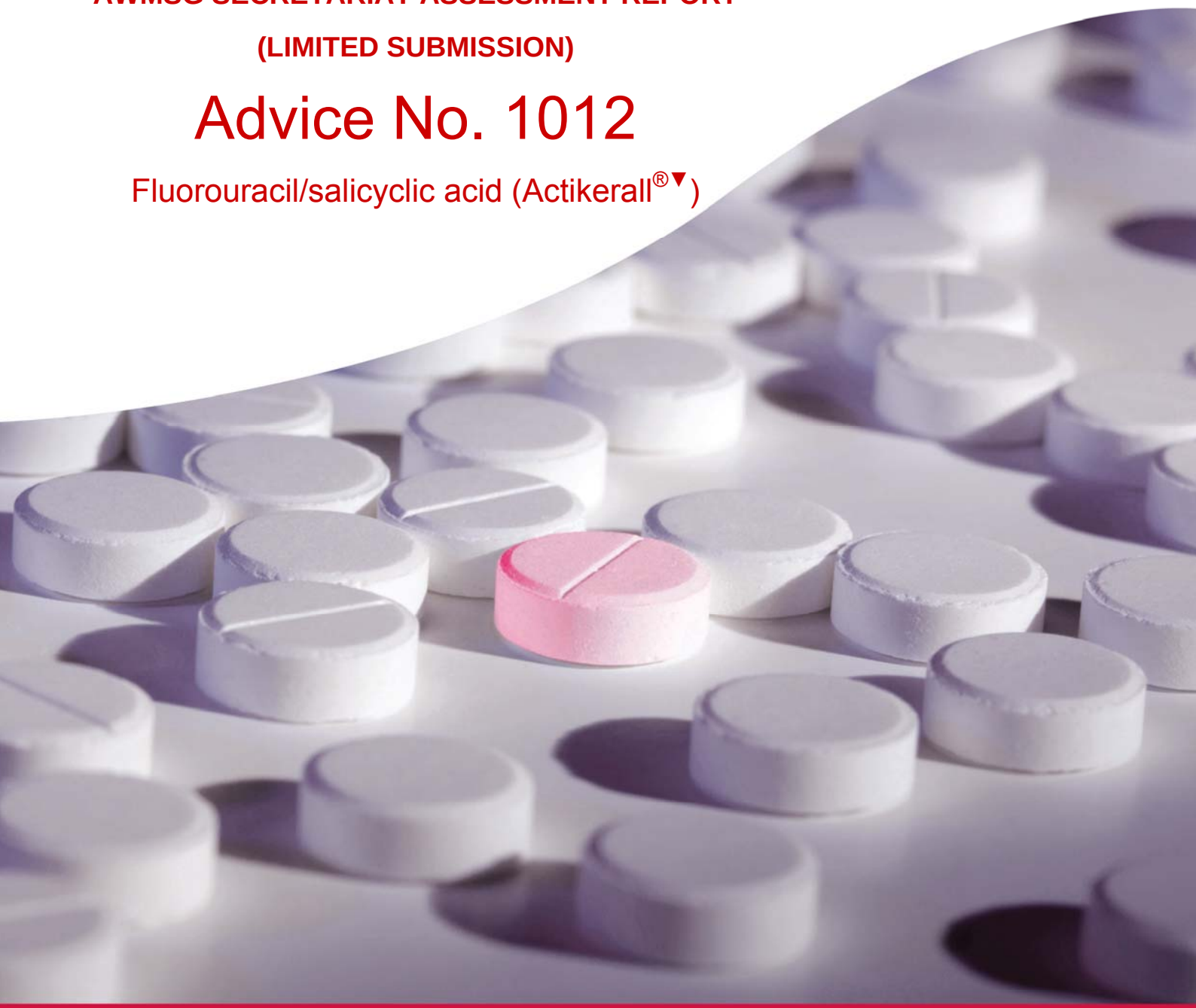
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(LIMITED SUBMISSION)

Advice No. 1012

Fluorouracil/salicyclic acid (Actikerall®▼)



AWMSG Secretariat Assessment Report – Advice no. 1012
Fluorouracil 5 mg/g (0.5%) and salicylic acid 100 mg/g (10%) cutaneous solution (Actikerall®)

This assessment report is based on evidence from a limited submission by Almirall Ltd on 7 December 2011.

