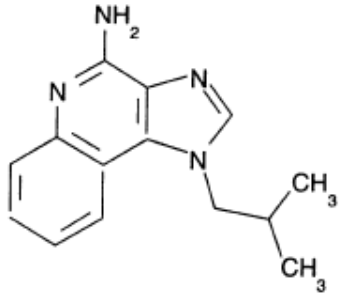
APO-IMIQUIMOD CREAM

NAME OF THE MEDICINE

Imiquimod.

Chemical Name: 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine

Structural Formula:



Molecular Formula: $C_{14}H_{16}N_4$

Molecular Weight: 240.3

CAS Registry Number: 99011-02-06

DESCRIPTION

Imiquimod is an odourless, white to off-white crystalline solid.

PHARMACOLOGY

Pharmacodynamics

Imiquimod is an immune response modifier. Imiquimod has been shown to stimulate the innate and adaptive immune response through the induction of interferon-α (IFN-α) and other cytokine production by multiple cell types (e.g. macrophages; monocytes; B cells; plasmacytoid dendritic cells (pDC)). pDCs, a major subset of (pre-)DCs, have the highest expression of Toll-like receptor7 (TLR7) amongst DC subsets.

Imiquimod activates immune cells by engaging TLR7 and (to a lesser extent) Toll-like receptor-8 (TLR8) signalling, and consecutively, activation of nuclear factor-kappa B (NF-κB) and induction of pro-inflammatory cytokines, chemokines and other mediators such as IFN-α, tumour necrosis factor (TNF)α, interleukin (IL)-2, IL-6, IL-8, IL-12.

Imiquimod induces an increase in markers for IFN-γ and the interferon inducible gene product 2’5’-oligoadenylate synthetase at the treatment site.

Imiquimod has no direct in vitro antiviral activity. The antiviral activity is indirect through cytokine induction of IFN-α and immune activation. In addition, HPVL1 mRNA and HPV DNA are significantly decreased following treatment. However the clinical relevance of these findings is unknown.

As well as enhancing pro-inflammatory cytokine secretion from pDCs, imiquimod enhances costimulatory marker expression, increase CCR7 (e.g. enabling migration into lymphatic vessels and into lymph nodes) and improve pDC viability.

Another important effect of imiquimod is to encourage pDC maturation, however the extent of pDC migration to skin is not well defined.

It is also possible that imiquimod can stimulate the proliferation of B cells *in vitro*.

Independent of TLR-7 and TLR-8, imiquimod appears to interfere with adenosine receptor (AR) signalling pathways, particularly A2A, and receptor-independent reduction of adenylyl cyclise activity may augment the pro-inflammatory activity of imiquimod.

Imiquimod appears to exert some pro-apoptotic activity against tumour cells.

Two mechanism of action studies were performed to determine the nature of cellular immune responses early in the course of treatment or at the time of tumour erosion in superficial basal cell carcinoma tumours and surrounding tissue after treatment with imiquimod 5% cream. The studies focused on the survival mechanisms of the tumour cells, and whether imiquimod therapy alters the immune cell composition in the area of the tumour, thereby causing basal cell carcinoma tumour cells to be more susceptible to killing. The results of these studies are consistent with a mechanism of action that involves immune-mediated tumour cell destruction.

These studies showed that imiquimod cream stimulates the infiltration of tumour-destructive cells (T-cell lymphocytes, dendritic cells and macrophages) at the superficial basal cell carcinoma lesions and reduces the defense mechanism of the tumour.

Superficial basal cell carcinoma and solar keratosis occurs in patients with chronic UV-damaged skin.

A study in solar keratosis patients evaluating the systemic exposure to imiquimod following topical applications of 12.5 mg (one sachet) of imiquimod cream to facial lesions, or 25 mg (two sachets) of imiquimod cream to scalp lesions, or 75 mg (six sachets) of imiquimod cream to lesions on both hands and arms three times per week for 16 weeks showed that after 16 weeks of dosing serum imiquimod levels were low, reflecting minimal percutaneous absorption of imiquimod (see **PHARMACOLOGY**, Pharmacokinetics). The levels of biomarkers sensitive to imiquimod cream increased up to approximately 2 to 15 fold over baseline. These biomarkers included interleukin-1 receptor antagonist, interferon-α and 2'5'-oligoadenylate synthetase. The increases in biomarkers were associated with a small number of systemic adverse events.

