Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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fluorouracil 0.5% / salicylic acid 10% cutaneous solution (Actikerall®) SMC No. (728/11)

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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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission

fluorouracil 0.5% / salicylic acid 10% cutaneous solution (Actikerall®) is accepted for use within NHS Scotland.

Indication under review: the topical treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade I/II) in immunocompetent adult patients.

Fluorouracil 0.5% / salicylic acid 10% cutaneous solution was superior to another topical treatment for the histological clearance of a specified target actinic keratosis lesion.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

The topical treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (AK) (grade I/II) in immunocompetent adult patients. Grade I/II intensity is based on the 4-point scale of Olsen et al. (1991).

Dosing Information

For cutaneous use. In general fluorouracil 0.5% / salicylic acid 10% cutaneous solution (hereafter referred to as 5-FU-SA) is applied to AK once daily. Response increases over time and data are available for treatment up to 12 weeks. Complete healing of the lesion(s) or optimal therapeutic effect may not be evident for up to eight weeks after treatment cessation.

Multiple AK can be treated simultaneously. There is experience in treating up to ten lesions at the same time. The total area of skin being treated with 5-FU-SA at any one time should not exceed 25cm^2 (5cm x 5cm). 5-FU-SA should only come into contact with the AK and a rim of maximum 0.5 cm of the healthy skin surrounding the lesion. The treated area should not be covered after application and the solution should be left to dry to form a film over the applied area. Each time 5-FU-SA is reapplied the existing film coating should be removed beforehand by simply peeling it off.

Product availability date

6 June 2011

Summary of evidence on comparative efficacy

Actinic (or solar) keratosis (AK) is a common skin lesion, caused by chronic sun exposure, with the potential to transform into squamous cell carcinoma. The UK prevalence of AK in the over 60-year old is around 20%. The combination of fluorouracil 0.5% and salicylic acid 10% in a cutaneous solution (5-FU-SA) is a new treatment option for AK. Fluorouracil (also known as 5-fluoruracil) is a pyrimidine analogue and an anti-metabolite that prevents the synthesis of DNA and RNA resulting in inhibition of growth of AK. The addition of salicylic acid, which has a keratolytic effect, improves the penetration of fluorouracil in hyperkeratotic AK.

Evidence supporting the licence is from one randomised, double-blind, phase III study that compared 5-FU-SA with the cutaneous solution vehicle and with diclofenac 3% gel in patients with AK. The study included 470 patients aged 18 to 85 years; with Fitzpatrick skin type I to IV, in generally good health, and with histologically confirmed AK and 4 to 10 lesions on the face, forehead or bald scalp. These were classified as grade I (mild) or grade II (moderate) according to the Olsen scale: (0 (none); I (mild) = flat, pink maculae without signs of hyperkeratosis and erythema, slight palpability, easier to feel than see; II (moderate) = pink to reddish papules and erythematous plaques with hyperkeratotic surface, moderately thick AK that are easily seen and felt; III (severe) = very thick and/or obvious AK. The AK lesion diameter size was required to be between 0.5 cm and 1.5 cm and the total selected study area encompassing all single lesions could not exceed 25 cm^2 and must not have been treated for AK in the previous three months.

Patients were randomised in a 2:1:2 ratio to treatment with 5-FU-SA once daily, diclofenac 3% gel (containing hyaluronic acid) twice daily or vehicle once daily (solution contained dimethyl

sulfoxide, ethanol, ethylacetate, pyroxyline, polybutylmethacrylate, methylmethacrylate which may cause skin irritation). Dose frequency could be reduced to three times a week for 5-FU-SA and vehicle, or to once daily for diclofenac gel in the event of severe toxicity. Treatment was continued until complete clearance of lesions or for a maximum of 12 weeks.

The number, size and clinical severity of AK lesions were assessed at baseline, during treatment at weeks 2, 4, 6, 10 and 12 and at week 20 (eight weeks after the end of treatment). Biopsies of one target lesion per patient were taken at baseline, repeated at week 20 and independently evaluated. The primary outcome, measured by histological clearance of the target lesion, was to test the superiority of 5-FU-SA treatment to vehicle and, if this was achieved, to test the non-inferiority to diclofenac gel. Superiority to diclofenac gel was a secondary outcome. Analyses of all secondary variables were exploratory.

The mean number of lesions per patient before treatment was 5.8 and the mean total size of the lesions was 348.8 mm^2. Approximately 40% of lesions were grade I (mild) and 60% were grade II (moderate).