1.0 PRODUCT DETAILS

Licensed indication under consideration	Fluorouracil/salicylic acid (5-FU/SA, Actikerall®) is indicated for the topical treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade I/II) in immunocompetent adult patients. Grade I/II intensity is based on the four-point scale of Olsen et al. (1991) (see Glossary)[1,2].
Dosing	In general, 5-FU/SA is applied to actinic keratoses once daily. Data are available for treatment for up to 12 weeks, but complete healing of the lesions or optimal therapeutic effect may not be evident for up to eight weeks after treatment cessation[1]. Multiple actinic keratoses can be treated simultaneously. There is experience in treating up to ten lesions at the same time. The total area of skin being treated at any one time should not exceed 25 cm^2 (5 cm × 5 cm)[1]. 5-FU/SA should be applied using the supplied brush, to the lesion and a rim of a maximum of 0.5 cm of surrounding healthy skin. After application, the treated area should be left uncovered to dry and form a film; the film coating should be peeled off before 5-FU/SA is reapplied.
Marketing authorisation date	3 June 2011[1].

2.0 DECISION CONTEXT

2.1 Background

Actinic keratoses (AKs) are skin lesions considered to be precursors to squamous cell carcinoma[3]. They present as dry, rough, yellowy-brown scaly plaques which may become thickened and horny[4]. AKs occur most commonly on areas of increased sun exposure (for example the face, scalp, hands and forearms), suggesting that most result from chronic exposure to ultraviolet radiation, and occur more frequently in individuals with fairer skin types[3,5]. Prevalence of AKs increases with age and is higher in men than women[6,7]. A 1996 study conducted in South Wales estimated the prevalence of AKs in individuals aged 60 or over to be 33% in men, 16% in women and 23% for both sexes combined[6]. A study conducted in Merseyside in 2000 found the prevalence of AKs in individuals aged 60 or over to be 19%. Within the same age group, prevalence was also found to be strongly related to age in both sexes, being 23.3% and 10.3% in men and women respectively[7].

The risk of progression of an AK to malignancy is low and lesions may undergo spontaneous regression without treatment; rates of spontaneous regression over one

year have been reported as 15–25%[5,6,8]. However, most individuals present with multiple lesions, and the risk of malignant transformation of at least one lesion over a ten-year period has been estimated as 10%[5]. In addition to prevention of progression to squamous cell carcinoma, treatment may also aim to provide relief of symptoms or disfigurement resulting from the presence of lesions[5]. Clinical opinion appears to be divided on whether all AK cases require treatment; some guidelines recommend no therapy as a reasonable option for mild lesions[5], others argue that it is impossible to predict which lesions will become malignant and therefore all cases should be treated[9]. Treatment strategies include palliative treatment with an emollient, topical treatment (options available in the UK include fluorouracil cream, salicylic acid ointment and 3% diclofenac gel), surgical excision, cryotherapy or photodynamic therapy[5]. 5-FU/SA is a topical treatment option, containing a fixed dose of fluorouracil (0.5%, 5 mg/g) and salicylic acid (10%, 100 mg/g)[1,10]. Salicylic acid removes overlying keratin from the lesion; fluorouracil is an antineoplastic agent that acts by interfering with DNA and RNA synthesis, inhibiting cell proliferation[5,11].

2.2 Comparators

The All Wales Therapeutics and Toxicology Centre (AWTTC) requested 5% fluorouracil cream (Efudix®) as the comparator to 5-FU/SA. The company submission compares 5-FU/SA with both 5% fluorouracil cream and 3% diclofenac sodium gel (Solaraze®) (see Section 3.3)[10].

