Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2211

imiquimod 3.75% cream (Zyclara®)

Meda Pharmaceuticals

04 October 2019

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

ADVICE: following a full submission

imiquimod (Zyclara®) is accepted for restricted use within NHSScotland.

Indication under review: for the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic, visible or palpable actinic keratosis of the full face or balding scalp in immunocompetent adults when other topical treatment options are contraindicated or less appropriate.

SMC restriction: for the treatment of large field actinic keratosis (>25cm^2).

In two randomised, double-blind, phase III studies, a greater proportion of adults with actinic keratosis affecting an area >25cm^2 on the face or balding scalp achieved complete clearance when treated with imiquimod 3.75% cream compared with vehicle.

Chairman
Scottish Medicines Consortium

Indication

For the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic, visible or palpable actinic keratosis of the full face or balding scalp in immunocompetent adults when other topical treatment options are contraindicated or less appropriate.[1]

Dosing Information

Up to two sachets of imiquimod 3.75% cream to be applied once daily before bedtime and remain on the skin for approximately 8 hours to the skin of the affected treatment field (area) for two treatment cycles of 2 weeks each separated by a 2-week no-treatment cycle or as directed by the physician.

The treatment area is the full face or balding scalp.

The clinical outcome of therapy has to be determined after regeneration of the treated skin, approximately 8 weeks after the end of treatment and on appropriate intervals thereafter based on clinical judgment. Lesions that do not respond completely to treatment at 8 weeks after the second treatment cycle should be carefully re-evaluated and one additional 2-week treatment of imiquimod 3.75% cream may be considered.

A different therapy is recommended if the treated lesion(s) show(s) insufficient response to imiquimod 3.75% cream.

Actinic keratosis lesions that have cleared after two imiquimod 3.75% cream treatment cycles of 2 weeks and subsequently recur can be re-treated with one or two further imiquimod 3.75% cream treatment cycles of 2 weeks following an at least 12 weeks treatment pause.[1]

Product availability date

2012

Summary of evidence on comparative efficacy

Imiquimod is an immune response modifier which has well-established safety and efficacy in the treatment of actinic keratosis. This 3.75% formulation (Zyclara®) allows treatment of an area >25cm^2 and a higher number of lesions.[1-3] The submitting company has requested that SMC considers imiquimod 3.75% cream for the treatment of large field actinic keratosis (>25cm^2).

The key evidence to support this formulation comes from two identical, double-blind, randomised studies (GW01-0702 and GW01-0704) which compared two strengths of imiquimod cream (3.75% and 2.5%) with vehicle in patients with actinic keratosis on either the face or balding scalp. Eligible patients had 5 to 20 visible or palpable actinic keratosis lesions in an area >25cm^2 on either the face or balding scalp on clinical assessment by the investigator. Patients were randomised equally

to imiquimod 3.75% cream (n=160), imiquimod 2.5% cream (n=160) or vehicle cream (n=159). Only the licensed formulation (3.75%) will be discussed further. The investigator selected the treatment area on the face or balding scalp to which patients applied up to two (250mg) sachets of study cream. This was applied daily at bedtime and washed off after approximately 8 hours for a 2-week cycle which was repeated after 2 weeks of no treatment.[2, 4]

The primary outcome was the complete clearance rate, defined as the proportion of patients with no lesions in the treatment area at the end of study visit (8 weeks after finishing treatment).This was assessed in the intention-to-treat (ITT) population which included all enrolled.[2, 4]

The secondary outcomes were partial clearance rate (defined as the proportion of patients with a ≥75% reduction in the number of actinic keratosis lesions in the treatment area from baseline to the end of study visit) and the percentage change in the number of actinic keratosis lesions in the treatment area from baseline to the end of study visit.[2, 4]

Table 1: Results of the primary outcome of complete clearance[2, 4]

