New Medicine Assessment

Fluorouracil 5% Cream

Recommendation: GREEN for the following indications:

Topical treatment of superficial pre-malignant skin lesions.

Prescribers should refer patients with skin lesions suggestive of skin cancers using the principles of the NICE suspected cancer guideline.

Patients must be counselled in full on the correct use of fluorouracil 5% Cream, its risks and side effects.

Summary of supporting evidence:

- Efficacy has been proven through use over many years and incorporation into national and international guidelines
- Short course, not for chronic use therefore long-term funding not required
- Data shows widespread prescribing in primary care already occurs
- The British Association of Dermatologists (BAD) advises that most actinic keratoses can be diagnosed and treated in primary care
- Actinic keratosis does not always require treatment to prevent malignant change
- If pre-cancerous lesions are managed in primary care then physicians should know when to refer patients for specialist review
- Patients should be made aware of the timeline and pattern of response to Fluorouracil 5% Cream
- If Fluorouracil 5% Cream is used as field treatment the side effects can be substantial
- Due to the genotoxic potential of fluorouracil, counselling is vital for females and males regarding contraception, fertility, pregnancy and breast feeding
- Pan Mersey and GMMMG both support the use of fluorouracil 5% cream in primary care

Details of Review

Name of medicine (generic & brand name)**:**

Fluorouracil (Efudix)

Strength(s) and form(s):

5% cream

Dose and administration:[1]

Efudix cream is for topical application.

The hands should be washed carefully after applying Efudix. Also, care should be taken to avoid contact with mucous membranes or the eyes when applying the cream.

The total area of skin being treated with Efudix at any one time should not exceed 500 cm^2 (approximately 23 x 23 cm). Larger areas should be treated a section at a time.

Pre-malignant conditions

The cream should be applied thinly to the affected area once or twice daily; an occlusive dressing is not essential.

Usual duration of initial therapy 3–4 weeks.[2]

Efudix is not recommended for use in children.

BNF therapeutic class / mode of action:

Antimetabolite.

Cytostatic preparation.

Licensed indication(s):

Efudix is used for the topical treatment of superficial pre-malignant and malignant skin lesions; keratoses including senile, actinic and arsenical forms; keratoacanthoma; Bowen's disease; superficial basal-cell carcinoma.

Deep, penetrating or nodular basal cell and squamous cell carcinomas do not usually respond to Efudix therapy. It should be used only as a palliative therapy in such cases where no other form of treatment is possible.[1]

Proposed use (if different from, or in addition to, licensed indication above):

For the topical treatment of superficial pre-malignant lesions.

Course and cost:

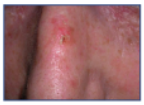
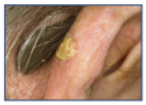
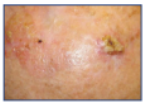
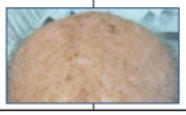
40g £32.90

Course approx. 3-4 weeks. Number of tubes issued dependent on size of lesion.

Price as per drug tariff Feb 2023

Current standard of care/comparator therapies:

Primary Care Dermatology Society: Actinic (Solar) Keratosis – Primary Care Treatment Pathway[12]

			Grade I	Grade II	Grade III	Field Change	
	Generic Name	Brand Name	Single or few lesions, better felt than seen 	Moderately thick lesions, easily felt & seen 	Thick hyperkeratotic lesions 	Small – up to 25cm²	Large 
Topical	3% Diclofenac with HA	Solaraze	✓✓	✓	✗	✓✓	✓✓
Topical	5% Fluorouracil (5-FU)	Efudix	✓✓	✓✓	✗	✓✓	✓E
Topical	5% Imiquimod	Aldara	✓	✓	✗	✓	✗
Topical	0.5% 5-FU+10% Salicylic acid	Actikerall	✓✓	✓✓	✗	✓	✗
Topical	3.75% Imiquimod	Zyclara	✓	✓	✗	✓	✓✓
Other	Liquid Nitrogen		✓	✓	✓	✗	✗
Other	Curettage		✓	✓	✓	✗	✗
	Legend	✓ relative recommendation ✓✓ Strong recommendation ✗ Not recommended in Primary Care					

Other therapies:

Cryosurgery

Systemic and topical retinoids

Photodynamic therapy

Ingenol mebutate cream

Laser therapy

Tirbanibulin (Klisyri®) ointment

Relevant NICE guidance:

Skin cancer, Quality Standard 130 (2016) (update due December 2023)

Quality statement 2: GPs managing low risk basal cell carcinoma

Low-risk basal cell carcinoma can sometimes be managed by GPs in the community, which can be more convenient for patients. Treatment in the community can also frequently be provided at a lower cost and free up capacity in hospitals. However, it is essential that this is balanced with ensuring that care offered in the community is as safe and effective as that in hospital. Maintaining and auditing records of their caseload can help in demonstrating competence.

