Scottish Medicines Consortium

imiquimod 5% cream (Aldara) No. (385/07)

Meda Pharmaceuticals Ltd

04 April 2008

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 resubmission

imiquimod (Aldara®) is accepted for restricted 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**.** It should be restricted to use in patients after specialist advice.

Imiquimod was more effective than vehicle in clearing actinic keratosis lesions.

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 four to eight, (five to nine in the European study), clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic AK lesions located within a contiguous 25-cm^2 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. The proportion of patients with Fitzpatrick skin type I, (fair skinned Caucasians who burn very easily and never tan), was 16% (82/505) and with Fitzpatrick skin type II, (fair skinned Caucasians who burn easily and tan slowly and with difficulty), was 45% (226/505). 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 vehicle in achieving these endpoints.

Primary endpoint results of pivotal studies

STUDY	IMIQUIMOD	95%CI	VEHICLE	95%CI
Overall complete clearance				
USA study	54% (66/123)	45 to 62	15% (18/123)	8.4 to 21
European study	55% (71/129)	46 to 64	2.3% (3/130)	0.0 to 4.9
Complete clearance at end of course one				
USA study	27% (33/123)	19 to 35	4.1% (5/123)	0.6 to 7.6
European study	37% (48/129)	29 to 46	0.8% (1/130)	0.0 to 2.3

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 both trials was 27% (35/128) vs 47% (8/17) for imiquimod vs vehicle respectively. The recurrence rates for individual lesions were 5.6% (41/737) and 7.5% (6/80) respectively. The rate of progression to SCC was 1.6% (2/128) of imiquimod patients and 0% (0/17) of vehicle patients.

An open-label, randomised, controlled, single centre study in Germany compared the initial and 12-month clinical clearance, histological clearance and cosmetic outcomes in 75 AK patients. Treatments were imiquimod 5% cream, (licensed dosing regimen), 5% 5-fluorouracil (5-FU) ointment, (twice daily for four weeks) or one or two sessions of cryosurgery. Patients were Caucasian, immunocompetent, had a minimum of five typical, visible and histologically proven AK lesions in one anatomical area of up to 50cm^2 on the head, neck or chest, mean age 73 years (range 57 to 88), 81% were male.

Initial clinical clearance was achieved in 85% (22/26), 96% (23/24), and 68% (17/25) of patients treated with imiquimod, 5-FU and cryosurgery respectively. The histological clearance rates were 73% (19/26), 67% (16/24) and 32% (8/25) for imiquimod, 5-FU, cryosurgery, respectively. The 12-month follow-up showed a high rate of recurrent and new lesions in the 5-FU and cryosurgery arms. The sustained clearance rate of initially cleared individual lesions was 73% (19/26), 54% (13/24) and 28% (7/25) for imiquimod, 5-FU and cryosurgery, respectively. Sustained clearance of the total treatment field was 73% (19/26), 33% (8/24) and 4% (1/25), of patients after imiquimod, 5-FU, and cryosurgery, respectively. Patients in the imiquimod group were judged to have the best cosmetic outcomes.

Summary of evidence on comparative safety

The European Medicines Agency (EMEA) noted: “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 with vehicle.

Summary of clinical effectiveness issues

According to the European Medicines Agency (EMEA), the short-term lesion clearance rates with imiquimod appear to be of the same order of magnitude as with other topical treatments. However, differences in study design and patient populations make comparisons problematic. Similar problems arise when comparing data on recurrence rates with those cited in the literature.

The only evidence of comparative efficacy is from a small, single centre, open-label study, described above, in which initial and 12-month clearance rates were significantly better for imiquimod compared with 5-FU or crysosurgery. However, this study allowed treatment of areas out-with the licence (i.e. neck and chest).

As 53% and 67% of patients in the US 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.

EMEA 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 fewer than eight lesions.

The duration of follow-up is currently limited to one year. Since AK can progress to SCC, EMEA has requested 3-year follow-up data.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing imiquimod treatment with photodynamic therapy (PDT) in patients with actinic keratoses when size or number of lesions limit the efficacy and/or acceptability of cryotherapy and other topical treatment options are contraindicated or less appropriate. A decision tree was used to estimate the costs and benefits of treatment over a one year time horizon and an indirect comparison was carried out as no direct comparative data were available. The analysis showed that treatment with imiquimod was £221 cheaper but was also slightly less effective than PDT.