The mechanism of the immune stimulation was evaluated in SK patients treated with imiquimod. Imiquimod treatment was associated with increases in lymphocytes, dendritic cells, macrophages, and cells bearing activation markers in the SK lesions. Statistically significant differences between baseline and week 2 biomarker levels were seen for the imiquimod treatment for CD3, CD4, CD8, CD11c, CD86/CD11c double stain, CD68, class II human leukocyte antigen-DR, and terminal deoxynucleotidyl transferase mediated deoxyuridine triphosphate nick end labeling (TUNEL). The cellular infiltration observed in the imiquimod treated SK lesions was consistent with activation of the innate and acquired immune responses.

Pharmacokinetics

In patients with solar keratosis (n=58), only minimal systemic absorption of imiquimod across the affected skin was observed when imiquimod cream was applied three times per week for 16 weeks. At the end of week 16, a urinary recovery of imiquimod and its metabolites of less than 0.6% of the applied dose were 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 applications to face (12.5 mg imiquimod, 1 sachet), scalp (25 mg, 2 sachets) and hands/arms (75 mg, 6 sachets) respectively.

A small number of systemic adverse events such as 'flu-like' symptoms that could be associated with innate immune response activity (IFN induction) were reported (e.g. 'flu-like symptoms 4/58). These were mild and no dose response was observed. An apparent terminal half-life of imiquimod was approximately 10 times greater than the 2 hour half-life seen following subcutaneous application, suggesting prolonged retention of imiquimod in the skin for greater than 24 hours after the cream is removed.

Percutaneous absorption of imiquimod following topical administration of imiquimod cream has been studied over a wide spectrum of skin types, from keratinised skin of genital warts to intact healthy skin to the lesions of sun damaged skin. The results from these studies 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 cream 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 solar 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 superficial basal cell carcinoma should not pose any systemic safety concern.

In subjects with intact healthy skin (n=6), less than 0.9% of a single topically applied 5 mg dose of [C^{14}] labeled 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 (n=12) treated with imiquimod cream three times a week for 16 weeks median imiquimod peak serum concentrations of approximately 0.1 and 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 cream.

CLINICAL TRIALS

Solar (Actinic) 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 SK lesions on the balding scalp or face within a contiguous 25 cm^2 treatment area. 4-8 SK lesions were treated. The complete clearance rate, defined as the percentage of patients with no clinically visible SK lesions in the treatment area for the two trials combined, was 54.4% (137/252) for imiquimod and 8.3% (21/253) for vehicle, resulting in a significant difference of 46.1% (CI 39.0%, 53.1%).

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 imiquimod patients).

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

Up to 16 Weeks Treatment

A total of 1214 patients were enrolled in 5 Phase III double-blind, randomised, vehicle-controlled, parallel-group, multi-centre studies that evaluated the efficacy and safety of imiquimod for the treatment of solar keratosis (SK). In three of the studies patients with SK were treated with imiquimod or vehicle cream once daily 3 times per week for up to 16 weeks. In the remaining two studies patients with SK were treated with imiquimod or vehicle cream once daily 2 times per week for up to 16 weeks. Patients with 4-8 SK lesions within a 25 cm^2 contiguous treatment area on either the face or scalp were enrolled and randomised to active or vehicle treatment. The primary variable was the complete (100%) clearance rate, defined as the proportion of patients with no SK lesions in the treatment area at 8 weeks post treatment. This included clearance of all baseline lesions as well as any new or subclinical SK lesions which appeared in the treatment area during treatment. The secondary variable was the partial clearance rate, defined as the proportion of patients with at least a 75% reduction in the number of SK lesions in the treatment area at 8 weeks post treatment.

In all but one study clearance was determined by clinical assessment. In the remaining study (EU 3x/week study), clearance was determined by both clinical and histological assessment. In this study the clinical diagnosis of SK lesion clearance was confirmed by histology for 94.2% of subjects. The complete and partial clearance rates are shown below:

Table 1:

Complete Clearance Rates for Combined Studies (ITT)

Study	Imiquimod	Month 48
EU 3x/Week	57.1% (84/147)	2.2% (3/139)
Combined US 3x/Week	48.3% (117/242)	13.6% (34/250)
Combined US 2x/Week	45.1% (97/215)	11.8% (26/221)

Table 2:

Partial (≥ 75%) Clearance Rates for Combined Studies (ITT)

Study	Imiquimod	Vehicle
EU 3x/Week	72.1% (106/147)	4.3% (6/139)
Combined US 3x/Week	64.0% (155/242)	13.6% (34/250)
Combined US 2x/Week	59.1% (127/215)	11.8% (26/221)

The overall reduction of individual SK lesions in the imiquimod group was 78.8% (708/898 lesions) in the EU 3x/week study, 74.0% (1000/1352 lesions) in the combined US 3x/wk studies and 70.2% (851/1212 lesions) in the combined US 2x/wk studies versus 8.7% (67/766 lesions), 24.6% (347/1409 lesions) and 17.0% (213/1255 lesions) respectively for the vehicle group.

