



New Zealand Data Sheet

APO-IMIQUIMOD

Imiquimod 5% w/w cream

Presentation

APO-IMIQUIMOD is a white cream with a uniform appearance. Each sachet contains 250 mg of cream for use as a single application.

Uses

Actions

Imiquimod is an immune response modifier and its mechanism of action is believed to be secondary to local cytokine induction in the skin. In animal models imiquimod is an effective antiviral and antitumour agent. Imiquimod is not a nucleoside analogue and its activity is principally due to induction of alpha interferon but other cytokines are also involved. Saturable binding studies suggest a membrane receptor for imiquimod exists on responding cells. Binding kinetics indicate a high and low affinity binding site. When imiquimod cream is applied topically to the back of mice, mRNA for alpha interferon and increased protein levels of interferon and tumour necrosis factor alpha are detected in the skin.

Several studies were conducted to determine the effects of topical imiquimod application to the skin of healthy subjects. The results showed that imiquimod cream had minimal photo-irritation, phototoxicity, photo-allergenicity, cumulative irritation or contact sensitization potential.

Actinic Keratosis

The mechanism of action of APO-IMIQUIMOD cream in treating actinic keratosis (AK) lesions is unknown. Systemic exposure to imiquimod has been evaluated in actinic keratosis patients following topical application of 12.5mg (one sachet) of ALDARA cream to facial lesions, 25mg (two sachets) of imiquimod cream to scalp lesions, or 75mg (six sachets) of imiquimod cream to lesions on both hands and arms three times per week for 16 weeks. Levels of biomarkers sensitive to imiquimod increased up to approximately 10 fold over baseline after 16 weeks of dosing. These included interleukin-1 receptor antagonist, interferon-alpha and 2'5'-oligoadenylate synthetase. The increases in biomarkers were not associated with evidence of any systemic or clinically meaningful adverse events. No meaningful correlation between pharmacokinetic parameters (C_{max} and AUC) of imiquimod and these biomarkers was observed.

Superficial Basal Cell Carcinoma

The mechanism of action of APO-IMIQUIMOD cream in treating superficial basal cell carcinoma (sBCC) lesions is unknown. However, clinical observations are consistent with a mechanism of action that involves the stimulation of a local immune-mediated response at the site of application that is similar to classic cell-mediated immune reactions in the skin. Two clinical studies have shown that imiquimod stimulates the infiltration of tumour-destructive cells (T-cell lymphocytes, dendritic cells and macrophages) into the basal cell carcinoma lesion and reduces the defence mechanisms of the tumour.

Nodular Basal Cell Carcinoma

A randomised, open-label, multi-centre, dose-response study was conducted in Australia and New Zealand to evaluate the safety and efficacy of imiquimod cream for the treatment of nodular basal cell carcinoma (nBCC). Patients with biopsy-confirmed nBCC were enrolled and randomised to one of four treatment arms: once daily 3 days per week (3x/week); twice daily 3 days per week (6x/week); once daily 7 days per week (7x/week); and twice daily 7 days per week (14x/week) for 6 weeks. Six weeks after the treatment period the target tumour was excised and examined histologically for the presence of tumour. Following six weeks treatment the once daily 7 days per week treatment group had the highest histological clearance rate (71%) with an

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acceptable safety profile. Dose response was not evident in this study. The efficacy of imiquimod in patients with nBCC needs to be confirmed in larger clinical trials.

External Genital / Perianal Warts

Imiquimod has no direct antiviral activity in cell culture. Imiquimod applied topically to external genital warts induces mRNA encoding cytokines including interferon alpha at the treatment site. In addition HPVL 1 mRNA and HPV DNA are significantly decreased following treatment. However, the clinical relevance of these findings is unknown.

Pharmacokinetics

Percutaneous absorption of imiquimod following topical administration of imiquimod cream has been studied over a wide spectrum of skin types, from the keratinised skin of genital warts to intact healthy skin to the lesions of sun damaged skin. The results should also encompass the likely pharmacokinetics of imiquimod across the affected skin of patients with sBCC. The percutaneous penetration of imiquimod following topical application of imiquimod for 8-12 hours was minimal (<1%) across the intact skin of healthy subjects and the affected skin of subjects with either genital warts or actinic keratosis. Because of this low percutaneous absorption, serum levels of imiquimod and its metabolites were low or undetectable in these subjects. These low imiquimod serum levels indicate that the topical use of imiquimod cream in patients with actinic keratosis or superficial basal cell carcinoma should not pose any systemic safety concern.

