

## New Medicine Recommendation

### 5% imiquimod cream (Aldara) and 5% fluorouracil cream (Efudix) for the treatment of small superficial basal-cell carcinomas in adults

**Recommendation:**

**5% imiquimod cream** (Aldara) for the treatment of small superficial basal-cell carcinomas in adults: **Red**

**5% fluorouracil cream** (Efudix) for the treatment of small superficial basal-cell carcinomas in adults: **Red**

Only to be prescribed by skin cancer specialists or a suitably qualified GP with specialist interest (GPwSI) with demonstrable clinical skills and competencies, training and experience.<sup>8</sup>

**Summary of supporting evidence**

A trial including 501 patients with nodular and superficial basal-cell carcinoma randomised the patients to be treated with either surgical excision or imiquimod 5% cream. At 3 years, 84% of the participants in the imiquimod group were treated successfully compared with 98% in the surgery group (RR 0.84, 98% CI 0.78–0.91; p<0.0001).<sup>11</sup>

A 5 year follow up of 401 patients from up of the above trial showed success rates for imiquimod were 82.5% compared with 97.7% for surgery.<sup>12</sup> Although surgery is shown to be superior to imiquimod, this study shows sustained benefit for lesions that respond early to topical imiquimod.

Results from two phase III, placebo-controlled studies in which 724 patients with superficial basal cell carcinoma were randomised to one of 4 groups for 6 weeks showed clearance rate, for imiquimod 5 times/week and 7 times/week of 75% and 73% versus placebo rate of 2% (5 and 7 times weekly).<sup>13</sup>

Five-Year Results of a randomized controlled trial comparing effectiveness of photodynamic therapy, topical Imiquimod, and topical 5-fluorouracil in patients with superficial basal cell carcinoma showed that 5% imiquimod cream was superior and 5-fluorouracil cream not inferior to methyl aminolevulinate photodynamic therapy (MAL-PDT) at 1 and 3 years after treatment.<sup>14</sup>

In a small trial, 29 patients with 31 biopsy-proven superficial basal cell carcinoma lesions on the trunk or limbs were treated with 5% 5-FU cream twice daily for up to 12 weeks. The histologic cure rate was 90% (28/31 lesions cured) and the mean time to clinical cure was 10.5 weeks with 5-FU being generally well tolerated with a good cosmetic outcome.<sup>16</sup>

**Details of Review**

**Name of medicine (generic & brand name):** imiquimod 5% cream (Aldara®) and fluorouracil 5% cream (Efudix®)

**Strengths and forms:**

5% imiquimod cream 12 x 250mg sachets  
5% fluorouracil cream 40g

**Dose and administration:****Imiquimod 5% cream (Aldara)**

Superficial basal cell carcinoma in adults: Apply imiquimod cream for 6 weeks, 5 times per week (example: Monday to Friday) prior to normal sleeping hours, and leave on the skin for approximately 8 hours. Sufficient cream should be applied to cover the treatment area, including one centimetre of skin surrounding the tumour. The cream should be rubbed into the treatment area until the cream vanishes. Response of the treated tumour to imiquimod cream should be assessed 12 weeks after the end of treatment. If the treated tumour shows an incomplete response, a different therapy should be used. A rest period of several days may be taken if the local skin reaction to imiquimod cream causes excessive discomfort to the patient, or if infection is observed at the treatment site. In this latter case, appropriate other measures should be taken.<sup>1</sup>

**Fluorouracil 5% cream (Efudix)**

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

Malignant conditions: The cream should be applied once or twice daily under an occlusive dressing where this is practicable.

The cream should not harm healthy skin. The total area of skin being treated with Efudix at any one time should not exceed 500 cm<sup>2</sup> (approximately 23 x 23 cm). Larger areas should be treated a section at a time. Treatment should be continued until there is marked inflammatory response from the treated area, preferably with some erosion in the case of pre-malignant conditions. The usual duration of treatment for an initial course of therapy is three to four weeks, but this may be prolonged. Healing may not be complete until one or two months after therapy is stopped.<sup>2</sup>

**BNF therapeutic class / mode of action:** Chapter 13, Skin.

**Imiquimod** – antivirals / immune response modifiers. Imiquimod works by stimulating antigen-presenting cells via TLR7. Toll-like receptors (TLRs) are highly conserved pattern-recognition receptors that function as regulators and controllers of the immune system. Imiquimod also induces the production of interferon-alpha (IFN- $\alpha$ ), interleukin-12 (IL-12), and tumour necrosis factor- $\alpha$ , with a resulting cytokine cascade that may induce and/or support a Th1 (T helper 1) immune response. Interferon induction is a critical function of imiquimod for the treatment of viruses and tumours in animal models.