A statistically significant trend was observed between the complete clearance rate and severity of local skin reactions (erythema) for the imiquimod treated patients in the Phase III studies. The complete clearance rate tended to increase as the intensity level of erythema increased. Based on the appearance of local skin reactions (LSRs) and their association with clearance, LSRs can be considered an extension of the pharmacological effects of imiquimod cream.

Sub-clinical SK lesions may become apparent in the treatment area during treatment with imiquimod cream. The proportion of imiquimod treated patients with an increase in their SK lesion count relative to the number present at baseline during the course of treatment, and the proportion that were completely clear 8 weeks post treatment is presented in the following table:

Table 3:

	No. of Imiquimod Patients with an Increase in SK Lesions During the Treatment Period	Complete Clearance Rate in Imiquimod Patients with an Increase in SK Lesion Counts	Complete Clearance Rate in Imiquimod Patients with No Increase in SK Lesion Counts
EU 3x/Week	12.9% (19/147)	63.2% (12/19)	56.3% (72/128)
Combined US 3x/Week	42.6% (103/242)	54.4% (56/103)	43.9% (61/139)
Combined US 2x/Week	47.9% (103/215)	48.5% (50/103)	42.0% (47/112)

Imiquimod treated patients with an increase in SK lesion counts had higher clearance rates compared to imiquimod patients with no increase.

The pharmacodynamic response seen with imiquimod treatment may have led to unblinding of the

studies to some extent, and the magnitude of the efficacy reported may be an over-estimate of the real value.

Information from an observational follow-up study of patients who had demonstrated complete clearance of their SK lesions at 8 weeks post treatment showed that 24.7% (19/77) of the imiquimod treated patients in the 3x/week dosing group and 42.6% (23/54) of the imiquimod treated patients in the 2x/week dosing group had a recurrence of SK within the treatment area after a median follow up of 16.6 months. Overall, in those subjects who experienced a recurrence of SK, the median number of lesions that recurred was 1.

The above two regimens for the treatment of solar keratosis have not been compared directly in clinical trials and it is, therefore, not known how they directly compare with respect to efficacy or safety.

The potential additive therapeutic effects of using sunscreens simultaneously with imiquimod have not been explored systematically in clinical trials.

A comparative, randomized, double-blind, vehicle-controlled, parallel-group design study was performed to determine (in the treatment of patients with SK): (i) the therapeutic equivalence of APO-Imiquimod 50 mg/g (5% w/w) with the Canadian and U.S. reference products (analyses of the Australian reference product against the Canadian reference product demonstrated identical composition); (ii) the superiority of the active treatments over treatment with vehicle (placebo) alone, and; (iii) the safety and tolerability of APO-Imiquimod 50 mg/g (5% w/w), the Canadian reference product, the U.S. reference product and vehicle (placebo) alone. The study involved 3 analysis populations: modified intent-to-treat (mITT), per-protocol (PP), and safety.

A total of four hundred and ninety (490) adult male and female patients (≥ 18 years of age), with 4 to 8 non-hyperkeratotic, non-hypertrophic SK lesions located within a contiguous 25 cm^2 area on the face or balding scalp, were enrolled in the 16 week study (including an 8 week follow-up period). Each patient applied the study medication before bedtime to the target treatment area twice weekly, 3 or 4 days apart.

The primary efficacy end-point was the complete clearance rate (i.e. the proportion of patients with no clinically visible SK lesions in the target treatment area at the week 24 visit [8 week post-treatment]). The secondary end-point was the partial clearance rate, defined as the clearing of at least 75% of lesions at week 24. Efficacy was evaluated by statistical comparisons of the proportion of patients judged to have attained complete or partial clearing for the test, reference and vehicle treatments. Therapeutic equivalence of the investigational treatments was based on the difference in their complete clearance rates at the week 24 visit. Analyses were conducted using Wald's method with Yate's continuity correction to determine whether the 90% continuity-corrected confidence interval on the difference was contained within the equivalence intervals -0.20 to +0.20. The analysis on the PP subject population was considered primary while the analysis on the mITT subject population was considered secondary.