In subjects with intact healthy skin, less than 0.9% of a single topically applied 5mg dose of [C^{14}] labelled imiquimod cream was recovered in the urine and faeces. Radioactive imiquimod levels could not be quantified in the serum of these subjects. In patients with genital/perianal warts treated with imiquimod cream three times per week for 16 weeks median imiquimod peak serum concentrations of approximately 0.1 to 0.3 ng/mL were observed during the study. Median urinary recoveries of imiquimod and its metabolites following the last dose of week 16 were approximately 0.09% and 1.2% of the dose for males and females respectively, indicating only minimal systemic absorption of imiquimod. Similarly, in patients with actinic keratosis only minimal systemic absorption of imiquimod across the affected skin was observed when imiquimod was applied three times per week for 16 weeks. At the end of week 16, urinary recovery of imiquimod and its metabolites of less than 0.6% of the applied dose was observed in these patients. Peak serum imiquimod concentrations were observed between 9 and 12 hours and were approximately 0.1, 0.2 and 1.6 ng/mL for the applications to face (12.5mg imiquimod, 1 sachet), scalp (25mg, 2 sachets) and hands/arms (75mg, 6 sachets) respectively. An apparent terminal half-life of imiquimod was approximately 10 times greater than the 2 hour half-life seen following subcutaneous dosing, suggesting prolonged retention of imiquimod in the skin for greater than 24 hours after the cream is removed.

Indications

APO-IMIQUIMOD cream is indicated for the topical treatment of:

- actinic keratosis on the face and scalp in immunocompetent adults.
- superficial basal cell carcinoma where surgical excision is considered inappropriate.
- external genital and perianal warts (condyloma acuminata).

Dosage and Administration

Before applying APO-IMIQUIMOD cream, the patient should wash the treatment area with mild soap and water, and allow the area to dry thoroughly. APO-IMIQUIMOD cream should be applied prior to normal sleeping hours and should remain on the skin for 8 (6-10) hours.

APO-IMIQUIMOD should be applied with the fingertip and rubbed into the affected area until the cream vanishes. Showering or bathing during the period that the cream is on the affected area should be avoided. The affected area should be washed with soap and water after the treatment

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period. Cream in a single use sachet is sufficient to cover a treatment area of 20 cm² and should not be reused after opening.

Hand washing before and after cream application is recommended.

Where APO-IMIQUIMOD is used to treat genital/perianal warts, the cream should be applied after, rather than before, sexual activity.

Local skin reactions such as erythema, erosion, excoriation/flaking and oedema at the treatment site area are common. These reactions may be due to the pharmacological response of the body's immune system to APO-IMIQUIMOD. A rest period of several days may be taken if required due to the patient's discomfort or severity of the local skin reaction. These local skin reactions generally decrease in intensity or resolve after APO-IMIQUIMOD therapy ceases. Treatment may resume once the reaction subsides. Any rest periods taken by patients in the clinical studies were considered part of the treatment period. The treatment period was not extended to make up for rest periods or missed doses.

The dosing frequency of APO-IMIQUIMOD is different for each indication.

Actinic Keratosis

Treatment should be initiated and monitored by a physician. Imiquimod cream should be applied 3 times per week (example: Monday, Wednesday and Friday) for four weeks prior to normal sleeping hours, and left on the skin for approximately 8 hours. Sufficient cream should be applied to cover the treatment area. After a 4-week treatment-free period, clearance of AKs should be assessed. If any lesions persist, treatment should be repeated for another four weeks.

The maximum recommended dose is one sachet. The maximum recommended treatment duration is 8 weeks.

An interruption of dosing should be considered if intense local inflammatory reactions occur (see Precautions) or if infection is observed at the treatment site. In this latter case, appropriate other measures should be taken. Each treatment period should not be extended beyond 4 weeks due to missed doses or rest periods.

