Scottish Medicines Consortium

imiquimod 5% cream (Aldara®) No. (167/05)

3M Health Care

8 April 2005

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Imiquimod 5% (Aldara®) is accepted for restricted use within NHS Scotland for the topical treatment of small superficial Basal Cell Carcinoma in adult patients in whom standard treatment with surgery or cryotherapy is contraindicated**.** Its use should be supervised by specialists in dermatology.

At 12 weeks post treatment the composite clearance rates in the randomised controlled trials were between 73-77% and initial clearance rates in the open label studies were between 90-94%. There is only limited follow-up data beyond 12 months.

Overleaf is the detailed advice on this product.

Vice Chairman
Scottish Medicines Consortium

Imiquimod 5% cream (Aldara®)

Licensed indication under review

Topical treatment of small superficial Basal Cell Carcinoma (sBCC) in adult patients.

Dosing information under review

The cream is applied once daily, prior to normal sleeping hours and left on the skin for 8 hours, five times per week for six weeks. Response to treatment is assessed 12 weeks after the end of treatment. If the treated tumour shows an incomplete response a different therapy should be used.

UK launch date

4 October 2004

Comparator medications

fluorouracil cream, methyl aminolaevulinate cream

Cost per treatment period and relevant comparators

Drug	Dose	Cost per treatment course
Imiquimod 5% cream	**Applied 5x/week for 6 weeks**	**£138**
Fluorouracil 5% cream	Applied once or twice daily for three to four weeks (2x20g tubes used for treatment course)	£37
Methyl aminolaevulinate 160mg/g cream	Apply a 1mm thickness of cream for 3 hours covered with an occlusive dressing. Remove the cream and immediately expose to irradiation with red light. Repeat after 7 days. (1x2g used)	£208

Summary of evidence on comparative efficacy

Three phase III double blind randomised vehicle controlled trials have been conducted with imiquimod 5% cream for superficial basal cell carcinoma. Data from the two US based studies were pooled and the results published. Inclusion criteria included patients = 18 years with a primary, histologically confirmed sBCC at least 0.5cm^2 in area with a maximum diameter of 2cm and the lesion suitable for excision. Lesions could be located on the limbs, trunk (excluding the anogenital area), neck or head (excluding scalp, nose, mouth, ears and eyes). Patients were excluded if there was dermatological disease in the target sBCC site or surrounding area that could be exacerbated by imiquimod or cause difficulty in examination. 724 patients were randomised, in blocks of four, to one of 4 groups; application of imiquimod 5 times/week, vehicle 5 times/week, imiquimod 7 times/week or vehicle 7 times/week, for a duration of 6 weeks. The cream was applied just prior to bedtime and was rubbed into the lesion, and area approximately 1cm surrounding the lesion, until the cream vanished. The cream was allowed to remain on the skin for at least 8 hours without occlusion and then removed with mild soap and water. Rest periods could be prescribed by the investigators. Patients were assessed at weeks 1, 3 and 6 during treatment and weeks 4 and 12 post

treatment. At week 12 the sBCC was excised, with a 3-4mm margin around the original lesion margins if the sBCC was clinically evident or a 1-2mm margin if not clinically evident. The primary efficacy variable was complete composite clearance defined as the proportion of patients at the 12 week post-treatment visit who were complete responders to treatment. A complete responder was defined as a patient with no clinical evidence and no histological evidence of BCC at the target lesion site or clinical evidence suspicious of BCC but no histological evidence of BCC at the target site and where the histological findings provided an explanation for the false positive clinical assessment. The histological part of the endpoint was considered a secondary endpoint as well. A sample size of 90 patients per treatment group (for each trial) was calculated which gave at least 90% power to detect a between-treatment difference in complete clearance rates of 20% for vehicle subjects and 50% for imiquimod subjects at either dosing frequency.

The complete composite clearance rate, for the imiquimod 5 times/week and 7 times/week groups, was 75% (95% confidence interval: 68-81%) and 73% (95% CI: 66-79%), respectively. The combined vehicle composite clearance rate was 2%.

The histological clearance rates for the imiquimod 5 times/week and 7 times/week groups were 82% (95% CI: 76-87%) and 79% (95% CI: 73-85%) respectively, and for the combined vehicle group 3%. The degree of concordance between the clinical and histological assessments was calculated using the pooled imiquimod groups. The positive predictive value; probability of a positive (sBCC present) clinical assessment confirmed to be positive histologically was 36% and the negative predictive value; probability of a negative (clear of sBCC) clinical assessment confirmed as being negative histologically was 93%.

Two open label long-term studies are being conducted to assess the long-term clinical outcome (up to 5 years) of patients being treated with imiquimod 5% cream and who do not have their tumour site excised following treatment. In both studies patients = 18 years with a biopsy-confirmed sBCC located on limbs, trunk (excluding anogenital area) neck or head (except scalp, nose, mouth ears and eyes) and with a minimum area of 0.5cm^2 and a maximum diameter of 2cm were recruited. Patients applied imiquimod 5 times/week or 7 times/week for 6 weeks. The primary efficacy endpoint was defined as no clinical evidence of sBCC at 12 weeks post-treatment and sustained clearance at follow-up visits at 3, 6 and 12 months and then annually for up to 5 years.