APO-Imiquimod 50 mg/g (5% w/w) was shown to be therapeutically equivalent to both the Canadian and U.S. reference products. There was a statistically significant difference in decrease from baseline to week 24 ($p \leq 0.0005$) for the mITT population and to week 16 ($p \leq 0.0320$) and week 24 ($p < 0.0001$) for the PP population in the number of lesions between each active treatment group and the vehicle group. Each active treatment was also demonstrated to be superior to the vehicle (placebo) treatment, based on complete and partial (≥ 75%) clearance rates of lesions in subjects with SK. APO-Imiquimod 50 mg/g (5% w/w) was shown to be safe and well tolerated in subjects with SK, with a safety profile comparable to that of the Canadian and U.S. reference products.

Superficial Basal Cell Carcinoma

In two double-blind, vehicle controlled studies, 364 patients with superficial basal cell carcinoma (sBCC) were treated with imiquimod cream or vehicle cream once daily for 5 consecutive days per week (5x/week) for 6 weeks. Patients with biopsy confirmed sBCC tumour were enrolled and randomized in a 1:1 ratio to active or vehicle treatment. On a scheduled dosing day the study cream was applied to lesions prior to normal sleeping hours; dosing continued for a total of 6 weeks. Twelve weeks after the last scheduled application of study cream, the clinical response of each patient was evaluated. At that time the entire target tumour area was excised and examined histologically for the presence of tumour. The complete clearance rate for the imiquimod treated group was 75% compared to 2% in the vehicle treated group. The complete clearance rate consisted of all patients whose histological response showed

no evidence of tumour excluding those where clinical appearances were suspicious of tumour presence and this appearance was not explained by the histological findings. The histological clearance rate for the imiquimod treated group (82%) was significantly greater ($p<0.001$) than the clearance rate of the vehicle treated group (3%). The histological clearance rate included patients whose histological response showed no evidence of tumour. The histological clearance rate following imiquimod therapy was statistically ($p<0.001$) higher (91%) in patients with moderate to severe local skin reactions compared to those patients who experienced no or mild local skin reactions (54%).

In an open-label, multi-centre study evaluating the long-term sustained clearance rate in patients with sBCC treated with imiquimod cream once daily for 5 consecutive days per week (5x/week) for 6 weeks, a clinical evaluation of treatment response was used as the sole measure of treatment outcome to represent clinical practice setting. At the 12-week post-treatment assessment 90% (163/182) of patients had no clinical evidence of sBCC at the target tumour site. At 12 months follow up 94% of patients who were clear at the 12-week post-treatment assessment remained clear. The long term recurrence rate following imiquimod treatment is unknown, and it is recommended that patients have regular follow-up to confirm sustained clearance.

In an open-label uncontrolled study in subjects (n=66) with tumours ranging from 2-48 cm^2 treated with imiquimod cream once daily 5 days per week for 6 weeks, the histological clearance rate was 83%. Analysis of tumour size in relationship to clearance rates showed some decrease in clearance rates when the tumour size was >7.25 cm^2 (see **PRECAUTIONS**).

In a second open-label uncontrolled study in subjects with multiple (2-6) tumours treated with imiquimod cream once daily 5 days per week for 6 weeks (n=36), 47% of subjects were histologically negative for all sBCC's treated. Of the individual sBCC's treated (n=111), 77% were histologically clear.

Nodular Basal Cell Carcinoma

The efficacy of imiquimod cream in the treatment of nodular BCC has not been adequately established.

External Genital / Perianal Warts

In a double-blind, placebo-controlled clinical trial (n=209), imiquimod 5% cream applied three times a week for the treatment of genital and perianal warts achieved wart clearance rates (50%) that were statistically significantly greater than the placebo control (11%). The percentage of patients treated with imiquimod 5% cream achieving total clearance was 72% for females and 33% for males. The percentage of patients achieving partial wart area (>50%) reduction was 85% for females and 70% for males. The median baseline wart area was 69 mm^2 (range 8 to 5525 mm^2). Visible reduction in wart area occurred as early as the second week of treatment. Total wart clearance occurred as early as 4 weeks and some patients required 16 weeks. The median time to total wart clearance was 10 weeks. A low percentage (13%) of the patients treated with imiquimod 5% cream who achieved total clearance of their warts experienced a recurrence of their warts during the 12-week follow-up period.