2.3 Guidance and related advice

- European Dermatology Forum. Guidelines for the management of actinic keratoses (2010)[9].
- Primary Care Dermatology Society. Clinical guidance: actinic keratoses (2010)[4].
- British Association of Dermatologists. Guidelines for the management of actinic keratoses (2007)[5].
- National Institute for Health and Clinical Excellence (NICE). Interventional Procedure Guidance 155. Photodynamic therapy for non-melanoma skin tumours (including premalignant and primary non-metastatic skin lesions) (2006)[12].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

No evidence is available to directly compare the clinical effectiveness of 5-FU/SA with 5% fluorouracil. However, the company submission included evidence from a systematic review investigating the effectiveness of fluorouracil for the treatment of AKs and included some comparison of 5% fluorouracil with 0.5% fluorouracil alone (not in combination with salicylic acid)[13]. Evidence comparing the clinical effectiveness of 5-FU/SA with diclofenac gel was supplied by results from a randomised phase III trial[11].

3.1 Clinical evidence comparing 5-FU/SA and 5% fluorouracil

Results from a 2009 systematic review by Askew et al, which investigated the clinical effectiveness of fluorouracil for the treatment of AKs, were included in the company submission[10,13]. Amongst the studies included in the review was one small study directly comparing 0.5% fluorouracil with 5% fluorouracil and three studies comparing 0.5% fluorouracil with placebo. No trials of 5-FU/SA were identified, and a literature search carried out by AWTTC did not identify any further evidence. Therefore, no direct comparison of 5-FU/SA with 5% fluorouracil is possible; however, some conclusions can be drawn to allow comparison of 0.5% fluorouracil with 5% fluorouracil from a pooled analysis. The average reduction in the mean number of lesions (grade not specified) was 79.5% with 5% fluorouracil (from an average of 24.0 lesions at

baseline to 4.0 lesions at follow up) and 86.1% with 0.5% fluorouracil (from an average of 13.9 lesions at baseline to 3.9 lesions at follow up). The number of patients achieving 100% clearance of AKs was 49.0% (range: 0–96%) for those treated with 5% fluorouracil and 34.8% (range: 14.9–57.8%) for 0.5% fluorouracil. However, the reviewers note that due to overall poor quality of evidence, as well as variation in endpoints, randomisation methods and comparators used, the results should be interpreted with caution[13].

Application site reactions are very common with both 5-FU/SA and 5% fluorouracil[1,14]. In the studies considered by the systematic review, the number of patients withdrawing due to adverse events (not reported for all studies) varied from 0 to 18%, but the proportion of these withdrawals that could be attributed to fluorouracil treatment is not clear[13].

3.2 Clinical evidence comparing 5-FU/SA and 3% diclofenac gel

The clinical effectiveness of 5-FU/SA and diclofenac gel were compared in a randomised, double blind, phase III study conducted at 38 centres in Germany[11]. Patients recruited into the study (n = 470) were aged 18 to 85 years, with four to ten AKs on their face, forehead or bald scalp. Approximately 40% of AKs were grade I (mild) and (60%) were grade II (moderate). Each lesion measured between 0.5 and 1.5 cm in diameter, with all single AK lesions restricted to a total area of no more than 25 cm^2. Patients were randomised to treatment with 5-FU/SA once daily (187 patients), diclofenac gel twice daily (185 patients) or placebo once daily in the form of the 5-FU/SA vehicle solution (98 patients). Treatment was administered until all lesions cleared or for a maximum of 12 weeks [11].

The primary efficacy variable was the rate of histological clearance for one representative AK, assessed by biopsy at eight weeks post-treatment (i.e. 20 weeks from the beginning of treatment). For the per-protocol patient set, rates of clearance in the 5-FU/SA treatment group (72.0%, 121/168) were statistically significantly higher when compared with the diclofenac (59.1%, 97/164, $p < 0.01$) and 5-FU/SA vehicle (44.8%, 39/87, $p < 0.0001$) treatment groups[11,15]. At week 20, reduction in mean lesion area (a secondary efficacy variable) was significantly superior for 5-FU/SA compared with diclofenac (91.8% and 78.5% reductions in the 5-FU/SA and diclofenac groups respectively, $p < 0.001$), as was the change in lesion count from baseline to week 20 (from 5.8 to 1.4 for 5-FU/SA and from 5.8 to 2.5 for diclofenac; $p < 0.001$)[11] .