	Imiquimod 3.75%	**Vehicle**
Primary outcome: complete clearance rate		
Combined analysis	36% (57/160)[a]	6.3% (10/159)
Study GW01-0702	26% (21/81)[a]	2.5% (2/80)
Study GW01-0704	46% (36/79)[a]	10% (8/79)
Secondary outcome: partial clearance rate		
Combined analysis	59% [a]	23%
Study GW01-0702	46% [a]	19%
Study GW01-0704	73%[a]	27%
Secondary outcome: percentage reduction in lesions from baseline (median, %)		
Combined analysis	82% [a]	25%
Study GW01-0702	73%[a]	21%
Study GW01-0704	91%[a]	30%

[a] p≤0.001 versus vehicle

The investigator global integrated photodamage (IGIP) score was an overall assessment of the patient's photodamage change in the treatment area from baseline to the end of study visit based on a 7-point symmetric scale: significantly improved (+3) to significantly worse (-3). The IGIP score was higher at the end of study in the imiquimod 3.75% group (+1.94) compared with the vehicle group (+0.73). Higher proportions of the imiquimod 3.75% group (68%) compared with the vehicle group (28%) were considered by the investigator to be significantly or much improved.[4]

Long-term complete clearance rates were assessed after an additional 12 months follow-up in a phase IIIb observational study. Patients who achieved complete clearance in the initial studies (n=116) were eligible and 89 patients enrolled. A sustained complete response was reported at 6 months by 67% (28/42) and 75% (6/8) of patients initially treated with two 2-weekly cycles of daily

imiquimod 3.75% and vehicle respectively. A sustained complete response was reported at 12 months by 40% (17/42) and 62% (5/8) of patients respectively.[5]

The submitting company performed a naïve unadjusted indirect comparison with florouracil 5% cream (Efudix®), diclofenac 3% gel (Solaraze®) and methylaminolevulinate (Metvix®) plus photodynamic therapy (MAL-PDT). This included the two key studies for imiquimod 3.75% cream, three studies each for fluorouracil 5% cream and diclofenac 3% gel and long-term follow-up of two studies for MAL-PDT and used pooled patient-weighed rates for complete clearance and recurrence rates from studies for each treatment as clinical outcomes. The company did not make a conclusion regarding the efficacy of imiquimod 3.75% cream relative to these comparators but used the complete clearance and recurrence rates from included studies directly in the economic analysis.

Summary of evidence on comparative safety

In the combined study populations, an adverse event was reported by 48% (77/160) of patients in the imiquimod 3.75% group and 33% (53/159) of patients in the vehicle group and these were considered treatment-related in 19% and 2.5% of patients respectively. A serious adverse event was reported in 3.3% of patients in the imiquimod 3.75% group and 1.3% of patients in the vehicle group; one serious adverse event (diarrhoea) in a patient who received imiquimod 3.75% cream was considered by the investigator as probably related to study medicine. Adverse events led to discontinuation from the study in two patients treated with imiquimod 3.75% and three patients treated with vehicle. More patients treated with imiquimod 3.75% cream required at least one rest period from treatment compared with the vehicle group (11% versus 0%) but this was not considered to affect the efficacy of imiquimod cream.[4]

Local skin reactions of severe intensity were reported by 34% of imiquimod 3.75% and 1.3% of vehicle-treated patients. The most common severe local skin reactions were erythema (25% and 0%) and scabbing/crusting (14% and 0%). In addition, flaking/scaling/dryness was reported by 8.2% and 1.3% of patients respectively, oedema by 5.7% and 0% respectively and weeping/exudate by 5.7% and 0% respectively. Application site reactions were the most frequently reported treatment-related adverse event by 11% and 1.3% of imiquimod 3.75% and vehicle-treated patients respectively.[4]

The SPC notes that some systemic adverse events, including headache (6.2% [10/160]) and fatigue (4.4% [7/160]), were reported by imiquimod 3.75% treated patients during the two key studies.[1]