The primary analysis of the primary outcome was performed in the final analysis set (FAS) which comprised all patients with confirmed study diagnosis who had used study medication for more than 12 days and had data on efficacy variables after this. The primary outcome was achieved in 70% (124/177) 5-FU-SA patients, 54% (99/183) diclofenac gel patients and 43% (41/96) vehicle patients. Similar results were obtained in the analysis in the per protocol (PP) set and the 97.5% confidence intervals indicated that 5-FU-SA was superior to diclofenac gel.

Assessments of secondary variables were carried out at eight weeks post-treatment. The mean reduction in number of AK lesions per patient was 4.4, 3.3 and 2.0 in the 5-FU-SA, diclofenac gel and vehicle groups, respectively, significant for the comparisons of each active drug with vehicle. However an initial temporary increase in mean lesion area at week two was observed in the 5-FU-SA group only. The mean lesion area was significantly reduced from baseline for the treatment groups relative to vehicle group and for 5-FU-SA relative to diclofenac gel. Significantly more patients had complete clinical clearance in the 5-FU/SA group (55%) compared with both diclofenac gel (32%) and vehicle (15%).

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

At the eight-week post-treatment visit, fewer patients in the 5-FU-SA group were considered by the investigators to have 'good' or 'very good' tolerability than in the diclofenac gel or vehicle groups, (70% versus 85% and 90%, respectively).

Treatment-emergent adverse events were mainly of mild or moderate intensity and were reported in 95%, 77% and 85% of the 5-FU-SA, diclofenac gel and vehicle groups, respectively. Most were application site reactions; 86%, 38% and 61% in the 5-FU-SA, diclofenac gel and vehicle groups, respectively. Excipients in the vehicle were thought to have contributed to the high rate reported in that group. Severe general disorders and administration site reactions were more frequent in the 5-FU-SA group (28%) compared with 12% in the diclofenac gel group and 4.1% in the vehicle group. There were no treatment-related serious adverse events.

Summary of clinical effectiveness issues

The pivotal study results for histological clearance of a specified target lesion favoured 5-FU-SA over solution vehicle and diclofenac 3% gel (Solaraze®). Clinical expert responses to SMC have indicated that treatment of AK in practice across NHS Scotland is variable. Diclofenac 3% gel is frequently used in primary care and in secondary care may be used as an adjunct to cryotherapy. Other treatments including cryotherapy and fluorouracil 5% cream are also widely used. As the use of cryotherapy has practical disadvantages it is not used by all GP practices.

The Summary of Product Characteristics for diclofenac gel (Solaraze®) notes that its long term beneficial effects are unproven.

The results of the pivotal study may not be generalisable to the Scottish population as the study was carried out in Germany where the prevalence of AK and the response to therapy may differ to that in Scotland due to differences in skin types. It is not known if response to treatment of AK would be different. A limitation of the study was the lack of robustness of the double-blind design. The 5-FU-SA product is a solution and the diclofenac product is a gel. Although attempts were made to conceal the treatments from staff performing the assessments and from patients it is not known whether this was successful. In addition, there is no evidence of the effect of 5-FU-SA on quality of life in patients with AK.

The company supplied an indirect comparison that, despite some weaknesses, suggested 5-FU-SA has comparable clinical effectiveness to diclofenac 3% gel.

This preparation is only suitable for use on relatively small areas of skin; the total area of skin to be treated with 5-FU-SA at any one time should not exceed 25cm^2 compared with 500cm^2 for fluorouracil 5% cream.

*Other data were also assessed but remain commercially confidential.**

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis over a one year time horizon comparing 5-FU-SA with diclofenac 3% gel in patients with AK. A decision analytic model was used based on the treatment pathway of the phase III study. End of treatment lesion clearance rates measured at week 20 in the clinical study were applied in the model in addition to the recurrence rates measured at week 52 from the follow-up study.

The utility values were taken from another study which estimated the cost-effectiveness of two alternative AK treatments. The values used seem reasonable and predict only a small utility gain for patients achieving complete lesion clearance (0.011). Resource use estimates were based on assumption and included one specialist visit to a dermatologist per patient and an additional consultation if a patient experienced recurrence.

The results of the analysis indicated that 5-FU-SA was the dominant treatment, with estimated savings of £32 per patient and a QALY gain of 0.002. The overall cost of treatment with 5-FU-SA was estimated to be £225 per patient vs £257 for diclofenac 3% gel. The drug acquisition

costs are equivalent therefore the savings and QALY gain are based on different lesion clearance and recurrence rates.