An additional secondary endpoint was patients' assessment of clinical outcome. For the full analysis patient set, at week 12 (end of treatment) the percentage of patients rating their clinical improvement as 'good' or 'very good' was comparable for 5-FU/SA (83.4%, 146/175 patients) and diclofenac gel (81.8%, 143/175 patients). However, at eight weeks post-treatment (i.e. week 20), the equivalent figures were 93.2% (163/175) and 81.6% (142/174) for 5-FU/SA and diclofenac gel-treated patients, respectively ($p < 0.0001$). The percentage of patients in the 5-FU/SA vehicle arm rating their treatment as 'good' or 'very good' was 72.1% (67/93) after 12 weeks and 66.7% (62/93) after 20 weeks[11]. Assessment of clinical outcome was also rated by physicians. For this endpoint, clinical improvement was rated as 'good' or 'very good' for significantly more patients receiving 5-FU/SA compared with diclofenac gel both at week 12 (82.3%, 144/175 for 5-FU/SA; 74.3%, 130/175 for diclofenac gel; $p = 0.0112$) and at week 20 (92.0%, 161/175 for 5-FU/SA; 73.8%, 129/175 for diclofenac gel; $p < 0.0001$)[11].

The rate of treatment-emergent adverse events (TEAEs) was higher for 5-FU/SA than for diclofenac gel or 5-FU/SA vehicle: 95.2% of patients in the 5-FU/SA arm reported at least one TEAE, compared with 76.8% and 84.7% in the diclofenac gel and 5-FU/SA

vehicle arms respectively[11]. In the 5-FU/SA treatment arm, 92% (172/178) of TEAEs were administration site reactions considered by the investigators to be related to treatment[10]. Despite this, the proportion of patients ceasing treatment due to TEAEs was low, and similar in the 5-FU/SA and diclofenac gel arms (3.7% and 4.9% respectively)[11]. Most TEAEs were mild to moderate in intensity; no patients experienced a serious adverse event considered to be related to study treatment[10].

3.3 AWTTC critique

- Following consultation with clinical experts in Wales, AWTTC requested 5% fluorouracil as the most appropriate comparator to 5-FU/SA. The company submission provides a comparison of 5-FU/SA with both 5% fluorouracil and diclofenac gel, and suggests that diclofenac gel may be the more appropriate comparator, as this is the most commonly prescribed treatment in Wales for actinic keratoses (see Section 5 for more details).
- No evidence is available to directly compare the clinical effectiveness of 5-FU/SA and 5% fluorouracil. The systematic review of fluorouracil by Askew et al highlights that although 5% fluorouracil is widely considered clinically effective for the treatment of AKs, the evidence base to support this is weak: studies identified were small (maximum 75 patients) and therefore inadequately powered to detect differences between treatments; lacked robust outcome measures; and none were placebo-controlled[13]. A literature search by AWTTC has not identified any studies adding to the evidence base since the publication of this systematic review in 2009.
- Despite differences in formulation and methods of application between 5-FU/SA and diclofenac gel, measures were undertaken to maintain blinding throughout the study by Stockfleth *et al* which compared these two treatments.
- AKs are more common in individuals with fairer skin types[5]. In the study by Stockfleth et al (conducted in Germany), all subjects were Caucasian and around 90% had Fitzpatrick skin type II or III (a classification system based on how easily skin burns, II indicating burns easily and III burns moderately, see also Glossary)[15]. In the 1996 Welsh population sample studied by Harvey et al, 77.3% had a skin type corresponding to Fitzpatrick type II or III[6]. No ethnicity or skin type data was provided for studies evaluating 5% fluorouracil, or comparing 0.5% fluorouracil and 5% fluorouracil.
- Treatment with 5-FU/SA should not exceed a skin area greater than 25 cm^2 at any one time[1]. By comparison, up to 500 cm^2 skin area can be treated with 5% fluorouracil[14], and a maximum of 8 g of diclofenac gel can be applied at any one time (0.5 g is normally sufficient to treat 25 cm^2 of skin)[16] .