If the treated lesion(s) show an incomplete response at the follow-up examination at 4-8 weeks after the second treatment period, a different therapy should be used

Superficial Basal Cell Carcinoma

APO-IMIQUIMOD cream is to be applied once daily for five consecutive days per week and treatment should continue for 6 weeks. Sufficient cream should be applied to cover the treatment area, including one centimetre of skin surrounding the tumour.

The clinical outcome of therapy can be determined after regeneration of the treated skin, approximately 6 to 12 weeks after the end of treatment. At this time the skin may appear different from the non-affected surrounding skin, including an increase in hypopigmentation and a decrease in the degree of rough/dry/scaly skin surface. These changes may be secondary to the appearance of the treated healing target tumour area, contrasting with the surrounding sun damaged skin.

External Genital / Perianal Warts

Adult male and female patients self-administer APO-IMIQUIMOD cream by applying to external warts once a day, 3 times per week (every other day followed by a 2 day treatment-free interval). Treatment should be applied until wart clearance is achieved or up to a maximum of 16 weeks.

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Contraindications

APO-IMIQUIMOD cream is contraindicated in patients with hypersensitivity to imiquimod or cream excipients.

Warnings and Precautions

General

Avoid contact with the eyes, lips and nostrils.

Local reactions such as erythema, erosion, excoriation/flaking and oedema are common. Other local reactions such as induration, ulceration, scabbing, and vesicles have also been reported. Most skin reactions are mild to moderate. These reactions are believed to result from the pharmacological response of the body's immune system to imiquimod. Should an intolerable skin reaction occur, the cream should be removed by washing the area with mild soap and water. These local skin reactions generally decrease in intensity or resolve after cessation of APO-IMIQUIMOD cream therapy. Treatment with APO-IMIQUIMOD can be resumed after the skin reaction has moderated. Any rest periods taken by patients in the clinical studies were considered to be part of the treatment period. The treatment period was not extended to make up for rest periods or missed doses. The use of an occlusive dressing is not recommended with APO-IMIQUIMOD. Higher than recommended doses may lead to increased local skin reactions.

Rarely, intense local inflammatory reactions including skin weeping or erosion can occur after only a few applications of APO-IMIQUIMOD cream. Local inflammatory reactions may be accompanied, or even preceded, by flu-like systemic signs and symptoms, including malaise, pyrexia, nausea, myalgias and rigors. An interruption of dosing should be considered.

There is limited clinical experience with imiquimod therapy immediately following treatment of skin conditions with other cutaneously applied therapies or procedures. APO-IMIQUIMOD therapy is therefore not recommended for such patients until the skin has healed. Application to broken skin could result in increased systemic absorption leading to a greater risk of adverse events.

APO-IMIQUIMOD, as an immune response modifier, has the potential to exacerbate inflammatory conditions of the skin, including chronic graft versus host disease.

APO-IMIQUIMOD should be used with caution in organ transplant patients and in patients with pre-existing autoimmune conditions (see *Interactions*). In these patients consideration should be given to balancing the benefit of treatment with APO-IMIQUIMOD with the risk associated with the possibility of organ rejection or graft versus host disease, or a possible worsening of the autoimmune condition.

APO-IMIQUIMOD cream should be used with caution in patients with reduced haematological reserve.

The excipients methyl hydroxybenzoate, propyl hydroxybenzoate, cetyl alcohol and stearyl alcohol may cause allergic reactions.

Actinic Keratosis

Lesions clinically atypical for AK or suspicious for malignancy should be biopsied to determine appropriate treatment.

APO-IMIQUIMOD has not been evaluated for the treatment of actinic keratoses on the eyelids, the inside of the nostrils or ears, or the lip area inside the vermilion border.

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There is very limited data available on the use of imiquimod for the treatment of actinic keratoses in anatomical locations other than on the face and scalp. The available data on actinic keratosis on the forearms and hands do not support efficacy in this indication and, therefore, such use is not recommended.

APO-IMIQUIMOD cream is not recommended for the treatment of AK lesions with marked hyperkeratosis or hypertrophy as seen in cutaneous horns.

