

Imiquimod cream (Aldara) for superficial basal cell carcinoma

(ih-MIH-kwih-mod)

Summary

- Imiquimod is an immune response modifier PBS-subsidised for treating biopsy-confirmed superficial basal cell carcinoma (BCC).
- Surgical excision remains first-line treatment for superficial BCC — it has a higher cure rate than imiquimod and allows histological assessment of tumour clearance.
- Imiquimod is not indicated for recurrent, invasive or nodular BCC. Do not use imiquimod on tumours that extend to within 1 cm of the hairline, eyes, ears, nose or lips.
- Local skin reactions are common with imiquimod and may be uncomfortable. Patients should rest from treatment for a few days if the skin reaction is severe.
- Patients need to follow the dosing regimen for a total of 6 weeks (including any rests from treatment).

PBS listing

Authority required

Treatment of superficial basal cell carcinoma (BCC) in immunocompetent patients who cannot have surgical excision, cryotherapy, or curettage with diathermy. The lesion must be previously untreated and the diagnosis confirmed by biopsy, and the patient or carer must be able to follow the dosing regimen.¹

The maximum quantity is 1 pack of 12 sachets with 1 repeat.

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing on the basis that, for people with superficial BCC who cannot have surgical excision, cryotherapy or curettage, the cost per successful treatment with imiquimod is acceptable compared with non-intervention monitoring.²

The PBAC considered that imiquimod should not be first-line treatment for superficial BCC, as surgical excision is more effective. They noted that there are no absolute contraindications to surgical excision, cryotherapy or

curettage, making the choice of therapy a matter of clinical judgment. The PBAC considered that there would be a place for imiquimod in treating patients with frequent multiple primary lesions when access to surgery is difficult.²

When the PBAC assessed imiquimod previously, they agreed that, while there is no direct comparative evidence that imiquimod is less effective than surgical excision, this was probably a reasonable conclusion. The PBAC was concerned that imiquimod might be used instead of surgery primarily for convenience or because a better cosmetic result was desired.³

Place in therapy

Imiquimod is an immune response modifier and is PBS-subsidised for primary treatment of biopsy-confirmed superficial BCCs. It is also used to treat solar keratoses on the face and scalp, and genital and perianal warts, although these indications are not PBS listed and the treatment schedules are different. Surgical excision remains first-line therapy for superficial BCC, as imiquimod is associated with a lower cure rate. Imiquimod may be useful when surgery is contraindicated, for patients who are willing and able to follow the 6-week course of therapy and tolerate possible adverse skin reactions.

Use imiquimod only on suitable lesions

Diagnosis of superficial BCC should be confirmed by biopsy before treatment is started. Do not use imiquimod on recurrent, nodular, invasive or infiltrating BCCs or on other non-superficial histological subtypes.⁴ The efficacy of imiquimod cream has not been adequately established for nodular BCC⁴ and no trial data exist for other types. Treating these types of lesions risks residual or recurrent disease that, with aggressive tumours, could present late with involvement of deeper structures.

Do not use imiquimod on tumours that extend to within 1 cm of the scalp, hairline, eyebrows, eyes, ears, nose or lips. Tumours in these areas are less likely to be purely superficial and there is a greater risk of hard-to-manage recurrence. In clinical trials tumours in these locations were not eligible for imiquimod treatment.⁴ Overall there are few trial data about treating superficial BCC on the face with imiquimod cream (in the US imiquimod is not indicated for any superficial BCC on the face⁵).

Information about treating large tumours with imiquimod is limited, but cure rates appear to decrease as tumour size increases. In one small trial the clearance rate was 65% (95% CI 38% to 86%) when the tumour size was > 7.25 cm², but 90% (95% CI 78% to 97%) for smaller tumours.^{4,6} In the UK imiquimod is licensed for use on superficial BCCs < 7.25 cm² (e.g. circular BCCs < 3 cm diameter).⁷ Larger tumours are more likely to be of mixed type and may require referral for specialist management.⁸

Choose imiquimod only for patients who will use it correctly

Unlike other common treatments for superficial BCC, success of imiquimod therapy depends on the willingness and ability of the patient or carer to follow the treatment regimen for the required 6-week period. This includes carefully applying the cream to the treatment area daily before bed, and washing it off with soap and water in the morning (see Information for patients, page 17). Lesions that are out of sight (e.g. on the back or neck) may present a difficulty if the patient has no assistance in applying the cream. Patients may be more likely to discontinue prematurely if they are unwilling to tolerate uncomfortable skin reactions.

Surgical excision is the standard treatment for superficial BCC

Excisional surgery is the standard method for managing non-melanoma skin cancer.^{8,9} Compared with non-surgical methods, surgery has the advantage that it provides a complete specimen to confirm the diagnosis and adequacy of excision.⁸ The 5-year cumulative recurrence rate of primary basal cell carcinoma (across all types) after surgical excision is estimated to be about 5%¹⁰, although the actual rate may be higher or lower, depending on the skill of the surgeon.