Melanoma: assessment and management (2015) (updated 2022)

Consider topical imiquimod to treat stage 0 melanoma in adults if surgery to remove the entire lesion with a 0.5 cm clinical margin would lead to unacceptable disfigurement or morbidity.

Photodynamic therapy for nonmelanoma skin tumours (including premalignant and primary non-metastatic skin lesions)

Background and context

Precancerous skin consists of various premalignant changes in the skin cells that increase the likelihood of developing into skin cancer. These changes often appear as growths or lesions. Precancerous lesions can be found on the outermost layer of skin (epidermis). They are usually seen in sun-exposed areas of the body—such as the head, hands, and forearms—and are mostly found in older adults. Precancerous skin can be considered a cancer warning sign, as it may naturally progress into squamous or basal cell carcinoma, which are two types of skin cancer that differ in prevalence and prognosis. The main types of precancerous lesions include actinic keratosis, actinic cheilitis, Bowen disease, and leukoplakia.[3]

Actinic keratosis (AK) is the most common precancer that forms on skin damaged by chronic exposure to ultraviolet (UV) rays from the sun and/or indoor tanning. Solar keratosis is another name for the condition.[4] They represent focal areas of abnormal keratinocyte proliferation and differentiation that carry a low risk of progression to invasive squamous cell carcinoma (SCC).

Some actinic keratoses will resolve without treatment, especially if they are smaller and milder. Others will need treatment. Several types of cream or gel can be prescribed for use at home. These include 5-fluorouracil or imiquimod which are effective treatments. However, they often cause temporary redness and soreness of the treated areas. Diclofenac and retinoic acid are other drugs in cream or ointment form that are helpful when applied to milder actinic keratoses. Other options include cryotherapy, surgical removal, photodynamic therapy, and laser treatment.[5]

Efudix is a topical cytostatic preparation which exerts a beneficial therapeutic effect on neoplastic and pre-neoplastic skin lesions while having less effect on normal cells. The pattern of response follows this sequence: erythema, vesiculation, erosion, ulceration, necrosis and epithelisation.[1]

In 2013 LMMG reviewed several treatments for actinic keratoses, including fluorouracil/salicylic acid.

Summary of evidence

Summary of efficacy data in proposed use:

British Association of Dermatologists guidelines for the care of patients with actinic keratosis (2017)[6]

Actinic keratoses are generally considered to be premalignant lesions with low individual potential for invasive malignancy and potential for spontaneous regression. Clinically, they are graded on a three point scale according to magnitude. Diagnosis of AK may be made in primary or secondary care and as part of a general skin examination associated with assessment of sun damage, focal keratotic lesions or skin cancer.

People with chronic fluctuating disease may learn self-diagnosis but are advised to corroborate their assessment with a healthcare professional. The natural history of individual lesions suggests that treatment is not universally required on the basis of preventing progression into SCC. There is a body of professional opinion that believes AKs are part of a spectrum that includes SCC in situ, and that prevention of SCC is therefore the reason for therapy. A Cochrane review of treatment of AK did not find any evidence that treatment of AK resulted in reduction in presentation of invasive SCC. There is inadequate evidence to justify treatment of all AKs to try to prevent malignant change.

At the outset of management, the location and grade of the AKs should be defined to enable monitoring, response to treatment or evolution. This can be done using drawings, body maps and photography, often with lesions numbered. Management can be directed at individual lesions or over a wider area. This distinction represents lesion vs. field treatment.

A European AK guideline achieved consensus through a voting and weighting method with advice grouped according to the isolated, field-associated or skin-cancer-associated distribution of the AKs. There remained a preference for cryosurgery for isolated lesions and curettage for larger ones. Otherwise, preferences revolved largely around different strengths of the common main agents, namely 5-fluorouracil (5-FU), imiquimod, ingenol mebutate and variants of PDT. Diclofenac in hyaluronic acid and imiquimod at 25% were not favoured. In immunosuppressed patients there was a preference for the stronger formulations of all products. Laser was not considered a good choice for any circumstance other than treatment of field disease.