**Fluorouracil** – antineoplastic drugs / antimetabolites. 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.

**Licensed indication(s):**

**Imiquimod 5% (Aldara)** cream is indicated for the topical treatment of:

- External genital and perianal warts (condylomata acuminata) in adults.
- **Small superficial basal cell carcinomas (sBCCs) in adults.**
- Clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AKs) 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.<sup>1</sup>

**Fluorouracil 5% (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.**<sup>2</sup>

Deep, penetrating or nodular basal cell and squamous cell carcinomas do not usually respond to 5-fluorouracil therapy. It should be used only as a palliative therapy in such cases where no other form of treatment is possible

**Proposed use:** Small superficial basal cell carcinomas (sBCCs) in adults.

**Course and cost:**

**Imiquimod 5% cream** - 5 times per week for 6 weeks, i.e. 30 sachets are used in each treatment.

12 sachets of imiquimod 5% cream costs £48.60 (DT price).<sup>3</sup> 36 sachets will cost £145.80. If a pack is split, **30 sachets will cost £121.50**

**Fluorouracil 5% cream** - once or twice daily for three to four weeks i.e. 40 – 80g (1-2 tubes) will be used in each treatment.

DT price for **1 x 40g tube costs £32.90, 2 x 40g tubes will cost £65.80**<sup>3</sup>

**Relevant NICE and other guidance:**

- Skin cancer NICE Quality Standard Published: 21 September 2016<sup>4</sup>
- NICE Skin Cancer overview – interactive pathway<sup>5</sup>
- SMC 167/05 Imiquimod 5% cream (Aldara<sup>®</sup>) for the topical treatment of small superficial Basal Cell Carcinoma<sup>6</sup>
- British Association of Dermatologists guidelines for the management of basal cell carcinoma 2008<sup>7</sup>
- Guideline on the Treatment of Basal Cell Carcinoma, European Dermatology Forum 2012<sup>8</sup>

**Disease Background**

Basal cell carcinoma (BCC) is a very common skin cancer, almost exclusively of white populations. Basal cell carcinoma is an unusual cancer in that it grows slowly and is locally invasive, but does not often metastasise. It is rarely fatal, but if not treated can result in extensive local tissue damage, and can track along embryonic fusion planes or nerve tracts producing morbidity and deformity. Tumours are often multiple, even when the patient is first seen. Along with other non-melanoma skin cancer (NMSCs), new BCCs are highly likely to appear over time, in particular within the first year after treatment of the primary lesion and treatment of patients developing large numbers of tumours presents a management problem.

The majority of BCCs are low risk, the most common pattern being nodular, which accounts for 45%-60% of cases. The superficial subtype is also low risk and accounts for approximately 15%-35% of BCCs.

High risk BCCs include infiltrative, morpheaform (sclerosing), and micronodular subtypes, which tend to infiltrate more diffusely such that subsequent recurrence is more common. The nodular subtype, especially, may become pigmented. It can resemble a seborrhoeic keratosis, and occasionally malignant melanoma has to be considered in the differential diagnosis.

Cancer registries often summarise BCC together with squamous cell carcinoma (SCC) under the single label of NMSC, and rates for the individual histological subtypes are even more difficult to identify. Despite these limitations, BCC is considered the most common skin cancer in white adults.

The importance of BCC is underestimated, probably because it is rarely fatal. The annual incidence in Europe is estimated between 40 – 140 cases per 100 000, and has been rising

markedly over the last 20 years, coming to represent a significant burden on health care systems.

Incidence rates increase with age, and most patients present after age 60. Generally speaking BCC is more common in men than women, especially in the older age groups, although the sex ratio for sBCCs seems more equal.

