

**BHR CCGs GPs and DMC Dermatology**

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| Fluorouracil (Efudix) 5% cream  Indications: Superficial malignant and pre-malignant skin lesions including Skin Keratoses, Bowen’s Disease and Basal Cell Carcinomas (BCC) |

### *DOCUMENT TO BE SCANNED INTO ELECTRONIC RECORDS AS AND FILED IN NOTES*

**Patient Name : Date of Birth: NHS No:**

**Name of Referring Consultant: Contact number:**

#### INTRODUCTION – Indication and Licensing

Topical fluorouracil (5-FU), Efudix 5% cream is licensed for the topical treatment of superficial pre-malignant and malignant skin lesions in adults. Including keratoses including seborrheic (senile), actinic (solar) and arsenical forms; keratoacanthoma; Bowen's disease (squamous carcinoma in situ); and superficial basal-cell carcinoma (BCCs)

Fluorouracil cream destroys cancer cells and cells which may become cancerous, whilst having little effect on normal cells.

It is also used outside it’s licensed indication for the treatment of warts to good effect.

In view of the lack of clinical data available, Efudix is not licensed for use in children

#### PATIENT PATHWAY

It is appropriate for the diagnosis and management of actinic keratoses (AK) to be undertaken for the most part in primary care, as recommended by NICE (2006). The initial advice may include sun avoidance and self-monitoring for new lesions or changes in existing lesions. Where there is clinical or patient concern, cryosurgery or a topical therapy is usually used.

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| Clinical Speciality / Indication | Prescribing Initiated and continued by | Monitored by *(detail when suitable for transfer to occur IF APPROPRIATE)* | Duration of treatment |
| AK with a treatment area not exceeding an area of 15x15cm at a time (this can be one area or several smaller areas, as long as the total area treated is not more than 225cm2). | GP following specialist advice from DMC. | GP | **3 weeks – maximum 4 weeks per area.**  Consider second treatment if skin is not clear or partially clear at that time. Further dermatology review should be consider if patient fails to respond to two courses. |
| AK in high risk patients e.g. history of skin cancer, extensive UV damage, immunosuppressed patients or the very young. AK with a treatment area over 15x15cm up to 500cm2 at each time. | Consultant | Consultant | **3 weeks – maximum 4 weeks per area.** |

Patients should be referred to a Consultant dermatologist if there is diagnostic uncertainty; concern about malignant risk; failure to respond to therapy; concerns about management (e.g. where lesions are multiple or confluent, thick and painful or at sites of poor healing such as the lower leg; or if the patient is at high risk (e.g. organ transplant recipients, multiple large lesions or previous SCC).

#### ORAL DOSE AND ADMINISTRATION

DOSE

* Apply once or twice daily to affected area of skin. Unless otherwise specified, the dose will be once a day to be applied at night.
* The total area of skin being treated at any one time should not exceed 500 cm2 (approximately 23 x 23 cm). In primary care each treatment area should not exceed an area of 15x15cm at a time (this can be one area or several smaller areas, as long as the total area treated is not more than 225cm2). This is sufficient to treat an area the size of the entire scalp in one go.
* Larger areas should be treated a section at a time. Further areas can be treated thereafter; ensuring in primary care the maximum treatment area is 15x15cm skin at a time.
* BAD patient leaflet (appendix 1) should be provided to patient.

Application advice:

* If using 5-FU cream once a day, the patient should apply it at night
* Marked inflammation should occur prior to resolution, warn the patient to expect this, usually 2-3 weeks into treatment (see normal pattern of response below)
* Optimum effect is seen 4-6 weeks post-treatment.
* Warn patients however that occasionally systemic symptoms occur reflecting an enzyme deficiency (deficiency in dihydropyrimidine dehydrogenase, DPD); Efudix must then be stopped and never used again for these patients. Document on the patient record that there is a potential DPD deficiency. **For topical 5-fluorouracil (5%), if systemic drug toxicity is confirmed or suspected, determination of DPD activity should be considered in line with existing UK product information**
* GP should remind patients that hands should be washed carefully and thoroughly after applying Efudix. Also, care should be taken to avoid contact with mucous membranes or the eyes when applying the cream
* Patient should wait 20 mins before applying moisturisers and/or make-up as part of usual skin care routine
* 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