Patients with AK will ask their general practitioner (GP) for diagnosis and treatment advice. Most AKs can

be diagnosed and treated in primary care. In healthcare systems with a primary-care physician as the first contact, skin monitoring of sun-exposed surfaces of the head and neck and dorsa of hands is possible on an opportunistic basis and can be coupled with relevant prevention and self-care advice. Actinic keratosis is a chronic disease. Once patients have the diagnosis of AK, it is usually the start of a continued process of further lesions and relapse.

Consider referral for specialist care when:

• AK fails to respond to standard treatments;

• multiple or relapsing AKs represent a management challenge;

• AK occurs in the long-term immunosuppressed;

• lesions are likely to be AK, but there is concern that they might be SCC (use the 2-week-wait route for possible skin cancer), for example when they are (i) bleeding, (ii) painful or (iii) thickened with substance when held between finger and thumb.

The majority of the data on topical therapies relate to the 5% concentration of 5-FU cream. 5-FU works by the inhibition of thymidylate synthetase, which is needed for DNA synthesis. It may also interfere with the formation and function of RNA. It is a widely used, flexible and low-cost treatment. It can be used either as lesional treatment or as part of field treatment. The side-effects with the latter can be substantial, and it is important that the patient is counselled about them, including soreness, redness and possible crusting. All of these can be minimized through reduction in the frequency of application or short breaks in a course of therapy. It is permitted to wash the area and apply thin emollient. If the reaction is excessive, weak steroid can be applied. It is important that the patient is enabled to learn how to use the treatment, as it is one they may require intermittently in the future and a bad initial experience can limit further use. Many regimens cite twice-daily application over 4 weeks, but less frequent initial use may enable titration of the frequency of application against reaction, tolerance and efficacy. Use at poor healing sites such as the lower leg should always be undertaken with caution and may need supervision.

A wide range of open trials, dose ranging studies and manipulations of the vehicle have been reported over the last 45 years, as well as two RCTs, confirming efficacy. A large, placebo-controlled RCT showed 5-FU 5% to be more effective than placebo in AK clearance and the reduction of follow-up cryosurgery treatments at 6 months. A Cochrane review with subsequent meta-analysis of complete clearance results ranked the efficacy of all of the main treatments and put 5-FU at the top.

Cost, efficacy, flexibility and setting of the main treatment options in AK. Data between treatment groups are not always based on similar sampling and outcome measures. The levels of evidence contributing to this table range from 1++ to 4

	Period of evaluation (longer than active treatment)	Reduction in AKs based on [a]observational studies, [b]RCTs or [c]meta-analysis (values do not reflect excess over control)	Cost range per item	Dispensed item	Add-on cost of staff time or equipment. Primary care or [secondary care]. [d]Typically requires 2 visits	Flexible regimens	Amenable to patient-directed care and monitoring	Amenable to primary care
No treatment	Periodic, indefinite	Up to 21%[a,15]	♦		0	•	•	•••
Emollient or vehicle	Periodic, indefinite	0–44%[b,57,60]	♦		0	•	•	•••
Sunscreen (UVA 3/ SPF 17–50)	Periodic, indefinite	17–36%[b,46,47]	♦	500 mL	♦[♦♦]	•	•	•••
5-Fluorouracil 5%	2–4 months	70–78%[b,36,66]	♦	40 g	♦♦[♦♦♦♦][d]	•••	••	••
Imiquimod 5%	2–4 months	50%[c] to 84%[b,74,75]	♦/♦♦	12–24 sachets	♦♦[♦♦♦♦][d]	•••	••	••
Imiquimod 3·75%	3–4 months	34–36%[b,85]	♦♦♦/♦♦♦♦	28–56 sachets	♦♦[♦♦♦♦][d]	•••	••	••
Diclofenac gel 3%	2–4 months	19–70%[b,57,90]	♦/♦♦	50–100 g	♦♦[♦♦♦♦][d]	••	••	•••
Ingenol mebutate (150 μg g^{-1} face, 500 μg g^{-1} limbs and trunk)	1–2 months	34–42%[b,92,93]	♦♦	2–3 single-application 0·47-g tubes	♦♦[♦♦♦♦][d]	•	❍	••
MAL-PDT	1–2 months	69–93%[b,107,119,127,176]	♦♦♦	Single treatment tube	£427–£928[177]	••	❍	❍
Cryosurgery	1–2 months	39–88%[a,103,106]	Not known	Not applicable	♦♦[♦♦♦♦][d]	••	❍	•
Combination therapies								
5-Fluorouracil 0·5% and salicylic acid 10%	2–4 months	55%[a] to 77%[b,71,72]	♦	25 mL	♦[♦♦]	••	••	•••
Diclofenac gel and cryosurgery	2–4 months	46–100%[a,156,157]	♦/♦♦	50–100 g	♦[♦♦]	••	•	•
Imiquimod and cryosurgery	2–4 months	59·5%[a,86]	♦/♦♦	12–24 sachets	♦♦[♦♦♦♦][d]	••	•	•
Imiquimod and MAL-PDT	2–4 months	89%[a,160]	♦/♦♦	12–24 sachets plus single treatment tube	♦♦[♦♦♦♦][d] plus £427–£928	••	•	❍
Comments			Standard package size or course of treatment: BNF 2014, edition 66		Costs drawn from NHS publications			