Early in 2009, NICE was made aware of concerns about the implementation of some aspects of its guidance on skin cancer services. These were in relation to the arrangements under which GPs could remove 'low-risk' basal cell carcinomas (BCCs) and how services for skin cancer patients were being commissioned. In April 2009, the National Collaborating Centre for Cancer (NCC-C) was commissioned by NICE to update the 2006 guidance to specifically address the management of low-risk BCCs in the community.<sup>9,10</sup>

Doctors managing superficial BCC in the community should have experience and knowledge of this condition<sup>1</sup> and all healthcare professionals managing BCCs in the community should provide information, advice and support for patients and their families or carers.

Medical, cream based treatment can be indicated for low risk BCC. The main advantages of medical treatment for BCC are good cosmetic outcome, preservation of surrounding tissue and potential for home application of certain treatments.

### **Current treatment options**

Current treatments tend to be carried out in secondary care and include surgical removal, radiotherapy, cryotherapy (freezing), phototherapy (light therapy) and creams. Surgery and radiotherapy appear to be the most effective treatments for basal cell carcinoma and Mohs' micrographic surgery (the removal of the tumour layer by layer until it has gone, as determined histologically) the most effective for high risk facial basal cell carcinoma.

Photodynamic therapy appears to be useful in the short-term, especially for people who wish to avoid scarring. However, long-term follow-up is needed. Cryotherapy, while convenient and less expensive, does not have a higher cure rate.

### **Summary of efficacy data in proposed use:**

#### **Imiquimod**

#### **Surgical excision versus imiquimod 5% cream for nodular and superficial basal-cell carcinoma (SINS): a multicentre, non-inferiority, randomised controlled trial<sup>11</sup>**

A multicentre, parallel-group, pragmatic, non-inferiority, randomised controlled trial at 12 centres in the UK, in which patients were recruited between June 19, 2003, and Feb 22, 2007, with 3 year follow-up from June 26, 2006, to May 26, 2010. The primary outcome was the proportion of participants with evidence of clinical success after 3 years from start of treatment. Clinically successful treatment was defined as no initial treatment failure or signs of subsequent local recurrence as reviewed by consultant dermatologists.

Participants were randomly assigned (1:1) via computer-generated blocked randomisation, stratified by centre and tumour type, to receive either imiquimod 5% cream once daily for 6 weeks (superficial) or 12 weeks (nodular), or surgical excision with a 4mm margin. Dosing was once daily because the study started before the manufacturers had decided on the final dosing regimen for basal-cell carcinoma. If a participant could not tolerate the cream because of side effects, they were advised to stop treatment for a week and then restart at a frequency of 5 days a week. If this schedule was tolerated, the participant could go back to 7 days a week; if not, or if 7 days a week was not tolerated, a second time, they could go back to 5 days a week after a further rest period of 1 week.

501 participants were randomly assigned to the imiquimod group (n=254) or the surgical excision group (n=247). At year 3, 401 (80%) patients were included in the modified intention-to-treat group. At 3 years, 178 (84%) of 213 participants in the imiquimod group were treated

successfully compared with 185 (98%) of 188 participants in the surgery group (RR 0.84, 98% CI 0.78–0.91;  $p < 0.0001$ ). No clear difference was noted between groups in patient assessed cosmetic outcomes.

Conclusion: Imiquimod was inferior to surgery according to the predefined non-inferiority criterion. Although excisional surgery remains the best treatment for low-risk basal-cell carcinoma, imiquimod cream might still be a useful first treatment option for small low-risk superficial basal-cell carcinoma in the community, dependent on factors such as patient preference, size and site of the lesion, and whether the patient has more than one lesion. With recurrences being dealt with by specialists through more sophisticated treatments such as excisional surgery.

#### Surgery Versus 5% Imiquimod for Nodular and Superficial Basal Cell Carcinoma: 5-Year Results of the SINS Randomized Controlled Trial<sup>12</sup>

This was a report of the 5 year data from the SINS trial (as detailed above).

Five-year success was defined as 3-year success plus absence of recurrences identified through hospital, histopathology and general practitioner records completed in 2012.

