

imiquimod 5% cream (Aldara®)

No. (385/07)

Meda Pharmaceuticals Limited

8 June 2007

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

ADVICE: following a full submission

imiquimod cream (Aldara®) is not recommended for use within NHS Scotland for the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adult patients when size or number of lesions limit the efficacy and/or acceptability of cryotherapy and other topical treatment options are contraindicated or less appropriate.

Imiquimod cream was more effective than placebo in clearing actinic keratosis lesions. However, the manufacturer did not provide a sufficiently robust economic analysis to gain acceptance by SMC.

The licence holder has indicated their decision to resubmit.

Overleaf is the detailed advice on this product.

**Chairman
Scottish Medicines Consortium**

Indication

Topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adult patients when size or number of lesions limit the efficacy and/or acceptability of cryotherapy and other topical treatment options are contraindicated or less appropriate.

Dosing information

To be applied, and left on the skin for approximately eight hours, three times weekly for 4 weeks. If lesions persist after a 4-week treatment-free period, treatment should be repeated for another 4 weeks.

Product availability date

February 2007

Summary of evidence on comparative efficacy

Actinic keratoses (AKs) are common sun-induced precancerous lesions that occur on chronically light-exposed adult skin and are confined to the epidermis. They represent focal areas of abnormal keratinocyte proliferation and differentiation that carry a low risk of progression to invasive squamous cell carcinoma (SCC). Imiquimod is an imidazoquinolinamine and acts as an immune response modifier.

A vehicle-controlled double blind study in the USA and an almost identical study in Europe enrolled 246 and 259 patients respectively. These adult patients had a total of 4 to 8, (5 - 9 in the European study), clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic AK lesions located within a contiguous 25-cm² treatment area on the balding scalp or face, but not both. In the European study one representative lesion was biopsied before and another after treatment for histological confirmation of AK. Over both studies 87% of patients were male and the median age was 65 to 73 years. 16% (82/505) patients had Fitzpatrick skin type I (fair skinned Caucasians who burn very easily and never tan), and 45% (226/505) had Fitzpatrick skin type II (fair skinned Caucasians who burn easily and tan slowly and with difficulty). Patients were randomised to imiquimod 5% cream or vehicle three times a week for one or two courses of four weeks each, with four weeks between courses. A single use sachet containing 250mg of cream was used for each application and was left on the skin for approximately eight hours.

The primary endpoints of overall complete clearance of AKs and complete clearance after one treatment course were defined in the USA study as the proportion of patients with no clinically visible AK lesions in the treatment area, and in the European study as the proportion of patients with no histological evidence of AK on biopsy of the post-treatment target lesion and no AK lesions in the remainder of the treatment area. In both studies imiquimod was significantly more effective than placebo in achieving these endpoints.

Primary endpoint results of pivotal studies

STUDY	IMIQUIMOD	VEHICLE	P-VALUE
Overall complete clearance			
USA study	53.7% (66/123)	14.6% (18/123)	<0.0001
European study	55.0% (71/129)	2.3% (3/130)	<0.0001
Complete clearance at end of course one			
USA study	26.8% (33/123)	4.1% (5/123)	<0.0001
European study	37.2% (48/129)	0.8% (1/130)	<0.0001

Two single visit observational studies investigated the recurrence rates in the subgroup of patients who had achieved complete clearance of AKs at their last visit in the pivotal studies. The recurrence rate, defined as the proportion of patients, at the 12 month follow up visit, with any current lesions or with relevant treatment interventions in the previous treatment area and calculated across the two trials was 27% (35/128) vs 47% (8/17) for imiquimod vs vehicle respectively.

Summary of evidence on comparative safety

The European Public Assessment Report (EPAR) notes that: "Given that the benefit in the prevention of progression to SCC has not been established and that several other treatment options are available, the ("absolute" and comparative) safety profile is of primary concern. Although the data made available at various steps throughout the procedure have allayed the concern that imiquimod is associated with an excess rate of recurrence and progression rates at one year, it is noted that only a subgroup of patients were followed up and no assessment was made as to whether SCCs arose from previous lesions."

Imiquimod may cause a variety of systemic reactions including stimulation or exacerbation of (auto)immune conditions, skin reactions resulting in hospitalisation and reductions in haematological parameters. Although the number of cumulative cases of such events is low in the context of the exposure and some of the reported cases may not be causally associated with imiquimod therapy, some demonstrate good temporal association with positive de-challenge and/or rechallenge.

No comparative safety data have been provided. In the pivotal studies 56% of imiquimod patients and 42% of vehicle patients reported at least one adverse event. Application site reactions were reported spontaneously as an adverse event by 22% vs 5% of imiquimod vs vehicle patients respectively. Local skin reactions were also assessed by the investigators in a prospectively defined manner. These included severe erythema (24%) and severe scabbing and crusting (20%) which were very common in imiquimod patients. Three imiquimod and no vehicle patients discontinued treatment due to local skin reactions. Myalgia and fatigue were also statistically significantly more common with imiquimod compared to vehicle.

Summary of clinical effectiveness issues

The EPAR comments that the two pivotal short-term trials demonstrated that treatment of AKs with imiquimod provided significant short-term benefit when compared to vehicle. Direct comparative data for cryotherapy or licensed topical treatments (5-fluorouracil, diclofenac, methyl-5-aminolevulinate) are not available. Comparisons with data reported in the literature suffer from several flaws and limitations, but indicate that short-term lesion clearance rates for imiquimod are within the same order of magnitude as reported for other topical treatments.

