatol* 2015; **54**: 509–515.