Of 501 participants randomized, 401 contributed to the modified intention-to-treat analyses at year 3 (primary outcome), 383 (96%) of whom had data at year 5. Five-year success rates for imiquimod were 82.5% (170/206) compared with 97.7% (173/177) for surgery (relative risk of imiquimod success = 0.84, 95% confidence interval = 0.77- 0.91,  $P < 0.001$ ). These were comparable to year 3 success rates of 83.6% (178/213) and 98.4% (185/188) for imiquimod and surgery, respectively. Most imiquimod treatment failures occurred in year 1.

A total of 18 patients did not have usable data at year 5. In the imiquimod group, three had died, and it was not possible to determine if recurrence had occurred in four (three not sure from records and one visit not done). In the surgery group, six had died, and it was not possible to determine if recurrence had occurred in five (three not sure, one visit done too early, and one not done). Additional recurrences between 3 and 5 years were small, with one additional recurrence for a superficial BCC treated with imiquimod and one for surgery.

Conclusion: Although surgery is shown to be superior to imiquimod, this study shows sustained benefit for lesions that respond early to topical imiquimod.

#### Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies<sup>13</sup>

724 patients were randomised, in blocks of four, to one of 4 groups; application of imiquimod 5 times/week, vehicle 5 times/week, imiquimod 7 times/week or vehicle 7 times/week, for a duration of 6 weeks. The cream was applied just prior to bedtime and was rubbed into the lesion, and area approximately 1cm surrounding the lesion, until the cream vanished. The cream was allowed to remain on the skin for at least 8 hours without occlusion and then removed with mild soap and water. Rest periods could be prescribed by the investigators. Patients were assessed at weeks 1, 3 and 6 during treatment and weeks 4 and 12 post treatment. At week 12 the sBCC was excised, with a 3-4mm margin around the original lesion margins if the sBCC was clinically evident or a 1-2mm margin if not clinically evident. The primary efficacy variable was complete composite clearance defined as the proportion of patients at the 12 week post-treatment visit who were complete responders to treatment. A complete responder was defined as a patient with no clinical evidence and no histological evidence of BCC at the target lesion site or clinical evidence suspicious of BCC but no histological evidence of BCC at the target site and where the histological findings provided an explanation for the false positive clinical assessment.

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

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

Conclusion: Imiquimod appears to be safe and effective for the treatment of sBCC when compared with vehicle cream. The difference in clearance rates between the two imiquimod dosing groups was not significant. The 5x/week regimen is recommended.

#### Five-Year Results of a Randomized Controlled Trial Comparing Effectiveness of Photodynamic Therapy, Topical Imiquimod, and Topical 5-Fluorouracil in Patients with Superficial Basal Cell Carcinoma<sup>14</sup>

This was a follow up to a prospective, noninferiority, randomized controlled multicentre trial with 601 patients which showed that 5% imiquimod cream was superior and 5-fluorouracil cream not inferior to methyl aminolevulinate photodynamic therapy (MAL-PDT) at 1 and 3 years after treatment. However, at these time points no definite conclusion could be drawn regarding the superiority of imiquimod over 5-fluorouracil.

601 patients with a primary, histologically proven sBCC were randomly assigned to treatment with MAL-PDT (n = 202), imiquimod (n = 198), or 5-fluorouracil (n =201). From randomization until 5 years after treatment, 70 tumour recurrences were found in the MAL-PDT group, 36 in the imiquimod group, and 57 in the 5-fluorouracil group. Thirteen of the 70 recurrences occurred between 3 and 5 years of follow-up (four after MAL-PDT, two after imiquimod, and seven after 5-fluorouracil treatment).

Five years after treatment, the probability of tumour-free survival was 62.7% for methyl aminolevulinate photodynamic therapy (95% confidence interval [CI] = 55.3-69.2), 80.5% for imiquimod (95% CI = 74.0-85.6), and 70.0% for 5- fluorouracil (95% CI = 62.9-76.0). The hazard ratio for treatment failure of imiquimod and 5-fluorouracil were 0.48 (95% CI =0.32-0.71, P < 0.001) and 0.74 (95% CI = 0.53-1.05, P =0.09), respectively, when compared with methyl aminolevulinate photodynamic therapy. Compared with 5-fluorouracil, imiquimod showed a hazard ratio of 0.65 (95% CI 0.43-0.98, P = 0.04).