A comparison of data on recurrence rates obtained from the single visit follow up trials with those cited in the literature for other topical treatments is problematic due to factors such as different study design, treatment areas and length of follow-up periods. Therefore a robust conclusion regarding comparative long-term efficacy could not be drawn.

As 53% and 67% of patients in the USA and European studies respectively had Fitzpatrick skin type I or II, it is probable that a substantial proportion of the clinical trial population reflects the likely predominant skin types of the Scottish patient population.

The EPAR notes that data from an open-label clinical trial suggest that patients with more than eight AK lesions showed a decreased rate of clearance compared to those with less than eight lesions

Summary of comparative health economic evidence

The manufacturer submitted a short term cost-effectiveness analysis of imiquimod cream used for up to two cycles of treatment for multiple AK lesions in immunocompetent adults followed by the use of photodynamic therapy in treatment failures compared to use of up to two administrations of photodynamic therapy alone. Photodynamic therapy (PDT) consisted of the administration of one application of methyl-5-aminolevulinate cream photosensitiser per treatment in a hospital outpatient setting, whereas imiquimod is patient self-administered, although still involves dermatology outpatient visits. The comparator is considered appropriate as PDT is used after other treatments and imiquimod cream is licensed for use if cryotherapy and other topical treatments are contraindicated or inappropriate due to number or size of lesions.

An indirect comparison of outcomes between pooled data from the two primary clinical trials of imiquimod cream and data from a single PDT study with similar patient population and outcome measure was performed. The comparator study was identified following a systematic review, but limited details were provided in the submission to assess the quality of that review and therefore the representativeness of the comparative efficacy data for PDT from the single study is uncertain. The outcome measure used was percentage of patients with $\geq 75\%$ lesion clearance rate, and the incremental cost per additional patient successfully treated based on this outcome was assessed. This produced a base case incremental cost of £458 per additional successfully treated patient for imiquimod compared to PDT, based on a difference in cost of £23 per patient and a 5% difference in outcomes. However, no attempt was made to evaluate the health or quality of life benefits associated with this outcome, and it was claimed in the submission that there is no evidence to determine any differential quality of life impact for imiquimod treatment.

There were several other limitations in the economic analysis. There was no attempt to translate an incremental cost per successfully treated patient into an assessment of patient health benefit. The estimation of the healthcare resource use in administration and patient follow-up lacked transparency. It was however confirmed by the manufacturer that imiquimod treatment can involve a greater number of outpatient visits than PDT despite the former being patient-administered. Also, the costs associated with the administration of PDT over several hours in a secondary care setting appeared not to have been included. Additional sensitivity analysis provided by the manufacturer indicated that the results were subject to a high degree of uncertainty when varying the relative efficacy and resource use estimates for imiquimod cream and PDT. In some cases imiquimod cream was the dominant treatment (cheaper and more effective) whereas in some cases it was dominated (more expensive and less effective than PDT).

Given the weaknesses in the economic case submitted, the manufacturer did not provide a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: previous SMC advice

In November 2003, following a resubmission, the Scottish Medicines Consortium advised that methyl aminolevulinate 160mg/g cream was accepted for use within NHS Scotland. The evidence of efficacy for Metvix for the treatment of thin or non-hyperkeratotic and nonpigmented actinic keratosis on the face and scalp is not strong. The health economic evidence is incomplete, though it suggests similar costs to the alternative treatment (cryotherapy). However, Metvix appears to have a place for treatment of those patients when other therapies are considered less appropriate and should be delivered by a dermatologist experienced in this therapy.

Additional information: comparators

The licensed indication for imiquimod is when the efficacy and/or acceptability of cryotherapy is limited by the size or number of lesions and other topical treatment options are contraindicated or less appropriate. Alternative treatment options include emollients, sunblock, 5-fluorouracil cream, diclofenac 3% gel, cryosurgery, photodynamic therapy, curettage and excisional surgery.

Additional information: costs

Product	Regimen	Cost per treatment course (£) *
imiquimod cream	applied three times weekly for 4 or 8 weeks	51 - 103
methyl-5-aminolevulinate cream	applied prior to irradiation during photodynamic therapy session (one or two sessions)	208 - 416
diclofenac gel (Solaraze)	applied twice daily for 60-90 days	50 - 67
5-fluorouracil cream (Efudix)	applied once or twice daily for 3 - 4 weeks	18 - 35

Doses are shown for general comparison and do not imply therapeutic equivalence.

*Costs based on treatment area of 25cm² as per pivotal trials, and use of 0.5g cream for 25cm² skin (Solaraze Summary of Product Characteristics)

Additional information: budget impact

The manufacturer estimated that approximately 28,600 patients per annum would be eligible for imiquimod cream treatment in Scotland. Although this could be an overestimate, based on these numbers the manufacturer estimated a minimum direct expenditure on imiquimod cream of £460,000 if 20% of eligible patients (5,720) were to receive imiquimod cream. However, as imiquimod is expected to replace current PDT use the overall drug budget impact would be net savings due to the higher direct cost of PDT.

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.

This assessment is based on data submitted by the applicant company up to and including 11 May 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.