AK, actinic keratosis; BNF, British National Formulary; NHS, National Health Service; MAL-PDT, methyl aminolaevulinate photodynamic therapy; RCT, randomized controlled trial; SPF, sun protection factor; UVA, ultraviolet A. Cost key: ♦ £0–50; ♦♦ £51–100; ♦♦♦ £101–150; ♦♦♦♦ £150–200. Care key: ❍ not amenable or flexible; • some flexibility/amenability; •• moderate flexibility/amenability; ••• very flexible/amenable. First hospital clinic attendance NHS tariff 2014–15: £104.[178] Hospital follow-up attendance: £68. GP visit: £44.[179]

British Association of Dermatologists guidelines for the management of people with cutaneous squamous cell carcinoma in situ (Bowen disease) (2022)

Offer topical 5-fluorouracil (5%) monotherapy to people with SCC in situ, for small lesions (e.g. <2cm) in low-risk sites, and in those who will not or cannot undergo alternative treatments. Initiate a standard regimen of once- or twice-daily application for 3–4 weeks. Counsel patients regarding the side-effects of local inflammation, ulceration and potential scarring.

Consider topical 5-fluorouracil (5%) monotherapy in people with SCC in situ, for larger lesions in low risk sites, and in those who will not or cannot undergo treatment with other better-established therapies. Initiate a standard regimen of once- or twice-daily application for up to 4 weeks. Counsel patients regarding the side-effects of local inflammation, ulceration and potential scarring.

Consider topical 5-fluorouracil (5%) monotherapy in people with SCC in situ, for larger lesions on poorly healing sites (e.g. the lower legs of older patients) as a practical alternative to surgical treatments. Initiate a standard regimen of once- or twice-daily application for up to 4 weeks.

Consider topical 5-fluorouracil (5%) in immunosuppressed people with SCC in situ, as a practical treatment for multiple and recurring lesions.

American Academy of Dermatology (2021)[7]

The literature on AK treatment supports a strong recommendation for field treatment with either 5-fluorouracil (5-FU) or imiquimod.

No.	Recommendation	Strength	Quality of evidence
Topical agents			
2.1	For patients with AKs, we recommend field treatment with 5-fluorouracil	Strong	Moderate
2.2	For patients with AKs, we recommend field treatment with imiquimod	Strong	Moderate
2.3	For patients with AKs, we conditionally recommend the use of diclofenac	Conditional	Low
	Remarks: As with other oral and topical medications in the class, NSAIDs carry a black box warning for cardiovascular and gastrointestinal side effects		

The benefits of 5-FU treatment for AK were assessed as moderate or large, based on moderate-to high quality efficacy data from 5 identified studies. Local irritation was the primary source of harm to patients and often the primary reason for the discontinuation of treatment. The overall assessment of the level of harm from 5-FU was small and based on data of moderate quality. The Work Group considered there to be potential variability in the value patients placed on AK clearance, considering side effects, such as irritation, which could affect treatment selection and adherence. All of the evaluated studies assessed field treatment with 5-FU. Thus, the Work Group recommends the use of topical 5- FU as a field treatment for AKs.

Cochrane: Interventions for actinic keratoses (Review) (2012)[8]

Databases searched up to March 2011; 83 RCTs in this review, with a total of 10,036 participants.