Conclusion: 5 years after treatment, the results of this trial show that 5% imiquimod cream is superior to both methyl aminolevulinate photodynamic therapy and 5-fluorouracil cream in terms of efficacy for superficial basal cell carcinoma.

#### Interventions for basal cell carcinoma of the skin. Cochrane Database of Systematic Reviews 2007<sup>15</sup>

Conclusion: Short-term studies suggest a success rate of 87 to 88% for imiquimod in the treatment of superficial BCC using a once-daily regimen for 6 weeks and a 76% treatment response when treating nodular BCC for 12 weeks, when measured histologically. However, overall there has been very little good quality research on treatments for BCC. Most trials have only evaluated BCCs in low risk locations. Surgery and radiotherapy appear to be the most effective treatments with surgery showing the lowest failure rates. Although cosmetic outcomes appear good with PDT, long-term follow-up data are needed. Other treatments might have some use but few have been compared to surgery. An ongoing study (as detailed above – SINS) comparing imiquimod to surgery cited as hoping to clarify whether imiquimod is a useful option.

#### **Fluorouracil**

Please also see above - Five-Year Results of a Randomized Controlled Trial Comparing Effectiveness of Photodynamic Therapy, Topical Imiquimod, and Topical 5-Fluorouracil in Patients with Superficial Basal Cell Carcinoma<sup>13</sup>

5% 5-Fluorouracil Cream for the Treatment of Small Superficial Basal Cell Carcinoma: Efficacy, Tolerability, Cosmetic Outcome, and Patient Satisfaction<sup>16</sup>

A total of 29 patients with 31 biopsy-proven superficial basal cell carcinoma lesions on the trunk or limbs were treated with 5% 5-FU cream twice daily for up to 12 weeks. Treatment could be stopped sooner if the lesion was clinically resolved. The lesional site was surgically excised 3 weeks after the end of treatment for histologic evaluation of cure. The histologic cure rate was 90% (28/31 lesions cured) and the mean time to clinical cure was 10.5 weeks. 5-FU was generally well tolerated with a good cosmetic outcome—the majority of patients had no pain or scarring and only mild erythema.

### **Overall conclusions on the clinical efficacy**

There is very little data available on the use of 5% fluorouracil cream for the treatment of basal cell carcinoma.

The data available for Imiquimod 5% cream for the treatment of small superficial basal cell carcinomas (sBCCs) in adults would support its use as potentially useful first treatment option for small low-risk superficial basal-cell carcinoma in the community.

## **Summary of safety data**

### **Imiquimod (Aldara)**

Surgical excision versus imiquimod 5% cream for nodular and superficial basal-cell carcinoma (SINS): a multicentre, non-inferiority, randomised controlled trial<sup>10</sup>

The most common adverse events were itching (211 patients in the imiquimod group vs 129 in the surgery group) and weeping (160 vs 81).

serious adverse events were recorded in 99 (40%) of 249 participants in the imiquimod group and 97 (42%) of 229 in the surgery group, but none were regarded as related to treatment. 12 (5%) participants in the imiquimod group withdrew because of adverse events compared with four (2%) in the surgery group.

Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies<sup>12</sup>

The pooled results of the two US double blind vehicle controlled trials indicated the proportion of patients discontinuing treatment due to an adverse event or local skin reaction was 4% and 2% for the imiquimod 5 times/week and 7 times/week groups respectively. There was a significant difference in the proportion of patients experiencing an application site reaction in the imiquimod 5 times/week group (28%) compared with the imiquimod 7 times/week group (44%).

Application site reactions most frequently reported for the imiquimod 5 and 7 times/week groups respectively, were itching at the target site (16% and 26%), burning at the target site (6% and 9%) and pain at the target site (3% and 6%) and the difference was statistically significant for itching. Other adverse events experienced during the treatment period by = 3% of patients in any treatment group were headache, upper respiratory tract infection, sinusitis, back pain and pain. There was a significant difference for headache between the imiquimod 5 times/week and vehicle 5 times/week groups only. Local skin reactions were more intense in the imiquimod groups compared with the vehicle groups. Erythema, oedema, vesicles, erosion and scabbing/crusting were all significantly higher in intensity in the imiquimod 7 times/week group compared with the 5 times/week group.