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

Cost effectiveness evidence is not required for a limited submission.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Due to a reported lack of recent data on the prevalence of AK in Wales, the company have used Welsh prescription cost analysis[17] and commercial market share data[18] to estimate the budget impact associated with the introduction of 5-FU/SA in Wales[10]. The number and share of prescriptions of topical products for the treatment of actinic keratosis, including imiquimod (Aldara® 5% cream; 1.33% share), 5% fluorouracil cream (11.85% share) and 3% diclofenac gel (86.82% share) were estimated. The

company assumes 5% annual growth in the number of AK prescriptions, and that 5-FU/SA will take 6% of the market share in 2012 rising to 16% in 2015, with displacement of equal proportions of the currently used treatments. Using these assumptions, the acquisition cost of 5-FU/SA in Wales would be £37,741 in 2012 rising to £116,524 in 2015, which corresponds to a net budget impact of £514 in 2012, rising to £1,588 in 2015 (see Table 1)[10].

Table 1. Company-reported costs associated with use of 5-FU/SA for topical treatment of actinic keratosis in immunocompetent adult patients

	2012	2013	2014	2015
Anticipated drug costs excluding 5-FU/SA	£590,985	£620,534	£651,561	£684,139
5-FU/SA uptake*	6%	11%	14%	16%
Number of 5-FU/SA prescriptions	986	1,897	2,535	3,042
5-FU/SA costs	£37,747	£72,662	£97,103	£116,524
Anticipated drug costs including 5-FU/SA	£591,499	£621,525	£652,884	£685,727
Net budget impact	£514	£991	£1,323	£1,588
*Assumes displacement of equal proportions of currently used drugs.				

5.1.2 AWTTC critique of the company's budget impact estimates

In the reported absence of recent data on the prevalence of AK in Wales, the company has pragmatically employed Welsh prescription costs and commercial market share data to estimate budget impact. The company's estimates of current treatment volumes include the use of imiquimod 5% cream, which is not licensed for the treatment of hyperkeratotic AK[19,20]; however, its inclusion would make only a marginal difference to the overall budget impact estimates. The acquisition costs of 5-FU/SA are likely to be very similar to that of other licensed treatments it would displace; therefore the company anticipates the net budget impact to be minimal.

5.2 Comparative unit costs

A comparison of costs for topical medicines licensed for the treatment of hyperkaratotic AK is problematic, as usage will depend on the surface area and number of lesions to be treated. Table 2 provides examples of drug acquisition costs for the treatment of AK in adult patients, but the relevant Summaries of Product Characteristics (SPCs) should be consulted for full treatment details[1,14,16].

Table 2. Examples of drug acquisition costs for topical treatment of actinic keratosis in adult patients.

	Regimen	Treatment duration	Cost per package[21]
Actikerall® 5-FU 0.5%, SA 10% cutaneous solution	Once daily	Up to 12 weeks	1 × 25 ml = £38.30 2 × 25 ml = £76.60
Solaraze® diclofenac sodium 3%, sodium hyaluronate 2.5% gel	Twice daily	60–90 days	1 × 50g = £38.30 1 × 100g = £76.60
Efudix® 5-FU 5% cream	Once or twice daily	Usually 3–4 weeks	1 × 40g = £32.76 2 × 40g = £65.52
This table does not imply therapeutic equivalence of the listed drugs or doses. SPCs should be consulted for full application details[1,14,16].			

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

AWTTC is of the opinion that fluorouracil/salicylic acid (Actikerall®) for the stated indication may be suitable for use within NHS Wales prescribed under specialist recommendation.

6.2 Ongoing studies

The company submission does not highlight any ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review in June 2015.

6.4 Evidence literature search

Date of evidence search: 9 December 2011.
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Fitzpatrick skin type[22]

Classification of skin phototypes, according to skin response following a significant sun exposure:
Phototype I: burns easily, never tans.
Phototype II: burns easily, tans minimally with difficulty.
Phototype III: burns moderately, tans moderately and uniformly.
Phototype IV: burns minimally, tans moderately and easily.
Phototype V: rarely burns, tans profusely.
Phototype VI: never burns, tans profusely.

Olsen scale[2]

Scale used to describe AK intensity according to clinical description:
0 (none): no lesion present, neither visible nor palpable.
I (mild): flat, pink maculae without signs of hyperkeratosis and erythema, slight palpability, with lesion felt better than seen.
II (moderate): pink to reddish papules and erythematous plaques with hyperkeratotic surface, moderately thick lesions that are easily seen and felt.
III (severe): very thick and/or obvious lesions.

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