The primary outcome 'participant complete clearance' significantly favoured four field-directed treatments compared to vehicle or placebo: 3% diclofenac in 2.5% hyaluronic acid (RR 2.46, 95% CI 1.66 to 3.66; 3 studies with 420 participants), 0.5% 5-fluorouracil (RR 8.86, 95% CI: 3.67 to 21.44; 3 studies with 522 participants), 5% imiquimod (RR 7.70, 95% CI 4.63 to 12.79; 9 studies with1871 participants), and 0.025% to 0.05% ingenol mebutate (RR 4.50, 95% CI 2.61 to 7.74; 2 studies with 456 participants).

The corresponding comparative risks in terms of number of participants completely cleared per 1000 were as follows: 313 with 3% diclofenac compared to 127 with 2.5% hyaluronic acid; 136 with 0.5% 5-fluorouracil compared to 15 with placebo; 371 with 5% imiquimod compared to 48 with placebo; 331 with ingenol mebutate compared to 73 with vehicle; 527 to 656 with ALA/MAL-PDT treatment compared to 89 to 147 for placebo-PDT; and 580 with ALA-PDT compared to 443 with cryotherapy.

Based on investigator and participant evaluation, imiquimod treatment and photodynamic therapy resulted in better cosmetic outcomes than cryotherapy and 5-fluorouracil.

Cochrane: Interventions for cutaneous Bowen's disease (Review) (2016)[9]

Databases search up to September 2012; 9 studies, with a total of 363 participants. The primary outcome measures were complete clearance of lesions after the first treatment cycle and recurrence rate at 12 months.

One study demonstrated statistically significantly greater clearance of lesions of Bowen's disease with MAL-PDT (methyl aminolevulinate with photodynamic therapy) when compared with placebo-PDT (RR (risk ratio) 1.68, 95% CI (confidence interval) 1.12 to 2.52; n = 148) or cryotherapy (RR 1.17, 95% CI 1.01 to 1.37; n = 215), but there was no significant difference when MAL-PDT was compared to 5-FU (5-fluorouracil). One study demonstrated statistically significantly greater clearance of lesions with ALA-PDT (5-aminolevulinic acid with photodynamic therapy) versus 5-FU (RR 1.83, 95% CI 1.10 to 3.06; n = 66), but no statistically significant difference in recurrence rates at 12 months (RR 0.33, 95% CI 0.07 to 1.53). Cryotherapy showed no statistically significant difference in clearance rates (RR 0.99, 95% CI 0.78 to 1.26) or recurrences at 1 year (RR 1.48, 95% CI 0.53 to 4.17) when compared to 5-FU in 1 study of 127 participants. The lack of quality data for surgery and topical cream therapies has limited the scope of this review to one largely about PDT studies. Specific recommendations cannot be made from the data in this review, so we cannot give firm conclusions about the comparative effectiveness of treatments.

Related regional approvals

Scottish Medicines Consortium (2011)[10]

Approved fluorouracil 0.5% / salicylic acid 10% cutaneous solution (Actikerall®) for use within NHS Scotland, for the topical treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade I/II) in immunocompetent adult patients.

All Wales Therapeutics and Toxicology Centre (2012)[11]

Fluorouracil / salicylic acid (Actikerall®) is recommended as an option for use within NHS Wales for the topical treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade I/II) in immunocompetent adult patients.

Summary of safety data:

Summary of Product Characteristics[1]

Contraindications

- Efudix is contraindicated in patients with known hypersensitivity to fluorouracil or any of the excipients.
- Coadministration of Efudix with antiviral nucleoside drugs (e.g. brivudine and analogues) may lead to a substantial increase in plasma levels of fluorouracil and associated toxicity and is contraindicated. Brivudine and analogues are potent inhibitors of DPD, a fluorouracil metabolising enzyme.
- Use of Efudix during pregnancy and in breast-feeding mothers is contraindicated.