### Special warnings and precautions for use

- Imiquimod has not been evaluated for the treatment of basal cell carcinoma within 1 cm of the eyelids, nose, lips or hairline
  - No clinical experience exists in patients with recurrent and previously treated BCCs, therefore use for previously treated tumours is not recommended.
  - Imiquimod cream therapy is not recommended until the skin has healed after any previous drug or surgical treatment.
  - The skin surface area treated should be protected from solar exposure.
  - The use of an occlusive dressing is not recommended with imiquimod cream therapy
- In trials with 5 times per week dosing 58% of patients experienced at least one adverse event. The most frequently reported adverse events from the trials judged probably or possibly related to imiquimod cream are application site disorders, with a frequency of 28.1%. Some systemic adverse reactions, including back pain (1.1%) and influenza-like symptoms (0.5%) were reported by imiquimod cream patients.

### Table of Adverse events for Imiquimod 5% cream<sup>1</sup>

Incidence of Event	Adverse Event
<b>Very Common (≥1/10)</b>	Application site pruritus
<b>Common (≥1/100 to &lt;1/10)</b>	Infection, pustules, lymphadenopathy, back pain, application site pain, Application site burning, Application site irritation, Application site erythema, Application site bleeding, Application site papules, Application site paraesthesia, Application site rash
<b>Uncommon (≥1/1,000 to &lt;1/100)</b>	Irritability, nausea, dry mouth, dermatitis, Influenza-like illness, Application site discharge, Application site inflammation, Application site oedema, Application site scabbing, Application site skin breakdown, Application site swelling, Application site vesicles, Lethargy

### Fluorouracil (Efudix)

#### Special warnings and precautions for use

- Use of Efudix during pregnancy and in breast-feeding mothers is contraindicated.
- 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<sup>2</sup> (approximately 23 x 23 cm). Larger areas should be treated a section at a time.
- Occlusive dressing may increase inflammatory reactions of the skin.
- Exposure to UV-radiation (e.g. natural sunlight, tanning salon) should be avoided
- 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).
- 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/deficiency of the enzyme dihydropyrimidine dehydrogenase.

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 sometimes be more severe and include pain, blistering and ulceration. Occlusive dressing may increase inflammatory reactions of the skin.



**Table of Adverse events for Fluorouracil 5% cream<sup>2</sup>**

Incidence of Event	Adverse Event
<b>Very rare (&lt;1/10,000)</b>	Allergic conditions, 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, alopecia and skin pain, haematological disorders, associated with systemic drug toxicity, Diarrhoea haemorrhagic, diarrhoea, vomiting, abdominal pain, stomatitis, associated with systemic drug toxicity. Pyrexia, chills and mucosal inflammation, associated with systemic drug toxicity.
<b>Not known</b>	Dysgeusia, headache, dizziness, conjunctival irritation, keratitis, increased lacrimation, nausea

**Strengths and limitations of the evidence:****Imiquimod**

## Strengths:

- Large clinical studies have shown imiquimod's efficacy in the treatment of basal cell carcinoma
- Longer term studies up to 5 year's duration have shown that the drug maintained its effect
- A large clinical study has showed that 5% imiquimod cream was superior and 5-fluorouracil cream
- Although excisional surgery remains the best treatment for low-risk basal-cell carcinoma, imiquimod cream might still be a useful first treatment option for small low-risk superficial basal-cell carcinoma in the community, dependent on factors such as patient preference, size and site of the lesion, and whether the patient has more than one lesion.
- One study showed that imiquimod 5% was not inferior to methyl aminolevulinate photodynamic therapy (MAL-PDT) at 1 and 3 years after treatment

## Limitations:

- Despite demonstrating efficacy, clinical studies have shown imiquimod to be less effective than surgery
- A proportion of patients were lost to follow up in the long term study
- Cryotherapy was not considered as a comparator
- The treatment of basal cell carcinoma will require the development of GPs with extended responsibilities (previously GPs with special interests)

**Fluorouracil**

## Strengths:

- One large study showed that 5-fluorouracil use resulted in the probability of tumour-free survival of 70.0%
- A small, short term study showed a histologic cure rate was 90% and the mean time to clinical cure was 10.5 weeks