#### *KEY ADVERSE EFFECTS & ACTIONS*

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| **Adverse effects** | **Symptoms/signs** *(specify what would prompt action)* | **Actions (***what action should the GP take if identified in primary care)* |
| Very common/common: erythema which may become intense and blotchy, skin erosion – see below for normal pattern of response | Inflammatory reaction on the skin being treated. | Skin reactions only gradually subside after the treatment. Skin will be inflamed at the end of treatment and it will take a further 3-4 weeks for the skin to return to normal.  Review patient 4-6 weeks after treatment. |
| Frequency not know: conjunctival irritation, excessive tearing, keratitis, taste altered | N/A | If systemic toxicity suspected, stop treatment |
| Very Rare: fever, abdominal pain, chills, diarrhoea haemorrhagic, leucocytosis, pancytopenia, neutropenia, skin irritation, skin ulcer, thrombocytopenia, allergic reactions dizziness, headache, diarrhoea, vomiting, stomatitis (associated with systemic drug toxicity) | 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 excessively, especially on skin areas in which the barrier function is impaired (e.g. cuts) and/or in individuals with deficiency in dihydropyrimidine dehydrogenase (DPD). | For skin irritation use a topical corticosteroid for severe discomfort associated with inflammatory reactions.  If systemic toxicity suspected, stop treatment. |

Normal pattern of response:

* Redness/pain with 5-fluorouracil:
* Mild to moderate redness and soreness should be expected and patients should be reassured that this usually indicates a good response.
* Marked inflammation should occur prior to resolution, warn the patient to expect this, usually 2-3 weeks into treatment.
* Soreness will settle in a week or two. Plentiful emollients may help
* Redness settles over 2 months.
* If very red/ painful/ ulcerated, stop and Consider topical 1% hydrocortisone cream bd for 3 days.
* If yellow crust/ exudate, possible secondary infection, so consider topical antibiotic bd for 5 days e.g. Fucidin or as per the NEL infection guide.
* If severe redness on course 1, course 2 can be shortened or may not be needed.

The normal pattern of response to topical 5-FU includes: early and severe inflammatory phases (typically characterised by erythema, which may become intense), a necrotic phase (characterised by skin erosion and crusting) and finally healing (when re-epithelialisation occurs). These local skin reactions usually occur in the second week of fluorouracil treatment and are generally well tolerated. However they may sometimes become more severe and cause pain, blistering and ulceration.

Any severe skin discomfort during treatment with topical 5-fluorouracil may be alleviated by the use of an appropriate topical steroid e.g. hydrocortisone 1% ointment/cream. The usual duration of treatment for an initial course of therapy is three to four weeks. Lesions on the face usually respond more quickly than those on the trunk or lower limbs whilst lesions on the hands and forearms respond more slowly. Healing may not be complete until one or two months after therapy is stopped.

The inflammation will only gradually subside after treatment, it takes around 3-4 weeks to reduce to normal. **Review the patient 4-6 weeks after treatment (not just after the course) and consider second treatment if the skin is not clear or partially clear. Further dermatology review should be considered if patient fails to respond to two courses.**

**This only lists the key important ADRs-For comprehensive information on cautions, contra-indications and interactions, please refer to the current British National Formulary and Summary of Product Characteristics.**

**Contraindications.**

* Fluoruracil 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**

**Cautions**

* avoid contact with eyes and mucous membranes and do not use on broken skin
* avoid excessive sunlight
* dihydropyrimidine dehydrogenase deficiency.
* do not apply to bleeding lesions
* do not use occlusive dressing

#### *PREGNANCY AND BREAST FEEDING*

Studies in animals have shown that fluorouracil is teratogenic. The potential risk for humans in unknown and therefore Efudix should not be used during pregnancy. It is recommended that the patient should not become pregnant whilst on topical 5-Fluorouracil. Both men and women patients will be counselled about contraception and what to do if pregnancy occurs. The counselling should be documented in the patient notes.

A patient information leaflet will be downloaded from [www.patient.co.uk](http://www.patient.co.uk) or [www.medicines.org.uk](http://www.medicines.org.uk).

No information is available on the excretion of fluorouracil into breast milk and due to potential risk of teratogenicity, Efudix should not be used in breastfeeding.

The specialist will ensure to discuss with patients the teratogenic risk, the advice not to become pregnant or use product if breast-feeding and document this on the letter to the GP.