Special warnings and precautions for use

- The normal pattern of response includes: early and severe inflammatory phases (typically characterised by erythema, which may become intense and blotchy), a necrotic phase (characterised by skin erosion) and finally healing (when epithelialisation occurs). The clinical manifestation of response usually occurs in the second week of Efudix treatment. However these treatment effects can sometimes be more severe and include pain, blistering and ulceration. Occlusive dressing may increase inflammatory reactions of the skin.
- Instruct patients not to smoke or go near naked flames - risk of severe burns. Fabric (clothing, bedding, dressings etc) that has been in contact with this product burns more easily and is a serious fire hazard. Washing clothing and bedding may reduce product build-up but not totally remove it.
- Exposure to UV-radiation (e.g. natural sunlight, tanning salon) should be avoided.
- Pre-existing subclinical lesions may become apparent following Efudix use.
- Any severe skin discomfort during treatment with Efudix may be alleviated by the use of an appropriate topical steroid cream.
- When used according to the approved prescribing information Efudix should have minimal effect on healthy skin.
- Significant systemic drug toxicity is unlikely via percutaneous absorption of fluorouracil when Efudix is administered as per the approved prescribing information. However, the likelihood of this is increased if the product is used on skin areas in which the barrier function is impaired (e.g. cuts), if the product is applied under an occlusive dressing, and/or in individuals with deficiency in dihydropyrimidine dehydrogenase (DPD). DPD is a key enzyme involved in metabolising and eliminating fluorouracil. Determination of DPD activity may be considered where systemic drug toxicity is confirmed or suspected. There have been reports of increased toxicity in patients who have reduced activity of the enzyme dihydropyrimidine dehydrogenase. In the event of suspected systemic drug toxicity, Efudix treatment should be stopped.
- An interval of at least four weeks should elapse between treatment with brivudine, sorivudine or analogues and subsequent administration of Efudix.
- The excipients stearyl alcohol and propylene glycol may cause local skin irritations (e.g. contact dermatitis); the excipients methyl parahydroxybenzoate and propyl parahydroxybenzoate may cause allergic reactions (possibly delayed).

Pregnancy

Due to the genotoxic potential of fluorouracil, women of childbearing potential should use effective contraceptive measures while being treated with fluorouracil and for 7 months following completion of treatment. If a pregnancy occurs during treatment the patient should be advised about the risk for the child of adverse effects associated with the treatment and genetic counselling is recommended.

Men are recommended to use effective contraceptive measures and to not father a child while receiving fluorouracil and for 4 months following completion of treatment.

Breast-feeding

No information is available on the excretion of fluorouracil into breast milk. Studies in animals have shown

the fluorouracil is teratogenic. A risk to the suckling child cannot be excluded, so Efudix should not be used in nursing mothers. If use during breastfeeding is absolutely necessary, breastfeeding must be discontinued.

Fertility

The use of topical 5-fluorouracil may impair female and male fertility. Topical fluorouracil is not recommended in men attempting to father a child.

Undesirable effects

Adverse reactions associated with exacerbations of normal pattern of response which are related to pharmacological activity of fluorouracil on the skin are the most frequently reported reactions. Allergic type skin reactions and reactions related to systemic drug toxicity are very rarely reported.

- Blood and lymphatic system disorders: Very rare - Haematological disorders, associated with systemic drug toxicity, e.g. pancytopenia, neutropenia, thrombocytopenia.
- Immune system disorders: Very rare - Allergic conditions (e.g. hypersensitivity and allergic reactions).
- Nervous system disorders: Frequency not known - Dysgeusia, headache, dizziness.
- Eye disorders: Frequency not known - Conjunctival irritation, keratitis, increased lacrimation.
- Gastrointestinal disorders: Very rare - Diarrhoea haemorrhagic, diarrhoea, vomiting, abdominal pain, stomatitis, associated with systemic drug toxicity. Frequency not known - Nausea.
- Skin and subcutaneous tissue disorders: Very rare - Pruritus, urticaria, rash (usually local but also generalised if associated with systemic drug toxicity); erythemas including erythema multiforme; dermal and epidermal conditions (such as skin burning sensation, skin exfoliation, skin swelling); skin and subcutaneous skin ulcerations; dermatitis and eczema conditions (such as contact dermatitis, skin irritation); blisters, and alopecia.
  Exposure to sunlight may increase the intensity of the reaction.
- General disorders and administration site conditions: Very rare - Pyrexia, chills and mucosal inflammation, associated with systemic drug toxicity. Frequency not known - Application site haemorrhage.

Pharmacokinetic properties

Fluorouracil is minimally systemically absorbed when applied topically to intact skin. When applied to the skin, the skin's barrier function is pathologically altered (e.g., as in ulceration), and the absorption rate can increase to 60%. In patients with AK, 2.4 – 6% of the topical dose was absorbed systemically. Similarly, under occlusion, significantly more fluorouracil is absorbed.