## Limitations:

- One large trial and a very small, limited trial provide the evidence for the drug's efficacy
- 5-fluorouracil, in the one comparative trial, was less effective than 5% imiquimod cream

## Prescribing and risk management issues:

GPs who manage low-risk basal cell carcinoma, including GPs with a special interest (GPwSI), need to maintain and audit records of their caseload. (NICE QS130 Skin Cancer)<sup>3</sup>

Doctors managing superficial BCC in the community should have experience and knowledge of this condition.<sup>8</sup>

## Commissioning considerations:

### Anticipated patient numbers and net budget impact

The non-melanoma skin cancer (age standardised) incidence rate per 100,000 population in the UK was 237.7 in 2015 (Cancer research UK).<sup>17</sup> In 2016, the population of Lancashire and South Cumbria was estimated at 1,735,000,<sup>18</sup> this would equate to a potential 4,124 patients.

## Associated additional costs or available discounts:

Not all patients are likely to be treated in Primary Care but for those who are, there will be the associated savings from no Secondary Care involvement i.e. no Out Patient appointment / surgery necessary. It may also be the patients preference to be treated in Primary Care by self-application of the cream.

However, if 4,124 patients were treated the costs would be:

- Imiquimod =  $4124 \times \text{£}121.50 = \text{£}501,066$
- Fluorouracil =  $4124 \times \text{£}65.80 = \text{£}271,359$  (2 tubes per patient)
- **Fluorouracil =  $4124 \times \text{£}32.90 = \text{£}135,680$  (1 tube per patient)**

If 50% of potential patients were treated the associated costs would be:

- Imiquimod =  $2062 \times \text{£}121.5 = \text{£}250,533$
- Fluorouracil =  $2062 \times \text{£}65.80 = \text{£}135,680$  (2 tubes per patient)
- **Fluorouracil =  $2062 \times \text{£}32.90 = \text{£}67,840$  (1 tube per patient)**

The cost effectiveness of treatment with surgery and imiquimod 5% cream was studied by a Spanish group which showed that imiquimod cream is a cost effective alternative to excision surgery in patient with sBCC.<sup>19</sup>

## Productivity, service delivery, implementation:

GPs who manage low-risk basal cell carcinoma, including GPs with a special interest (GPwSI), need to maintain and audit records of their caseload (NICE QS130 Skin Cancer).<sup>3</sup>

Doctors managing superficial BCC in the community should have experience and knowledge of this condition.<sup>8</sup>

## Innovation, need, equity:

Imiquimod 5% cream (Aldara) would allow for the treatment of small superficial basal cell carcinomas in the community, under the care of a GP with experience and knowledge of this condition. It would avoid the need for secondary care involvement i.e. surgery and it may be the preferred option of the patient.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
<b>Level 1</b>	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%)
<b>Level 2</b>	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	
<b>Level 3</b>	Disease-oriented evidence, or evidence from: consensus guidelines expert opinion case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

Midlands and Lancashire Commissioning Support Unit, 2018. The information contained herein may be superseded in due course. All rights reserved.

Produced for use by the NHS, no reproduction by or for commercial organisations, or for commercial purposes, is allowed without express written permission.

Midlands and Lancashire Commissioning Support Unit,  
Jubilee House, Lancashire Business Park, Leyland, PR26 6TR