Summary of clinical effectiveness issues

Actinic keratoses are chronic keratotic lesions on sun-exposed skin which have a low risk (≤1 in 1,000) of developing into invasive squamous cell carcinomas. It is not possible to determine which lesions are most likely to progress. Treatment is based on the extent and severity of lesions and other associated risk factors for skin cancer, previous treatments and patient's general health and preferences. Depending on the number of lesions and area affected, treatment can be directed at individual lesions or at an affected area of clinical and subclinical lesions. Treatment options include destructive methods (for example cryotherapy, curettage, chemical peels and photodynamic therapy) or topical medication (for example topical fluorouracil, imiquimod, diclofenac, or ingenol mebutate).[6-8] This 3.75% formulation of imiquimod (Zyclara®) is a lower concentration which allows treatment of a larger area and a higher number of lesions.[1-3] The submitting company has requested that SMC considers imiquimod 3.75% cream for the treatment of large field actinic keratosis (>25cm^2). This is in line with the concept of field-based treatment and that the new target for the treatment of actinic keratosis is the detection and clearance of clinical and subclinical lesions across an entire sun-exposed field.

The two key studies demonstrated the superiority of imiquimod 3.75% cream over vehicle in complete clearance, which is a clinically relevant outcome for the treatment of actinic keratosis. In the combined analysis, complete clearance was achieved by significantly more patients allocated to imiquimod 3.75% cream than vehicle (36% versus 6.3%). However the treatment effect varied between the two key studies and the proportions of patients achieving complete clearance was greater in Study GW01-0704 (46% versus 10% in the imiquimod 3.75% and vehicle groups respectively) than in Study GW01-0702 (26% versus 2.5% respectively). It is not clear why the results were so different but this may affect the appropriateness of the combined analysis.[2, 4]

The two key studies were double-blind in design but the higher incidence of local skin reactions in patients treated with imiquimod 3.75% may have led to unblinding of the investigators and patients.[4]

There were limited available long-term data and these were dependent on initial efficacy of treatment. The treatment groups were not balanced at entry into the long-term follow-up study and the results should be treated with caution.[2, 5]

The EMA notes that there is a lack of active comparative data to a first-line treatment and limits the use of Zyclara® to second-line therapy when other topical treatment options are contra-indicated or less appropriate. However, study patients were not required to be unsuitable for other topical treatments.[1, 2, 4]

There are no direct comparative data versus other topical treatments for actinic keratosis and the submitting company presented a naïve unadjusted indirect comparison with florouracil 5% cream (Efudix®), diclofenac 3% gel (Solaraze®) and MAL-PDT, as described above. The submitting

company provided no estimate of the relative treatment effect for imiquimod 3.75% cream (Zyclara®) versus comparators but applied the pooled patient-weighed rates for complete clearance and recurrence rates for each treatment directly to the economic analysis. There are a number of limitations including the naïve unadjusted methodology of the comparison and the pooling of results from assessment at different timepoints. In addition, the complete clearance rate used for imiquimod 3.75% (46%) was the highest of those reported in two studies and the company was asked to assess a range of rates as sensitivity analysis. There were also limitations associated with heterogeneity between the studies included in the indirect comparison in terms of study methods and design, patient populations, including treatment areas, size and timelines for assessment. Due to these limitations, no definitive conclusions can be made regarding the relative efficacy of imiquimod 3.75% to relevant comparators. The company subsequently provided an additional network meta-analysis.

The introduction of imiquimod 3.75% cream (Zyclara®) would offer a lower strength of imiquimod than the currently available 5% strength (Aldara®) so provide an option to treat a larger affected area and a higher number of lesions with imiquimod.[2]

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis evaluating imiquimod 3.75% for the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic, visible or palpable actinic keratosis of the full face or balding scalp in immunocompetent adults when other topical treatment options are contraindicated or less appropriate. The submitting company applied an additional restriction, positioning imiquimod 3.75% for treatment of large field actinic keratosis (>25cm^2). Comparisons were provided against diclofenac 3% (Solaraze), fluorouracil 5% cream (Efudix®), and methyl-amino levulinate plus photodynamic therapy (MAL + PDT). Imiquimod 5% cream (Aldara®) and ingenol mebutate (Picato® 0.015% or 0.05%) were excluded.