During therapy and until healed, affected skin is likely to appear noticeably different from normal skin. Local skin reactions are common but these reactions generally decrease in intensity during therapy or resolve after cessation of imiquimod cream therapy. There is an association between the complete clearance rate and the intensity of local skin reactions (e.g. erythema). These local skin reactions may be related to the stimulation of local immune response. If required by the patient's discomfort or the intensity of the local skin reaction, a rest period of several days may be taken. Treatment with imiquimod cream can be resumed after the skin reaction has moderated. Each treatment period should not be extended beyond 4 weeks due to missed doses or rest periods.

The clinical outcome of therapy can be determined after regeneration of the treated skin, approximately 4-8 weeks after the end of treatment.

No clinical experience exists with the use of APO-IMIQUIMOD cream in immuno-compromised patients.

No data are available on re-treating actinic keratoses that have cleared after one or two courses of treatment and subsequently recur, and any such use is therefore not recommended.

The safety and efficacy of APO-IMIQUIMOD cream in the re-treatment of residual solar keratoses has not been established. There is limited data of imiquimod cream on recurrence of SK (see *Clinical Studies*). No data is available on re-treating actinic keratoses that have cleared after one or two courses of treatment and subsequently recur, and any such use is therefore not recommended.

Exposure to natural or artificial sunlight should be avoided or minimised during use of APO-IMIQUIMOD cream.

Superficial Basal Cell Carcinoma

APO-IMIQUIMOD cream has not been evaluated for the treatment of sBCC within 1cm of the hairline, eyes, nose, mouth or ears.

During therapy and until healed, affected skin is likely to appear noticeably different from normal skin. Local skin reactions are common but these reactions generally decrease in intensity during therapy or resolve after cessation of imiquimod cream therapy. There is an association between the complete clearance rate and the intensity of local skin reactions (e.g. erythema). These local skin reactions may be related to the stimulation of local immune response. If required by the patient's discomfort or the intensity of the local skin reaction, a rest period of several days may be taken. Treatment with imiquimod cream can be resumed after the skin reaction has moderated.

The clinical outcome of therapy can be determined after regeneration of the treated skin, approximately 12 weeks after the end of treatment.

No clinical experience exists with the use of APO-IMIQUIMOD cream in immuno-compromised patients.

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No clinical experience exists in patients with recurrent and previously treated BCCs, therefore use for previously treated tumours is not recommended.

Data from an open label clinical trial suggest that large tumours (>7.25 cm²) are less likely to respond to imiquimod therapy.

The skin surface area treated should be protected from solar exposure.

External Genital / Perianal Warts

APO-IMIQUIMOD cream has not been evaluated for the treatment of internal genital warts and should not be used to treat urethral, intra-vaginal, cervical, rectal or intra-anal warts.

The effect of APO-IMIQUIMOD on the transmission of genital/perianal warts is unknown. Apo-IMIQUIMOD may weaken condoms and vaginal diaphragms. Therefore, concurrent use is not recommended. Alternate forms of contraception should be considered.

APO-IMIQUIMOD cream should be washed from the skin before sexual activity.

Uncircumcised males with warts under the foreskin should retract the foreskin and clean the area daily as foreskin tightness and stricturing have been reported with the administration of imiquimod cream. Early signs of stricture may include local skin reactions (e.g. erosion, ulceration, oedema, induration), or increasing difficulty in retracting the foreskin. If these symptoms occur, the treatment should be stopped immediately.

Special care should be taken if applying APO-IMIQUIMOD at the opening of the vagina, as local skin reactions on the mucosal surfaces can result in pain or swelling, and may cause difficulty in passing urine. This may sometimes require emergency catheterisation and treatment of the affected area.

Imiquimod cream has been applied to traumatised genital skin following wart ablation by electrocautery or cryotherapy in two pilot trials. Wound healing was not prolonged for these patients. No clinical experience exists with imiquimod cream immediately following treatment with other cutaneously applied drugs for treatment of external genital or perianal warts.

In immunocompromised patients, repeat treatment with APO-IMIQUIMOD cream is not recommended.

While limited data has shown an increased rate of wart reduction in HIV positive patients, imiquimod cream has not been shown to be as effective in terms of wart clearance in this patient group.