A number of weaknesses were identified with the analysis. These included the use of a short time horizon which excluded longer term benefits of treatment and failure to include the costs and quality of life impacts due to adverse events. In response to these issues, the manufacturer provided a revised cost-utility analysis of imiquimod compared to no treatment and also PDT. For this longer term analysis the manufacturer has used the limited 12 month follow-up data which suggested a greater recurrence rate between 3 and 12 months for PDT- treated patients. The results of the revised analysis found that imiquimod would dominate both no treatment and PDT (i.e. be cheaper and more effective). Sensitivity analysis indicated that the result was most sensitive to the estimate of PDT's efficacy at 12 months.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The European Dermatology Forum issued guidelines for the management of AK in 2006, which state that AK should be treated, as it is impossible to predict which lesions will become thicker or more invasive with a potential for destructive growth and risk of progression to metastatic SCC.

The British Association of Dermatologists issued guidelines for the management of AK in 2007. These state that there is inadequate evidence to justify treatment of all AKs to try to prevent malignant change. Treatment should be considered on an individual basis according to signs, symptoms and history.

Both of these guidelines predate imiquimod's licence for treatment of AK.

Additional information: previous SMC advice

After review of a full submission, SMC issued advice on 8th June 2007 that 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 keratoses lesions. However, the manufacturer did not provide a sufficiently robust economic analysis to gain acceptance by SMC.

After review of a resubmission, SMC issued advice on 10th November 2003 that methyl aminolevulinate 160mg/g cream (Metvix®) is 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

Alternative treatment options include emollients, sunblock, 5-fluorouracil cream, diclofenac 3% gel, cryosurgery, photodynamic therapy (PDT), curettage and excisional surgery. 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. EMEA has clarified that PDT is included in the term "other topical treatments."

Cost of relevant comparators

Product	**Regimen**	**Cost per treatment course (£) ***
imiquimod cream	**applied three times weekly for 4 or 8 weeks**	**51 to 103**
methyl-5-aminolevulinate cream	applied prior to irradiation during photodynamic therapy session (one or two sessions)	208 to 416
diclofenac gel (Solaraze)	applied twice daily for 60-90 days	50 to 67
5-fluorouracil cream (Efudix)	applied once or twice daily for 3 - 4 weeks	17 to 35

Doses are shown for general comparison and do <u>not</u> imply therapeutic equivalence.
Costs from eVadis on 30th January 2008 *Costs based on treatment area of 25cm^2 as per pivotal trials, and use of 0.5g cream for 25cm^2 skin (Solaraze Summary of Product Characteristics)

Additional information: budget impact

The manufacturer estimated that use of imiquimod would be associated with savings of up to £1.1m per year. This was based on its use in 4,900 AK patients per year who would be unsuitable for cryotherapy and who otherwise would have received PDT. The budget impact figures included outpatient visits and follow up visits as well as drug costs associated with PDT and imiquimod treatment. These estimated savings are likely to be overoptimistic as they were based on 100% uptake of imiquimod in patients unsuitable for cryotherapy and did not take account of some patients being treated with other topical treatments.

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 14 March 2008.

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.

The undernoted references were supplied with the submission.

Jorizzo J, Dinehart S, Matheson R et al. Vehicle-controlled, double-blind, randomized study of imiquimod 5% cream applied 3 days per week in one or two courses of treatment for actinic keratoses on the head. J Am Acad Dermatol 2007; 57: 265–268.

Alomar A, Bichel J, McRae S. Vehicle-controlled, randomized, double-blind study to assess safety and efficacy of imiquimod 5% cream applied once daily 3 days per week in one or two courses of treatment of actinic keratoses on the head. Br J Dermatol 2007; 157: 133–141.

Krawtchenko N, Roewert-Huber J, Ulrich M et al. A randomised study of topical 5% imiquimod vs. topical 5-fluorouracil vs. cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up. Br J Dermatol 2007; 157 (Suppl 2): 34–40.

European Medicines Agency (EMEA). European public assessment report (EPAR) for imiquimod. www.emea.eu.int