Interactions: An interval of at least four weeks should elapse between treatment with brivudine, sorivudine or analogues and subsequent administration of 5-fluoruracil.

**For comprehensive information please refer to the current British National Formulary and Summary of Product Characteristics.**

#### SHARED CARE

**Shared care guideline*:***

Thi*s* is a document which provides information allowing patients to be managed safely by primary care, secondary care and across the interface. It assumes a partnership and an agreement between a hospital specialist, GP and the patient and also sets out responsibilities for each party. The intention to shared care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. Intrinsic in the shared care agreement is that the prescribing doctor should be appropriately supported by a system of communication and cooperation in the management of patients. The doctor who prescribes the medicine has the clinical responsibility for the drug and the consequence of its use**.**

**Consultant**

* Diagnosis of AK, Bowens disease and BCCs in high risk patients referred by GP.
* Treatment of grade 3 AK and isolated AK lesions failing to respond to other therapies.
* Identify suitable patients and initiate treatment if deemed urgent
* **Counsel the patient on the side effects of Efudix including counselling on risk to pregnancy and advise about contraception.**
* Provide patient with relevant patient information leaflets
* Provide the GP with a full summary/ discharge letter at least 2 weeks before the intended implementation of the shared care scheme in patients where treatment was urgent and initiated by the consultant or the patient was high risk.
* Provide the opportunity for the GP and consultant to discuss the case and the shared care guideline.
* Evaluation of any reported adverse effects by GP or patient.
* Advise GP on review, duration or discontinuation of treatment where necessary. Where urgent action is required following tests the community dermatology team will telephone the patient and inform GP.
* Keep the GP informed of the patient’s progress after any further clinic appointment
* Inform the GP of any changes to drug therapy and dosage
* Arrange routine follow up of the patient at appropriate intervals

**General Practitioner**

* AK can safely be managed in primary care. High risk patients who may require referral to include those with a history of skin cancer, extensive UV damage, immunosuppressed patients or the very young
* Diagnosis of AK. Reinforce the patient’s understanding of the nature, effect and potential side effects of the drug before

prescribing it as part of and contact the specialist for clarification where appropriate.

* Initiate treatment and prescribing maintenance of fluorouracil according to the dose regimen

suggested by the Dermatologist. Including treatment of Grade 1 or 2 and single or field change AKs.

* Advise when they should return for review or if treatment is not working in the expected fashion.
* Monitor patient’s overall health and well-being.
* Help in monitoring the progression of disease
* Report adverse events suffered by the patient to the consultant and MHRA where appropriate
* Communicate with Dermatologist regarding any problems/compliance issues
* Refer back to consultant if condition has not improved after 4 weeks.

**Patient/ Carer**

1. Report any adverse effects to their GP and/or specialist
2. Ensure they have a clear understanding of their treatment.
3. Report any changes in disease symptoms to GP and/or specialist
4. Alert GP and/or specialist of any changes of circumstance which could affect management of disease e.g. plans for pregnancy
5. Administer the medication as prescribed
6. Undertake any monitoring as requested by the GP and/or specialist

**Costs**

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| Drug Product | Cost in primary care |
| Efudix | £32.90 |

Based on BNF online edition accessed <https://bnf.nice.org.uk/> last update 2 July 2020

#### *RESOURCES AVAILABLE*

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| **DMC Healthcare** | |  |
| Consultant via email | [dmc.admin@nhs.net](mailto:dmc.admin@nhs.net)  0207 635 1013 | |
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**References:**