Toxicology

Two year bio-studies in Wistar rats (up to 3 mg/kg orally per day) and CD-1 mice (up to 4.5 mg/kg applied topically 3 times per week) showed no evidence of a carcinogenic effect in male and female rats and female mice. Liver tumours were increased in male mice exposed to the highest dose concentration, compared to the unexposed controls. However, the number of tumours was within the range seen historically for male CD-1 mice. It is generally accepted that an increase in liver tumours in male mice, in the absence of other neoplastic responses in mice or rats, is not indicative of a carcinogenic risk for humans.

Imiquimod cream was evaluated in a photocarcinogenicity bioassay in albino hairless mice exposed to simulated solar ultraviolet radiation (UVR). Animals were administered either vehicle or imiquimod cream (0.03%, 0.1% or 0.3%) topically 3x/week and were irradiated once daily, 5 days per week (600 RBU/week) for 40 weeks. Mice were maintained for an additional 12 weeks for a total of 52 weeks. Tumours occurred earlier and in greater number in the group of mice

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administered the vehicle cream in comparison with the untreated control group exposed to UVR 600 RBU/week. Topical administration of imiquimod in the vehicle formulation resulted in no tumour enhancement at the low dose, and in the mid and high dose resulted in a dose-related reduction in tumour formation in comparison with the vehicle cream group.

Pregnancy and lactation

Animal studies with imiquimod have not revealed any teratogenic effects in rats and rabbits. No adverse effects were found on reproduction in a second generation rat study. There are no data in pregnant or lactating women and APO-IMIQUIMOD cream should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus.

Use in Children

The safety and efficacy of APO-IMIQUIMOD in patients below the age of 18 years have not been established. AK and sBCC are not conditions generally seen in the paediatric population.

APO-IMIQUIMOD should not be used in patients with molluscum contagiosum.

Use in Elderly

Clinical studies of limited numbers of elderly patients with AK lesions or with sBCC have shown no overall differences in safety or effectiveness between these patients and younger patients. No other clinical experience has identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Driving and Using Machinery

APO-IMIQUIMOD is unlikely to produce an effect on the ability to drive or use machinery.

Adverse Effects

The most frequent adverse events associated with imiquimod cream therapy are local application site reactions which include tenderness, itching, pain and burning sensation at the treatment site. Local skin reactions (including erythema, erosion, oedema, vesicles, scabbing, desquamation/flaking and induration) are seen in conjunction with decreasing wart size and are believed to be secondary to the pharmacological activity of imiquimod.

In clinical studies in patients with AK and in patients with sBCC there was a statistically significant observed association between the complete clearance rate and the most intense assessment of erythema made over the course of the study by the investigator.

The most common reason for clinical intervention was local skin reactions, which resulted in 10% of patients receiving rest periods from treatment. Most of the local skin reactions are mild to moderate in severity and resolved without sequelae within two weeks of discontinuing imiquimod.

Some systemic adverse reactions, including lymphadenopathy, headache, back pain, influenza-like symptoms, fatigue, diarrhoea and myalgia have been reported by patients in clinical trials.

Isolated reports of localised hypopigmentation and hyperpigmentation following the use of imiquimod cream have been received. Follow-up information suggests that these skin colour changes may be permanent in some patients.

Reductions in haemoglobin, white blood cell count, absolute neutrophils and platelets have been observed in clinical trials. These reductions are not considered to be clinically significant in patients with normal haematological reserve. Patients with reduced haematological reserve have not been studied in clinical trials. Reductions in haematological parameters requiring clinical intervention have been reported from post-marketing experience.

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Clinical studies investigating the use of imiquimod for the treatment of actinic keratosis have detected a 0.4% (5/1214) frequency of alopecia at the treatment site or surrounding area. Post-marketing reports of suspected alopecia occurring during the treatment of sBCC and EGW have been received.

Rare reports have been received of exacerbation of autoimmune conditions.

Rare cases of remote site dermatologic drug reactions, including erythema multiforme, have been reported from clinical trials. Serious skin reactions reported from post-marketing experience include erythema multiforme, Stevens Johnson syndrome and cutaneous lupus erythematosus.