Imiquimod appears to be less effective than surgical excision

In 2 key, randomised controlled trials the pooled clearance rate with imiquimod therapy was 82% (95% CI 76% to 87%), assessed by completely excising the treatment site at 12 weeks post treatment and evaluating it histologically.¹¹ Other trials have shown similar short-term clearance rates.^{6,12} In an ongoing open-label trial the estimated clinical clearance rate with imiquimod, based on 3 years' follow-up, was 81% (95% CI 75% to 86%).^{7,13} The rate of recurrence beyond 3 years is unknown. While there are no trials directly comparing imiquimod with surgical excision, imiquimod appears less effective than excision.

Imiquimod may be useful when other methods pose unacceptable risks

Surgical excision may have particular disadvantages for people who:

- are liable to form keloid scars
- are receiving warfarin therapy
- are at increased risk of wound infection (e.g. with lesions below the knee)
- require specialist surgery but can access a surgeon only with difficulty
- have multiple lesions and would need repeated treatment.^{8,14-16}

Cryotherapy (using repeated freeze–thaw cycles) or serial curettage and ablation (cautery or cryotherapy) may be useful alternatives to surgical excision (see Table 1). If cryotherapy and curettage are unsuitable, or a doctor with the necessary training in their use in BCC is unavailable, imiquimod may be the preferred treatment.

Table 1: Comparison of common treatments for superficial BCC^{7,8,10,15,17}

	Imiquimod	Surgical excision	Cryotherapy	Curettage
Recurrence rate*	20%	5%	~10%	~10%
Scarring	Possible	Less than with cryotherapy or curettage	Yes	Yes
Risk of keloid	Unlikely	Yes	Unlikely	Some
Pigmentation change	Yes	No	Yes	Yes
Bleeding risk	No†	Yes	No†,‡	Managed by cautery
Patient involvement	Daily application of cream	Minimal	Minimal	Minimal
Use in facial tumours	Not near hairline, eyes, ears, nose or lips	May require specialist	Not for lips, facial creases	Requires specialist

* For imiquimod, the proportion of cases not clear at 3 years of follow-up; for other treatments, 5-year cumulative recurrence rate.

† Biopsy is mandatory and entails some bleeding risk

‡ Will ooze haemoserous fluid for 4–6 weeks in patients receiving warfarin therapy

There are no specific data regarding the safety or efficacy of imiquimod when other methods of treatment are contraindicated.

Follow up 12 weeks after treatment finishes

Assess the success of imiquimod therapy at least 6 weeks after completion⁴; 12 weeks is recommended, as residual inflammation may persist beyond 6 weeks and make clinical assessment difficult.¹¹ Further follow-up at 12 months and 24 months is recommended.

Biopsy should be performed if there is any doubt that the tumour has cleared. When a patient with multiple tumours is treated, one tumour clearing does not indicate that all tumours will respond.¹² Recurrent or persistent tumours will need to be excised surgically, as imiquimod is only indicated for primary tumours.

In general, there are no data to guide the need for ongoing follow-up after the treatment of primary non-melanoma skin cancer.⁸ In the single long-term study of imiquimod therapy for superficial BCC, over the ensuing 2 years tumours recurred in 12 of 165 patients (7%) who were assessed as clear at 12 weeks after the end of imiquimod treatment.¹³ People who have been treated for non-melanoma skin cancer are at increased risk for further skin cancers.⁸

Safety issues

Imiquimod causes strong local inflammation in more than 50% of patients, so patients usually need one or more breaks in therapy. Systemic adverse reactions may occur — typically influenza-like symptoms or exacerbations of inflammatory skin conditions such as eczema or psoriasis.

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online (see www.tgasime.health.gov.au) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse drug reactions, see the Therapeutic Goods Administration website (www.tga.gov.au).

Local skin reactions are common and may be uncomfortable

Local skin reactions such as oedema, erosion, redness, flaking/scaling, thickening/hardening, and scabbing/crusting occurred in more than 50% of people using imiquimod in clinical trials; about 1% of patients experienced an infection at the application site.⁴ Individual response varies and a reaction may occur at any time during treatment.¹³ Local skin irritation was also common, with 16% experiencing itching, 7% burning and 3% pain.⁴

The manufacturer recommends a rest from therapy for several days if any skin reaction or associated discomfort becomes severe (see Patients should take a rest from treatment if the skin reaction is severe). In one trial a typical rest period began 4 weeks after starting imiquimod and lasted for 1 week, followed by 1 final week of treatment.¹¹ In the same trial 5% of participants discontinued imiquimod (for any reason) before completing 6 weeks' treatment and did not resume therapy.