1. Joint Formulary Committee. *British National Formulary* (online) London: BMJ Group and Pharmaceutical Press https://bnf.nice.org.uk/drug/fluorouracil.html [Accessed March 2020]
2. Cancer service guideline [CSG8] Improving outcomes for people with skin tumours including melanoma. Available ay <https://www.nice.org.uk/guidance/csg8> Published date: 22 February 2006 Last updated: 25 May 2010
3. Berker et al. (September 2016) Guidelines for the care of patients with actinic keratosis 2017, *British Association of Dermatologists Guidelines.* Available at <https://onlinelibrary.wiley.com/doi/full/10.1111/bjd.15107> [Accessed February 2020]
4. Primary Care Dermatology Society, Actinic Keratosis pathway, Available at [www.pcds.org.uk/clinical-guidance/actinic-keratosis-syn.-solar-keratosis 225/2/20](http://www.pcds.org.uk/clinical-guidance/actinic-keratosis-syn.-solar-keratosis%20225/2/20), [Accessed March 2020]
5. Mylan Efudix cream (5-FU), Summary of Product Characteristics (SPC), available at <https://www.medicines.org.uk/emc/product/9260> Date of revision of text April 2019, [Accessed February 2020]
6. Mylan Efudix cream (5-FU), Patient Information Leaflet (PiL), available at https://www.medicines.org.uk/emc/files/pil.9260.pdf Date of revision of text July 2020. [Accessed March 2020]
7. British Association of Dermatology website: AK factsheets. Available at <https://www.bad.org.uk/shared/get-file.ashx?id=66&itemtype=document> [Accessed February 2020]
8. 5-fluorouracil (intravenous), capecitabine, tegafur: DPD testing recommended before initiation to identify patients at increased risk of severe and fatal toxicity, Drug Safety Update, October 2020 [online] available from <https://www.gov.uk/drug-safety-update/5-fluorouracil-intravenous-capecitabine-tegafur-dpd-testing-recommended-before-initiation-to-identify-patients-at-increased-risk-of-severe-and-fatal-toxicity> [accessed date 26/11/20]

**Refer to the NHS Barking and Dagenham, Havering and Redbridge CCG website to obtain the latest version of this guideline**

Appendix 1

DMC Healthcare

**Fluorouracil**

SHARED CARE AGREEMENT LETTER

Name of GP ………………………….… Practice …………………………………. Email address …………………………………

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Dear GP

Re: Patient’s Name……………..………………………………

Date of Birth……………….………………………………

NHS Number……………..…………………………….

Indication for …….…………………………………

Route………(Topical)

Dose……………..

Enclosed is a copy of the shared care guidelines for [Fluorouracil cream] to be retained in the patient’s notes.

Should you agree to shared care, we will send a letter containing the details of the patient’s treatment plan, the dose to be prescribed and all relevant blood results.

Please sign below and return this letter to the Dermatology Specialist if you agree to the shared care arrangements for this patient.

Many thanks

Dermatology Specialist GP

Signature……………………... Signature……………………...

Name ………………..……... Name ………………………...

Date………………………... Date………………..…..……... Email to contact for queries:…………………… Email to contact for queries:………………………………………….

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If you are not taking on shared care for this patient please state the reason why and return this letter to the Dermatology Specialist.

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Appendix 1: BAD Patient Information Sheet

# Appendix Four: BAD Patient Information Leaflet

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**5-FLUOROURACIL CREAM**

**What are the aims of this leaflet?**

This leaflet has been written to help you understand more about 5-fluorouracil (5-FU) cream. It tells you what it is, how it works, how it is used to treat skin conditions, and where you can find out more about it.

What is 5-FU cream and how does it work?

5-FU cream is a treatment that selectively destroys sun-damaged cells in the skin whilst retaining the normal healthy skin cells. It has been in use for more than 50 years.

5-FU cream will induce inflammation in the skin. This will consist of redness, soreness, oozing, crusts and scabs. After completing the treatment course this reaction will settle over a few weeks. Sometimes your doctor may recommend using a steroid cream to help settle the inflammation more quickly.

In the UK, two forms are available: 5% 5-FU cream (Efudix®) and 0.5% 5-FU combined with 10% Salicylic acid (Actikerall®).

**What skin conditions are treated with 5-FU cream?**

5-FU cream is prescribed for the treatment of the pre-cancerous skin lesions, actinic keratoses and Bowen’s disease. It is also used for the treatment of superficial basal cell carcinoma.

It is sometimes used to treat other skin conditions such as viral warts, and rarer conditions such as disseminated superficial actinic porokeratosis.

**Will 5-FU cream cure my skin condition?**

Depending on your skin complaint, 5-FU cream may cure or improve it, but it does not work for everybody. If you have more severe sun-damage, you may require additional courses of treatment in the future.

**How do I apply 5-FU cream?**

Efudix® cream can be applied with a clean fingertip. Apply a thin layer of the cream to the entire treatment area. If you are using Actikerall® dab the solution on to the treatment site with the brush applicator provided. The solution will dry to leave a film at the site. Remove the film by peeling just prior to the next application. Warm water can be used to help loosen the film, if needed. Specific instructions will be provided by your doctor.

You should wash your hands thoroughly after applying 5-FU cream.