The company described the use of a published model originally, which was a two-year cohort-based decision-tree model.[9] In the original model, patients were assumed to receive treatment upon entry to the model, before transitioning through a series of decision nodes at 6 month intervals. At each node, patients were assumed to have complete clearance of actinic keratosis ('no actinic keratosis') or have incomplete clearance ('actinic keratosis'). At 12 months, patients achieving complete clearance from their first line treatment were modelled to either experience recurrence (at which point a second treatment was administered) or remain with 'no actinic keratosis'. Probabilities of complete clearance and actinic keratosis recurrence were estimated on data from a range of controlled and observational studies for imiqiuimod 3.75% and comparators, derived from the naïve unadjusted comparison discussed above. Utilities were derived from a previous publication ('no actinic keratosis' = 1.0; 'actinic keratosis' = 0.986). Adverse event disutilities were not applied in the model, despite the same publication highlighting a significant reduction in utility (estimated at-0.085).[10]

Medicines acquisition costs and the downstream treatment of non-responders were included in the base case analysis. The dose and duration of treatment was assumed to be consistent with the relevant summary of product characteristics (except for fluorouracil, where expert input was sought). Costs of adverse event management or downstream medical management (such as curettage or cryotherapy) were not included in the base case, although downstream medical management was included in a scenario analysis.

The base case results are presented in Table 2 below.

Table 2: Base case analysis

	QALY	Costs (£)	ICER (Imiquimod vs comparator)
Imiquimod 3.75%	1.89	967	N/A
Diclofenac 3%	1.89	1277	Dominant
Fluorouracil	1.89	969	£2,185/QALY
MAL + PDT	1.89	997	£4,963/QALY

QALY: quality adjusted life year. QALY estimates are rounded to two decimal places. ICER: incremental cost effectiveness ratio. Note: the estimates above have been corrected to incorporate a 3.5% discount rate. Dominant: imiquimod 3.75% is more effective and less costly than the comparator.

A number of additional sensitivity analyses were requested in the form of one-way deterministic analysis and additional scenarios. The key scenario analyses are provided in Table 3 below, highlighting that the ICER estimates are most sensitive to choice of comparator, the inclusion of adverse event disutilities, the source of the complete clearance rate for imiquimod 3.75% and the surface area treated.

Table 3: Key scenario analyses

#	Scenario	ICER (£/QALY) versus:		
		Diclofenac 3%	Fluorouracil	MAL+PDT
	Base case	Dominant	2,185	4,963
1	Inclusion of adverse event disutility (-0.085)	Dominant	Dominant	3,544
2	Pooled median imiquimod 3.75% clearance rate (35.6%)	Dominant	Dominated	Dominated
3	Treatment of 150cm^3 surface area (increased dose requirements)	Dominant	South-west quadrant	18,690

QALY: Quality-adjusted life year; Dominant: Imiquimod 3.75%is more effective and less costly than the comparator; Dominated: Imiquimod is less effective and more costly than the comparator. South-west quadrant: Imiquimod 3.75% is less effective and less costly than the comparator.

It is important to note that the wide range of ICER estimates is due to the very small incremental QALY estimates between the treatments. Therefore, a cost-minimisation analysis was requested to test the extent of cost-savings if clinical equivalence was assumed. This is shown in Table 4.