Interactions

No interactions have been identified. Due to its immunostimulating properties, APO-IMIQUIMOD should be used with caution in patients who are receiving immunosuppressive medication (see *Warnings and Precautions*).

Overdosage

Symptoms and Signs

Topical overdosage with APO-IMIQUIMOD is unlikely due to minimal systemic absorption. Animal studies reveal a dermal lethal dose of greater than 5000 mg/kg and an oral lethal dose ranging from 400 to 1600 mg/kg. Persistent overdosing of APO-IMIQUIMOD could result in severe local skin reactions. These usually subside within 2 weeks of APO-IMIQUIMOD discontinuation.

Following accidental ingestion, nausea, emesis, headache, myalgia and fever could occur after a single dose of 200mg imiquimod which corresponds to approximately 16 sachets. The most clinically serious adverse event reported following multiple oral doses of ≥ 200 mg was hypotension, which resolved following oral or intravenous fluid administration.

Pharmaceutical Precautions

Store at or below 25°C. Do not freeze.
Shelf life 2 years from the date of manufacture.

Medicine Classification

Prescription Medicine

Package Quantities

Each pack of APO-IMIQUIMOD contains either 1, 3, 6, 12 or 30 single use sachets of imiquimod cream

Further Information

Clinical Trials:

Solar (Aclinic) Keratosis:

One or two courses of 4 weeks treatment

The efficacy of imiquimod applied 3 times per week for one or two courses of 4 weeks, separated by a 4 week treatment-free period, was studied in two double-blind vehicle controlled clinical trials. Patients had clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic AK lesions on the balding scalp or face within a contiguous 25 cm² treatment area. 4-8 AK lesions were treated. The complete clearance rate (imiquimod minus placebo) for the combined trials was 46.1 % (CI 39.0%, 53.1%).

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One-year data from two combined observational studies indicate a recurrence rate of 27% (35/128 patients) in those patients who became clinically clear after one or two courses of treatment. The recurrence rate for individual lesions was 5.6% (41/737). Corresponding recurrence rates for vehicle were 47% (8/17 patients) and 7.5% (6/80 lesions). The rate of progression to squamous cell carcinoma (SCC) was reported in 1.6% (2/128 patients).

There is no data on recurrence and progression rates beyond 1 year.

Superficial Basal Cell Carcinoma:

The efficacy of imiquimod 5 times per week for 6 weeks was studied in two double-blind vehicle controlled clinical trials. Target tumours were histologically confirmed single primary superficial basal cell carcinomas with a minimum size of 0.5 cm² and a maximum diameter of 2 cm. Tumours located within 1 cm of the eyes, nose mouth, ears or hairline were excluded. In a pooled analysis of these two studies, histological clearance was noted in 82% (152/185) of patients. When clinical assessment was also included, clearance judged by this composite endpoint was noted in 75% (139/185) of patients. These results were statistically significant ($p < 0.001$) by comparison with the vehicle group, 3% (6/179) and 2% (3/179) respectively. There was a significant association between the intensity of local skin reactions (e.g. erythema) seen during the treatment period and complete clearance of the basal cell carcinoma.

Five-year data from a long-term open-label uncontrolled study indicate that an estimated 77.9% [95% CI (71.9%, 83.8%)] of all the subjects who initially received treatment became clinically clear and remained clear at 60 months. No data on recurrence rates beyond 60 months are available.

External Genital/Perianal Warts:

The results of 3 phase III pivotal efficacy studies showed that treatment with imiquimod for sixteen weeks was significantly more effective than treatment with vehicle as measured by total clearance of treated warts.

In 119 imiquimod-treated female patients, the combined total clearance was 60% as compared to 20% in 105 vehicle-treated patients (95% CI for rate difference: 20% to 61%, $p < 0.001$). In those imiquimod patients who achieved total clearance of their warts, the median time to clearance was 8 weeks.

In 157 imiquimod-treated male patients, the combined total clearance was 23% as compared to 5% in 161 vehicle-treated patients (95% CI for rate difference: 3% to 36%, $p < 0.001$). In those imiquimod patients who achieved total clearance of their warts, the median time to clearance was 12 weeks.

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