Local inflammation appears to be inherent to the tumour-clearing activity of imiquimod. Trials have found that histological clearance was higher in patients with moderate to severe local skin reactions, compared with those who experience no or mild skin reactions.⁴

There have been reports of hyper- and hypopigmentation of areas treated with imiquimod.⁴ Some of these skin colour changes may be permanent.⁴ In one trial in which patients used imiquimod 3 times a week for up to 12 weeks, 30% of patients had hyper- or hypopigmentation 6 months after discontinuing treatment.¹⁸

Imiquimod may sometimes cause influenza-like symptoms

Case reports and some clinical trials have detailed probable systemic reactions to imiquimod therapy — typically fatigue, headache and influenza-like illness.^{19–22} Postmarketing adverse event reports also include influenza-like symptoms and headache, with a frequency of < 1/1000.⁴ Systemic symptoms reported in 1 randomised controlled trial, without regard to cause, included headache in 8% of participants, lymphadenopathy in 2%, fatigue in 2%, and fever in 2%.⁴

Imiquimod may exacerbate inflammatory skin conditions

There have been cases in which imiquimod appears to have caused generalised exacerbations of existing stable psoriasis²³ or eczema²⁴, or in other cases, localised skin eruptions.^{25,26}

Dosing issues

Imiquimod has a different dosing regimen from that of typical creams and may be less convenient to use. It must be washed off 8 hours or so after it is applied, and breaks in dosing are often required. It should be applied 5 days per week for 6 weeks, with a rest of 1 week or

more during therapy if the local skin reaction is severe or intolerable. Do not apply imiquimod to skin that has not yet healed from previous procedures.⁴

Schedule a review during treatment

Reviewing treatment (e.g. after 1–4 weeks) may help the patient to adhere to therapy, allow for secondary treatment of any emergent adverse effects, and help manage any required rest from therapy. Early review (after 1–2 weeks) gives an opportunity to reassure patients that any skin reaction they are experiencing is in line with expectations, and may prevent premature discontinuations.

Patients should take a rest from treatment if the skin reaction is severe

A rest from imiquimod for several days is recommended if the local skin reaction is severe, e.g. painful ulceration with significant exudate or thick crusting with significant discomfort. Treatment may resume after the reaction subsides. In clinical trials 10–20% of patients took a rest, typically for about 1 week.^{11,13} The manufacturer advises that the proportion of patients taking rest periods is higher in clinical practice.²⁷ If a rest is taken, it is not necessary to make up any missed doses or to prolong therapy. The maximum PBS quantity of 2 packs, each of 12 sachets, implies that all patients will take a rest of a minimum of 1 week during the 6-week course. If a rest is not needed, treatment will stop when all 24 sachets have been used.

The manufacturer recommends against using 1 sachet for multiple doses

The manufacturer states that imiquimod sachets must be used on the day they are opened.⁴ The contents of a sachet are sufficient to cover roughly 150–200 cm² of skin, well in excess of what is likely to be required for a single dose, even when treating multiple lesions.²⁸ If sachets are reused the manufacturer does not guarantee the safety and efficacy of the product, as there are no data on the stability or sterility of opened sachets.²⁷

Information for patients

Instruct patients on how to use imiquimod cream correctly (see Box 1, page 18). The package insert includes illustrated instructions on how to apply it. For more detailed information about imiquimod, suggest or provide the Aldara consumer medicine information (CMI) leaflet, available at www.3m.com/intl/au/healthcare/Aldara/Aldara_CMI_vs9_Tear-off_Pad.pdf

Box 1. How to use imiquimod cream for superficial BCC

- Apply once a day at bedtime from Monday to Friday, with a break on Saturday and Sunday.
- Before applying, wash hands and the treatment area with soap and water and dry thoroughly.
- Squeeze a small amount of Aldara cream onto a fingertip. An amount the size of a pinhead is enough for a 0.5 cm tumour (one sachet can cover an area the size of the palm and fingers of one hand).
- Apply the cream to the tumour and about 1 cm of the surrounding skin (the width of a fingertip).
- Rub gently until the cream is absorbed.
- Wash your hands with soap and water.
- In the morning, wash the cream off with soap and water, after it has been on for 6–10 hours.

Schedule an appointment for review during treatment and discuss how to manage a rest from treatment.

Inform patients that:

- imiquimod cream should only be applied to the tumour(s) for which it is prescribed. It should not be applied in or near the hairline, eyes, ears, nose or lips
- imiquimod is less effective than removal by surgical excision and there is a 1 in 5 chance that a tumour will not clear or will return

- a local skin reaction is expected and, if severe, a rest from treatment is needed. If the skin becomes infected, or severely painful or irritated, wash the treatment area with soap and water and contact your doctor
- headache, fever, tiredness and influenza-like symptoms can occur. These are generally mild and may be treated with paracetamol, but if they are troublesome, stop applying imiquimod cream and contact your doctor
- areas treated with imiquimod may end up permanently lighter or darker in colour than the surrounding skin
- areas treated with imiquimod need to be protected from sunlight or sunlamps with clothing or a hat for the 6 weeks that the cream is used
- areas treated with imiquimod should not be covered with bandages or other dressings. Cotton gauze dressings may be used if needed (e.g. if the skin is oozing)
- treatment must continue either for 6 weeks or until two boxes of sachets have been used — whichever comes first
- missed doses should not be caught up, e.g. if a break is needed
- open sachets containing the unused portion of cream should be disposed of where children cannot reach them.^{4,29,30}

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.