After 20 minutes, you can apply moisturisers and/or make-up as part of your usual skin care routine.

If you have widespread sun-damage it is usually advisable to divide the affected area into smaller areas and to complete treatment in one area before moving on to the next. This will help make the treatment reaction more tolerable. Your doctor will provide further advice about this.

Only cover 5-FU cream with a plaster if advised to do so by your doctor, otherwise leave the treated area uncovered. Covering the treatment area with a plaster is likely to induce a more severe skin reaction. When treating superficial basal cell carcinomas, however, covering the area with a plaster is often recommended**.**

**How often should I use 5-FU cream?**

How often and for how long you should use 5-FU cream will depend on your skin condition and other factors, for example which part of your skin is affected. Efudix® cream is usually applied once or twice a day, for 3-4 weeks when treating actinic keratosis and Bowen’s disease, and for 6weeks when treatingsuperficial basal cell carcinoma. Occasionally, more prolonged courses may be used. Actikerall® should be applied once daily until the lesions have cleared or for up to a maximum of 12 weeks. Your doctor will recommend a specific treatment schedule for you.

**At what time of day should I apply 5-FU cream?**

If you are asked by your doctor to use 5-FU cream once a day, you should apply it at night. If twice-daily application is recommended then it is best to apply 5-FU cream in the morning and at night.

When should I not apply 5-FU cream?

5-FU cream should not be used around the eyes or lips, unless specifically recommended by your doctor for use in that area.

**Do not apply 5-FU cream if you are pregnant or breastfeeding.**

Do not use 5-FU cream if you are allergic to any of its ingredients.

**What are the common side effects of 5-FU cream?**

As mentioned above, inflammation of the skin is expected, but if the skin becomes very sore or uncomfortable stop using 5-FU cream. Bathe the area with water, dab the skin dry and apply petroleum jelly daily. The petroleum jelly that you apply should be newly opened and free from potential contamination from fingertips. When the skin settles, you may be able to continue 5-FU cream to complete the treatment course.

If you have any concerns about the severity of the treatment site reaction or are uncertain about whether you should continue treatment, get in touch with your doctor who may recommend a change to your treatment schedule. Your doctor may also have additional treatment site advice, which may include applying a steroid cream to settle the inflammation.

5-FU cream makes your skin more sensitive to sunlight at the site of application, and therefore you should avoid significant sun exposureduring and for a whileafter treatment. This may include modifying activities to limit sunexposure,wearing clothing and/or a hat to cover the treatment site, and the use of sunscreens.

**What are the rare side effects of 5-FU cream?**

If you have a severe reaction to 5-FU cream, there is a risk of prolonged inflammation and delayed healing and the potential for the development of an ulcer, particularly on the lower legs

Following a severe reaction, there is a small risk of altered skin pigmentation and scarring.

Skin infections at the site of application of 5-FU cream are rare but possible. If you have concerns about the severity of the skin reaction, get in touch with your doctor.

Very rarely, patients can be allergic to 5-FU cream. This usually causes a severe localised skin reaction. If you have concerns about the severity of your reaction to 5-FU cream, get in touch with your doctor.

Like all medications, 5-FU should be kept out of reach of children and pets. There have been reports of pets dying or being harmed from licking their owners’ skin after 5-FU had been applied, or from consuming the cream from the tube.

**Where can I get more information about 5-FU cream?**

Links to other Internet sites:

http://www.patient.co.uk/medicine/Fluorouracil-Cream.htm http://www.dermnetnz.org/treatments/5-fluorouracil.html http://www.medicines.org.uk/emc/medicine/6219/SPC/Efudix+Cream http://www.medicinenet.com/fluorouracil-topical/article.htm

For details of source materials used please contact the Clinical Standards Unit (clinicalstandards@bad.org.uk).

This leaflet aims to provide accurate information about the subject and is a consensus of the views held by representatives of the British Association of Dermatologists: individual patient circumstances may differ, which might alter both the advice and course of therapy given to you by your doctor.

This leaflet has been assessed for readability by the British Association of Dermatologists’ Patient Information Lay Review Panel

**BRITISH ASSOCIATION OF DERMATOLOGISTS PATIENT INFORMATION LEAFLET PRODUCED APRIL 2011 UPDATED APRIL 2014, MARCH 2017 REVIEW DATE MARCH 2020**