## References

- 
- <sup>1</sup> SPC for Aldara 5% Cream.  
<https://www.medicines.org.uk/emc/product/823/smpc#INDICATIONS>
  - <sup>2</sup> SPC for Efudix Cream.  
[https://www.medicines.org.uk/emc/product/1400#PHARMACOLOGICAL\\_PROPS](https://www.medicines.org.uk/emc/product/1400#PHARMACOLOGICAL_PROPS)
  - <sup>3</sup> NHSBSA Drug Tariff online May 2018: <https://www.nhsbsa.nhs.uk/sites/default/files/2018-04/Drug%20Tariff%20May%202018.pdf>
  - <sup>4</sup> Skin cancer NICE Quality standard [QS130] Published date: September 2016  
<https://www.nice.org.uk/guidance/qs130>
  - <sup>5</sup> NICE Pathway Published March 2014 Last updated April 2018  
<https://pathways.nice.org.uk/pathways/skin-cancer>
  - <sup>6</sup> SMC 167/05 Imiquimod 5% cream (Aldara®) for the topical treatment of small superficial Basal Cell Carcinoma <https://www.scottishmedicines.org.uk/medicines-advice/imiquimod-5-cream-aldara-fullsubmission-16705/>
  - <sup>7</sup> Guidelines for the management of basal cell carcinoma N.R. Telfer, G.B. Colver and C.A. Morton. British Journal of Dermatology 2008 159, pp35–48
  - <sup>8</sup> Guideline on the Treatment of Basal Cell Carcinoma, European Dermatology Forum  
[https://www.researchgate.net/publication/261605274\\_Update\\_of\\_the\\_European\\_guidelines\\_for\\_basal\\_cell\\_carcinoma\\_management\\_Developed\\_by\\_the\\_Guideline\\_Subcommittee\\_of\\_the\\_European\\_Dermatology\\_Forum](https://www.researchgate.net/publication/261605274_Update_of_the_European_guidelines_for_basal_cell_carcinoma_management_Developed_by_the_Guideline_Subcommittee_of_the_European_Dermatology_Forum)
  - <sup>9</sup> National Institute for Health and Clinical Excellence Guidance on cancer services Improving outcomes for people with skin tumours including melanoma (update).The management of low-risk basal cell carcinomas in the community. May 2010.
  - <sup>10</sup> NICE Cancer service guideline [CSG8] Improving outcomes for people with skin tumours including melanoma. <https://www.nice.org.uk/guidance/csq8>
  - <sup>11</sup> Surgical excision versus imiquimod 5% cream for nodular and superficial basal-cell carcinoma (SINS): a multicentre, non-inferiority, randomised controlled trial. Fiona Bath-Hextall et al. Lancet Oncol 2014; 15: 96–105
  - <sup>12</sup> Surgery Versus 5% Imiquimod for Nodular and Superficial Basal Cell Carcinoma: 5-Year Results of the SINS Randomized Controlled Trial. Hywel C. Williams et al. Journal of Investigative Dermatology (2017) 137, 614-619
  - <sup>13</sup> Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies. John Geisse et al. Journal of the American Academy of Dermatology Volume 50, Issue 5, May 2004, Pages 722-733
  - <sup>14</sup> Five-Year Results of a Randomized Controlled Trial Comparing Effectiveness of Photodynamic Therapy, Topical Imiquimod, and Topical 5-Fluorouracil in Patients with Superficial Basal Cell Carcinoma. Maud H.E. Jansen et al. Journal of Investigative Dermatology (2018) 138, 527- 533
  - <sup>15</sup> Interventions for basal cell carcinoma of the skin. Cochrane Database of Systematic Reviews 2007. Bath-Hextall FJ et al. Issue 1. Art. No.: CD003412.

<sup>16</sup> 5% 5-Fluorouracil Cream for the Treatment of Small Superficial Basal Cell Carcinoma: Efficacy, Tolerability, Cosmetic Outcome, and Patient Satisfaction. K.Gross et al. Dermatologic Surgery. 33(4):433–440, APR 2007

<sup>17</sup> Non-Melanoma Skin Cancer (C44), Number of New Cases, Crude and European Age-Standardised (AS) Incidence Rates per 100,000 Population, UK, 2015  
<http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/skin-cancer/incidence#heading-Ten>

<sup>18</sup> NHS England, STP footprint analysis pack Lancashire and South Cumbria, Five Year Forward View 2016. [http://allcatsrgrey.org.uk/wp/download/governance/integrated\\_care/457-1617-SCH-HSC-STP-Analysis-Lancashire-and-South-Cumbria.pdf](http://allcatsrgrey.org.uk/wp/download/governance/integrated_care/457-1617-SCH-HSC-STP-Analysis-Lancashire-and-South-Cumbria.pdf)

<sup>19</sup> Vanalocha F, Dauden E, Badia X, Guillen C, Conejo Mir J, Sainz de los Terreros M, Hamel L, Llorens M Cost-effectiveness of treatment of superficial basal cell carcinoma: surgical excision vs. imiquimod 5% cream.Br J Dermatol. 2007 Apr;156(4):769-71.