Table 4: Cost-minimisation analysis

	Costs	Cost difference (versus imiquimod 3.75%)*
Imiquimod 3.75%	£1,164	NA
Diclofenac 3%	£1,404	-£240
Fluorouracil	£1,179	-£15
MAL+PDT	£1,483	-£319

* A negative sign indicates that imiquimod 3.75% is cost-minimising against the comparator treatment

The main limitations to the analysis are as follows:

- The use of a naïve unadjusted comparison results in uncertain estimates of relative effectiveness. The submitting company was initially reluctant to undertake alternative comparisons, but did submit a network meta-analysis and corresponding economic analysis (CUA and CMA) to support the base case analyses.
- Changes to a number of assumptions in the estimation of clinical effectiveness (complete clearance rates, recurrence rates) result in a change from a small ICER for imiquimod 3.75%, to being dominated by fluorouracil and MAL-PDT. This is driven by very small incremental differences in health outcomes between the treatments.
- The dose of imiquimod 3.75% and each comparator is assumed consistent with the Summary of Product Characteristics rather than data observed within the clinical trials supporting efficacy estimates. In the case of imiquimod 3.75%, this may underestimate the number of sachets (and therefore cost) required to achieve the clinical outcomes reported in the clinical trial.

The results show extremely small QALY differences between treatments and given the concerns about various methods of the estimation of treatment differences, a cost-minimisation analysis was requested to test the influence of these estimates. This approach suggested that despite the uncertainties regarding relative effectiveness, imiquimod 3.75% has the potential to be cost-saving against the comparators. As such, the economic case was considered demonstrated.

Summary of patient and carer involvement

- We received a patient group submission from Melanoma Action and Support Scotland (MASScot), which is a Scottish Charitable Incorporated Organisation.

- MASScot has received 2.3% pharmaceutical company funding in the past two years, with none from the submitting company.

- Actinic keratosis (AK) is common in patients with sun-damaged skin. AK presents as rough patches of skin with a lumpy feel. It can be itchy, sore, red, widespread and weepy. AK is the first sign of a potential squamous cell skin cancer and finding a lesion can be a concern to patients until it has been checked by a dermatologist.

- Excision biopsy is a common method of treating suspicious lesions in patients who are fit and who have no more than a few lesions. Similarly, AK can be treated by freezing. However, freezing large areas of the face and scalp can be very painful and for some patients with multiple lesions, freezing would be inappropriate.

- Where large areas need to be treated a cream is the preferred treatment option. A simple to use cream would be welcomed by patients.

Additional information: guidelines and protocols

The British Association of Dermatologists published guidelines for the care of patients with actinic keratosis in 2017.[7] Management can be directed at individual lesions or over a wider area – field treatment. Field-based treatment can act to manage a range of actinic changes in an area such as the forehead, scalp or central face, and may provide some benefit in reduction of onset of new lesions. Topical therapy is suited to use as lesion- and field-based treatment. Where used for field treatment, the size of the field needs to be defined with the patient to ensure anticipation and tolerance of side-effects. For field treatment, the guideline categorises fluorouracil 5% cream as a good treatment; diclofenac 3% gel, imiquimod 5% and 3.75%, ingenol mebutate, MAL-PDT [methylaminolevulinate (Metvix®) photodynamic therapy] and cryotherapy as fair treatments; fluorouracil 0.5% cream in 10% salicylic acid cutaneous solution as "can be used depending on circumstances" and curettage as "rarely used in these circumstances".

The International League of Dermatological Societies in cooperation with the European Dermatology Forum published evidence and consensus-based guidelines for the treatment of actinic keratosis in 2015.[8] This guideline gives a strong recommendation for using the following treatment for patients who have multiple actinic keratosis lesions or field cancerisation: imiquimod 3.75% cream, fluorouracil 0.5% cream (only available in the UK in combination with 10% salicylic acid [Actikerall®]), ingenol mebtate 0.015% cream [Picato®] for lesions on the face or scalp (0.05% for lesions on the trunk or extremities). The guideline also suggests (weak recommendation) using cryotherapy, diclofenac 3% in hyaluronic acid 2.5% gel [Solaraze®], fluorouracil 5% cream [Efudix®], fluorouracil 0.5% cream in 10% salicylic acid cutaneous solution [Actikerall®], imiquimod 5% cream [Aldara®] and 2.5% cream, 5-aminolaevulinic acid [Ameluz®] photodynamic therapy (ALA-PDT) and methylaminolevulinate [Metvix®] photodynamic therapy (MAL-PDT).