One hundred and eighty-two patients were enrolled in the first study and interim results up to and including the 12 month follow-up visit have been reported. The initial clearance rate was 90% at the 12 week post-treatment assessment. The estimated sustained clearance rate, based on the Kaplan-Meier product limit estimate (i.e. the proportion of subjects who were clear at the 12 week post treatment visit and were still clinically clear of sBCC at their last available follow-up visit), was 97.5% (95% CI: 95.1-99.9%), 95.0% (95% CI: 91.6-98.4%) and 92.7% (95% CI: 87.9-97.4%) for the 3, 6 and 12 month follow-up visits, respectively.

Other data were also assessed but remain commercially confidential.*

Summary of evidence on comparative safety

The pooled results of the two US double blind vehicle controlled trials indicated the proportion of patients discontinuing treatment due to an adverse event or local skin reaction was 4% and 2% for the imiquimod 5 times/week and 7 times/week groups respectively. There was a significant difference in the proportion of patients experiencing an application site reaction in the imiquimod 5 times/week group (28%) compared with the imiquimod 7 times/week group (44%). Application site reactions most frequently reported for the imiquimod 5 and 7 times/week groups respectively, were itching at the target site (16% and 26%), burning at the target site (6% and 9%) and pain at the target site (3% and 6%) and the difference was statistically significant for itching. Other adverse events experienced during the treatment period by = 3% of patients in any treatment group were headache, upper respiratory tract infection, sinusitis, back pain and pain. There was a significant difference for headache between the imiquimod 5 times/week and vehicle 5 times/week groups only. Local skin reactions were more intense in the imiquimod groups compared with the vehicle groups. Erythema, oedema, vesicles, erosion and scabbing/crusting were all significantly higher in intensity in the imiquimod 7 times/week group compared with the 5 times/week group.

Summary of clinical effectiveness issues

The summary of product characteristics for imiquimod 5% cream states that there is no clinical experience for the use of imiquimod in recurrent and previously treated BCCs, and its use is not recommended for previously treated tumours. It is also noted in the summary of product characteristics that long-term clearance rates beyond 12 months post-treatment are not currently available and advises that other appropriate therapeutic modalities should be considered for sBCC.

The five times per week regimen is the licensed regimen; data from the clinical trials of the seven times per week regimen (not licensed) have been included for completeness.

Summary of comparative health economic evidence

The manufacturer submitted an economic comparison of imiquimod with surgical excision and methylaminolaevulinate--plus-PDT (photodynamic therapy). The summary results table is as follows:

	Efficacy rate	**Cost**
Surgical excision	91%	£350
methylaminolaevulinate + PDT	87-97%	£811
Imiquimod	**82-90%**	**£314**

The analysis suffers from a number of weaknesses. Cryotherapy was not considered as a comparator, indirect comparisons with other therapies were not undertaken using “good practice rules” and the possibility of lower long-term efficacy of imiquimod was not fully explored. There was no attempt to convert the health gain from treatment into QALYs.

Nonetheless imiquimod appears to offer a clinically useful alternative therapy for sBCC at costs similar to presently available treatment options.

Budget impact

The manufacturer states the number of patients with superficial BCC to be in the range 710 to 2,176 with its share of the market starting at 20% in year 1 rising to 50% by year 5. This suggests between 142 and 1088 patients will be on treatment. Imiquimod is predicted by the manufacturer to be cost-neutral if it replaces surgical excision and cost saving if it replaces methylaminolaevulinate + -PDT. If imiquimod costs £314 per course then this would add between £44k (year 1) and £342k (year 5) to the drug budget, before allowing for any offsetting savings on other budgets.

Guidelines and protocols

A Cochrane review of interventions for basal cell carcinoma of the skin, which included an assessment of imiquimod, had a substantial update in 2003.. The authors noted that local skin reactions were reported in all trials of imiquimod. In addition there was a comment regarding lack of long-term follow-up data for recurrence and the need for a long-term study comparing imiquimod with excision surgery. Patient self-application of the cream was regarded as an advantage.

Additional information

In November 2003, following a re-submission, the SMC accepted methylaminolaevulinate cream (+ PDT) for restricted use for the treatment of basal cell carcinoma in patients in whom standard treatment with surgery or cryotherapy was contraindicated.

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 including11 March 2005.

Drug prices are those available at the time of SMC assessment.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:* http://www.scottishmedicines.org.uk/

The reference numbers in this document refer to the under-noted references. Those shaded grey are additional to those supplied with the submission.

Geisse J, Caro I, Lindholm J, Golitz L, Stampone P, Owens M. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: Results from two phase III, randomized, vehicle controlled studies. JAAD 2004. 50 (5) 722 - 733

Gollnick H, Guillen Barona C, Frank RGJ et al. Long-term efficacy of imiquimod 5% cream for the treatment of superficial basal cell carcinoma : A European study. [poster] 12th Congress of the European Academy of Dermatology and Venereology; 2003 Oct 15-18; Barcelona.