Strengths and limitations of the evidence:

Topical 5-fluorouracil has been used over a long period of time to treat skin lesions. Its safety profile is well understood and widely documented. It is one of a number of therapies available to practitioners to treat pre-cancerous skin lesions. This review has not sought to prove its efficacy, but to confirm its place in therapy.

Summary of evidence on cost effectiveness:

None identified

Prescribing and risk management issues:

Instruct patients not to smoke or go near naked flames - risk of severe burns. Fabric (clothing, bedding, dressings etc) that has been in contact with this product burns more easily and is a serious fire hazard. Washing clothing and bedding may reduce product build-up but not totally remove it.

Exposure to UV-radiation (e.g natural sunlight, tanning salon) should be avoided.

Any severe skin discomfort during treatment with Efudix may be alleviated by the use of an appropriate topical steroid cream.

Avoid contact with eyes and mucous membranes.

Do not apply to bleeding lesions.

Occlusive dressing may increase inflammatory reactions of the skin.

Commissioning considerations:

Innovation, need and equity implications of the intervention:

Confirmation of RAG status potentially increases patient access to this therapy.

Financial implications of the intervention:

12 months up to and including November 2022

3657 prescriptions issued for fluorouracil 5% cream (Efudix) in LSCMMG primary care at a total cost of £112 749.

Localities	Sum of Items	Sum of Actual Cost
⊞Blackburn with Darwen	108	3323.484715
⊞Blackpool	76	2339.216242
⊞Chorley and South Ribble	98	3015.823589
⊞East Lancashire	697	21447.34128
⊞Greater Preston	58	1785.157334
⊞Morecambe Bay	2028	62527.78294
⊞West Lancs	201	6277.832139
⊞Fylde and Wyre	391	12032.52736
Grand Total	3657	112749.1656

Based on the current tariff price of £32.90 /item (Feb 2023), if prescribing in primary care increase by:

- 10%, this would result in an annual increased cost to primary care of approx. £12 041
- 50%, this would result in an annual increased cost to primary care of approx. £60 158

NB. East Lancashire already have a local RAG position of Green for this indication:

Photodamage

GREEN	Diclofenac sodium 3% gel *(Solaraze®)* - prescribe by brand
GREEN	Fluorouracil 5% cream *(Efudix®)* - for actinic keratosis and Bowen's disease
RED	Fluorouracil 5% cream *(Efudix®)* - for basal cell carcinoma
AMBER	Imiquimod 5% cream *(Aldara®)* - *(actinic keratosis and external genital warts)*
	Protocol for using Efudix 5% for actinic keratosis and Bowen's disease
GREEN	Tirbanibulin ointment *(Klisyri®)* - for non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade 1) of the face or scalp in adults. *See Prescribing Guidance*

Service Impact Issues Identified:

Increase in primary care prescribing anticipated.

Volume of increase unclear as some localities already consider fluorouracil cream 5% as a Green RAG rated product.

Equality and Inclusion Issues Identified:

None identified

Cross Border Issues Identified:

The **Pan Mersey APC** RAG rate fluorouracil 5% cream (Efudix) as Green for the indication 'photodamage'. They also list diclofenac sodium 3% gel (Solaraze) as Green for this indication. A Green RAG rating in the Pan Mersey APC indicates that a medicine is considered suitable for non-specialist prescribing in primary or secondary care.

The formulary links to the Primary Care Treatment Pathway for Actinic (Soloar) Keratosis, produced by the Primary care Dermatology Society[12]. It recommends fluorouracil 5% cream alone or in combination with 10% salicylic acid, for grade I lesions and grade II lesions, once daily for 4 weeks.[12]

NB. Fluorouracil 0.5%/Salicylic acid 10% solution (Actikerall) is RAG rated Black for actinic keratosis by LSCMMG.

The **Greater Manchester Medicines Management Group** (GMMMG) list fluorouracil 5% cream (Efudix) as first choice for 'photodamage'. The Greater Manchester guidelines for the management of Actinic Keratoses in primary care have Efudix as the only recommended treatment for this indication. Solaraze is not recommended.[13]

Efudix regime: Twice daily for 3 weeks to the face. Twice daily for 4 weeks on other sites.