Additional information: comparators

Other topical treatments for actinic keratosis depending on the size of the treatment area.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per course (£)
Imiquimod 3.75% cream (Zyclara®)	**Applied daily for 2 weeks, then 2 weeks of no treatment and then a further 2 weeks of daily treatment**	**55 to 110**
methyl-5-aminolevulinate cream (Metvix®)	Applied topically to lesions as part of photodynamic therapy. Can be repeated after 12 weeks if insufficient response.	172 to 344
5-aminolaevulinic acid gel (Ameluz®)	Applied topically to lesions as part of photodynamic therapy. Can be repeated after 12 weeks if insufficient response.	170 to 340
Ingenol mebutate 0.015% gel (Picato®)	Face or scalp: applied to lesions once daily for three days.	65
Diclofenac 3% gel (Solaraze®)	Applied twice daily for 60 to 90 days.	38 for 50g 77 for 100g
Fluorouracil 5% cream (Efudix®)	Applied once or twice daily for up to 28 days.	33 for 40g

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS online on 31 July 2019. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 123,000 patients**.** Based on an estimated uptake of 1.07% (1,236 patients) in year 1 and 4.21% (4,945 patients) in year 5, the impact on the medicines budget was estimated at £68k in year 1 and £271k in year 5.

The net medicines budget impact was estimated at savings of £20k and £80k in year 1 and year 5, respectively.

References

1. Meda Pharma Gmb H. Zyclara 3.75% cream - Summary of Product Characteristics (SmPC). 2018.
2. European Medicines Agency (EMA) European Public Assessment Report imiquimod (Zyclara). 03/08/2012 EMEA/H/C002387
3. Meda Pharma Gmb H. Aldara 5% Cream - Summary of Product Characteristics (SmPC). 2017.
4. Swanson N, Abramovits W, Berman B, Kulp J, Rigel DS, Levy S. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: Results of two placebo-controlled studies of daily application to the face and balding scalp for two 2-week cycles. Journal of the American Academy of Dermatology. 2010;62(4):582-90.
5. Hanke C, Swanson N, Bruce S, Berman B, Kulp J, Levy S. Complete clearance is sustained for at least 12 months after treatment of actinic keratoses of the face or balding scalp via daily dosing with imiquimod 3.75% or 2.5% cream. Journal of drugs in dermatology : JDD. 2011;10(2):165-70.
6. BMJ Best Practice. Actinic Keratosis. 2018 [cited 12 June 2019]; Available from: https://bestpractice-bmj-com.knowledge.idm.oclc.org/topics/en-gb/616.
7. De Berker D, McGregor JM, Mohd Mustapa MF, Exton LS, Hughes BR. British Association of Dermatologists' guidelines for the care of patients with actinic keratosis 2017. British Journal of Dermatology. 2017;176(1):20-43.
8. Werner RN, Stockfleth E, Connolly SM, Correia O, Erdmann R, Foley P*, et al.* Evidence- and consensus-based (S3) Guidelines for the Treatment of Actinic Keratosis – International League of Dermatological Societies in cooperation with the European Dermatology Forum – Short version. Journal of the European Academy of Dermatology and Venereology. 2015;29(11):2069-79.
9. Soini EJ, Hallinen T, Sokka A-L, Saarinen K. Cost-utility of first-line actinic keratosis treatments in Finland. Advances in therapy. 2015;32(5):455-76. Epub 2015/05/26.
10. Wilson ECF. Cost effectiveness of imiquimod 5% cream compared with methyl aminolevulinate-based photodynamic therapy in the treatment of non-hyperkeratotic, non-hypertrophic actinic (solar) keratoses a decision tree model. PharmacoEconomics. 2010;28(11):1055-64.

This assessment is based on data submitted by the applicant company up to and including 13 September 2019.

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

Advice context:

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

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in

determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.