A potential weakness of the analysis related to the place in therapy of diclofenac 3% gel and whether or not this is the most appropriate comparator. SMC clinical experts have indicated that fluorouracil 5% and cryotherapy are also used to treat AK. In response to this, the submitting company provided additional analyses to compare against each of these alternative treatments. These showed that 5-FU-SA was dominant (cheaper and more effective) than fluorouracil 5% and had a cost per QALY of £5,675 against cryotherapy. These analyses were, however, based on simple indirect comparison methodologies which had a number of important weaknesses, thus the results are less robust than for the primary comparison against diclofenac 3% gel.

Additional limitations were:

- The economic model used data from the secondary endpoint of lesion clearance. The data for progressive disease, stable disease and partial response were pooled to give an estimate of incomplete clearance. While these patient groups may be quite different, as the majority of patients were partial responders this is unlikely to have caused any major bias.
- The cost of recurrence may be slightly overestimated but this would not affect the overall conclusion that 5-FU-SA is cost-saving versus diclofenac 3% gel.

Despite these limitations, the economic case was considered demonstrated.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Skin Care Campaign Scotland
- Melanoma Action & Support Scotland

Additional information: guidelines and protocols

NHS Scotland Dermatology Referral and Management Pathway, solar (actinic) keratoses and Bowen's disease, was developed in conjunction with the Scottish Dermatological Society in November 2010 and recommends that if diagnosis is certain and keratoses are non-tender and non-infiltrated, treatment options are:

- small non-tender keratoses can be left alone or treated with 3% diclofenac gel (Solaraze®) twice daily.
- cryotherapy or 5—fluorouracil for more extensive, thicker keratoses.
- solitary cutaneous horns should be removed by curettage for histopathology

British Association of Dermatologists Guidelines for the management of actinic keratoses (2007) state that: overall, the data comparing individual treatments are not good enough to justify making a single recommendation. Decisions for an individual patient will be based on the clinical presentation, the efficacy, morbidity, availability and cost of relevant treatments and patient preference. The guidelines note that 2% salicylic acid ointment BP may be used for its

combined emollient and mild keratolytic effects, either alone or as pretreatment for topical 5-fluorouracil.

Both guidelines predate the availability of 5-FU-SA in the UK for the treatment of AK.

Additional information: comparators

Diclofenac 3% gel (Solaraze®) and fluorouracil 5% cream (Efudix®) are licensed for the indication under review.

Imiquimod (Aldara®) cream is not considered a comparator as it is licensed to treat nonhyperkeratotic, nonhypertrophic AK 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.

Other therapies for AK include cryosurgery – alone or in combination with topical treatments; photodynamic therapy – used in combination with photosensitising cream (5-aminolaevulinic acid, 5-methylaminolaevulinate); laser, chemical peels and dermabrasion and surgery.

Cost of relevant comparators

Drug	Dose Regimen	Cost per 12 week course (£)
Fluorouracil 0.5% + salicylic acid 10% cutaneous solution	**To be applied to actinic keratoses once daily**	**77**
Diclofenac 3% gel	To be applied to actinic keratoses twice daily	77
Fluorouracil 5% cream	To be applied thinly to the affected area once or twice daily	33 to 65

Doses are for general comparison and do not imply therapeutic equivalence. Costs are based on treating a 25cm^2 area. Costs from eVadis on 21 June 2011.

Additional information: budget impact

The submitting company estimated the budget impact based on the prescription volume of topical treatments for actinic keratosis. In year 1 it was estimated there would be 20,543 prescriptions rising to 24,970 in year 5. Based on an estimated uptake of 2% in year 1 and 16% in year 5, the impact on the medicines budget was estimated at £8k in year 1 and £153k in year 5. It was assumed that 5-FU-SA would displace existing topical treatments all of which are a similar price to 5-FU-SA. Therefore, the estimated net budget impact would be negligible.

References

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

Almirall Hermal GmbH. Clinical study report: Study on the efficacy of Verrumal® compared to placebo and Solaraze® in the treatment of actinic keratosis grade I to II H 1005 6002 – 0702 7 October 2009

Almirall Hermal GmbH. Clinical study report: Addendum 1 to the integrated report with 6 and 12 months follow-up data for Study on the efficacy of Verrumal® compared to placebo and Solaraze® in the treatment of actinic keratosis grade I to II H 1005 6002 – 0702 19 November 2010

Stockfleth E, Kerl H, Zwingers T, Willers C. Low-dose 5-fluorouracil in combination with salicylic acid as a new lesion directed option to treat topically actinic keratoses – histological and clinical study results. Accepted for publication in British Journal of Dermatology 13 April 2011

This assessment is based on data submitted by the applicant company up to and including 13 August 2011.

**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/About_SMC/Policy_Statements/Policy_Statements*

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. 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.