NB. The GMMMG guideline was published April 2019 and was due for review in January 2022. Minutes from the Clinical Reference Group Meeting in Feb 2022 state:

CRG reviewed an application to add Tirbanibulin (Klisyri®) ointment to the GM formulary as a GREEN item. Tirbanibulin is indicated for the field treatment of non-hyperkeratotic, nonhypertrophic actinic keratosis of the face or scalp in adults. Klisyri® is more expensive; a five-day course of Klisyri® costs £59.00, whereas a 40g package of fluorouracil 5% cream (Efudix®; the current treatment within the GM formulary) is £32.90. (Source: dm+d.) Despite the increased cost, the Tirbanibulin treatment course is a single five-day, once-a-day course, compared to 3-4 weeks of daily use of fluorouracil 5% cream, and may be more tolerable as a result. The application received by CRG referred to the Primary Care Dermatology Society pathway for actinic keratosis. There is a current GM pathway for actinic keratosis treatment in primary care, which only includes 5% fluorouracil cream as a treatment option. It was questioned whether CRG should approve a treatment knowing its position in the pathway is unclear. It was noted that although fluorouracil 5% cream (Efudix®) is the only treatment option in the current GM pathway, there are high rates of prescribing of diclofenac 3% gel (Solaraze®). It was suggested that the pathway needs looking at here as it may not match current practice. It was also noted that Efudix® is used significantly in secondary care, too, so a formulary change (I.e. the addition of Klisyri® as a GREEN option) may cost more than is anticipated based solely on primary care numbers. It was suggested that the application estimate of 200 patients per year was an underestimate of potential patients using Tirbanibulin. It was asked whether community dermatology teams were involved in application process and this was not clear. It was suggested that CRG does not proceed with approval until pathway concerns are resolved. Decision: Tirbanibulin needs to be considered within the review of the Greater Manchester actinic keratosis pathway.

Legal Issues Identified:

None identified

Media/ Public Interest:

None identified

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

References

[1] Electronic Medicines Compendium, "Summary of Product Characteristics Efudix 5% Cream", Mylan, Jan 2022 [Online]. Available: https://www.medicines.org.uk/emc/product/9260/smpc

[2] British National Formulary, “Fluorouracil” [Online]. Available: https://bnf.nice.org.uk/drugs/fluorouracil/ [Accessed 16 February 2023]

[3] Osmosis from Elsevier, “Precancerous Skin”

[4] Skin Cancer Foundation, “Actinic Keratosis Overview”, 2022. Available: https://www.skincancer.org/skin-cancer-information/actinic-keratosis/

[5] British Association of Dermatologists, “ACTINIC KERATOSES (Also known as solar keratoses)”, Updated December 2020. Available: https://cdn.bad.org.uk/uploads/2021/11/29200022/Actinic-Keratoses-PIL-Dec-2020.pdf

[6] Berker D et al, “British Association of Dermatologists’ guidelines for the care of patients with actinic keratosis 2017”, *British Journal of Dermatology,* vol 176, pp 20-43, 2017

[7] Eisen DB et al, “Guidelines of care for the management of actinic keratosis”, *Journal of the American Academy of Dermatology*, vol 85(4), 2021

[8] Gupta AK et al, “Interventions for actinic keratoses (Review)”, *Cochrane Database of Systematic Reviews*, 2012

[9] Bath-Hextall FJ et al, “Interventions for cutaneous Bowen's disease (Review)”, *Cochrane Database of Systematic Reviews*, 2016

[10] Scottish Medicines Consortium, “fluorouracil + salicylic acid (Actikerall)”, October 2011. Available: https://www.scottishmedicines.org.uk/medicines-advice/fluorouracil-plus-salicylic-acid-actikerall-fullsubmission-72811/

[11] All Wales Therapeutics and Toxicology Centre, “fluorouracil/salicylic acid (Actikerall®)”, 2012. Available: https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/fluorouracil-salicylic-acid-actikerall/

[12] Primary Care Dermatology Society, “Actinic (Solar) Keratosis – Primary Care Treatment Pathway”, Updated February 2020. Available: https://www.pcds.org.uk/files/gallery/AK_guidelines_Macrh_2020.pdf

[13] Greater Manchester Medicines Medicines Management Group, “Greater Manchester Guidelines for the Management of Actinic Keratoses (AK) in Primary Care”, 2019. Available: https://gmmmg.nhs.uk/wp-content/uploads/2021/08/GM-guidelines-for-the-management-of-AKs-in-primary-care-GMMMG-FINAL-3-1.pdf