Table 4:

Results of a Double Blind Placebo Controlled Clinical Trial (n=209)

	Female		Male		All	
	Imiquimod 5%	**Placebo**	**Imiquimod 5%**	**Placebo**	**Imiquimod 5%**	**Placebo**
N	46	40	63	60	109	100
Total wart clearance (%)	72%	20%	33%	5%	50%	11%
N	33	8	21	3	54	11
Time to achieve total clearance (weeks)						
Median	8*	13*	12*	10*	10*	12*
Range	(4-16)	(4-16)	(6-16)	(10-16)	(4-16)	(4-16)
N	27	7	18	3	45	10
Recurrence rate (%)	19%*	14%*	6%*	0%*	13%*	10%*
N	46	40	63	60	109	100
Baseline wart area (mm^2)	58	71	92	87	69	77
	(15-2294)	(7-1468)	(8-5525)	(10-5000)	(8-5525)	(7-5000)
Partial (>50%) wart area reduction	85%	38%	70%	22%	76%	28%

** Not statistically significant compared to placebo*

INDICATIONS

APO-Imiquimod 50 mg/g (5%) cream is indicated for:

- Treatment of solar (actinic) keratosis on the face and scalp (see **PRECAUTIONS**);
- Primary treatment of confirmed superficial basal cell carcinoma where surgery is considered inappropriate;
- Treatment of external genital and perianal warts/condyloma acuminata in adults (see **PRECAUTIONS**).

CONTRAINDICATIONS

Known hypersensitivity to imiquimod or to any other excipients in APO-Imiquimod cream (see **PRESENTATION AND STORAGE CONDITIONS**).

PRECAUTIONS

Local skin 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 may be due to the pharmacological response of the body's immune system to imiquimod. Should severe local skin reactions occur, the cream should be removed by washing the treatment area with mild soap and water. These local skin reactions generally resolve after cessation of therapy with imiquimod and are generally less intense during a second course of therapy. Treatment with imiquimod cream can be resumed after the skin reaction has subsided. In patients requiring a 'rest period' during treatment with imiquimod it is not necessary to make up the missed doses or to prolong the duration of imiquimod therapy. The use of an occlusive dressing is not recommended with 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 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.

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

From an open-label multi-centre long-term sustained clearance sBCC study, the following pigmentation outcomes were observed among patients at the final 60 month post treatment visit:

Table 5:

Skin Pigmentation Assessments *At Target Tumour Site*: Last Follow-Up Visit

Skin Assessment	n	None	Mild	Moderate	Severe
Hypopigmentation	128 (100%)	67 (52%)	52 (41%)	9 (7%)	0 (0%)
Hyperpigmentation	128 (100%)	127 (99%)	1 (1%)	0 (0%)	0 (0%)
Irregular Pigmentation	128 (100%)	126 (98%)	2 (2%)	0 (0%)	0 (0%)

Table 6:

Skin Pigmentation Assessments *Within Surrounding Area*: Last Follow-Up Visit

Skin Assessment	n	None	Mild	Moderate	Severe
Hypopigmentation	128 (100%)	122 (95%)	6 (41%)	0 (0%)	0 (0%)
Hyperpigmentation	128 (100%)	128 (100%)	0 (0%)	0 (0%)	0 (0%)
Irregular Pigmentation	128 (100%)	128 (100%)	0 (0%)	0 (0%)	0 (0%)

It is thought that the changes noted at the target site and surrounding area may be partly explained by tissue remodelling processes. For example, hypopigmentation may be secondary to regenerated skin at the treated site that has not sustained ultraviolet damage, particularly when compared to the surrounding chronically sun-damaged skin.

There is limited clinical experience with imiquimod cream therapy immediately following the treatment of skin conditions with other cutaneously applied therapy or procedures; therefore imiquimod cream administration is not recommended until tissue is healed from any previous therapy or procedure. Application to broken skin could result in increased systemic absorption leading to a greater risk of adverse events.

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

Rare reports have been received of exacerbation of autoimmune conditions (see **ADVERSE EFFECTS**).

Imiquimod cream should be used with caution in organ transplant patients and in patients with pre-

existing autoimmune conditions (see **PRECAUTIONS**, Interactions with Other Medicines). In these patients consideration should be given to balancing the benefit of treatment with imiquimod with the risk associated with the possibility of organ rejection or graft versus host disease or a possible worsening of the autoimmune condition respectively.

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.

Solar (Actinic) Keratosis

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

Imiquimod has not been evaluated for the treatment of solar keratoses on the eyelids, the inside of the nostrils or ears, or the lip area inside the vermilion border. Contact with the eyes, lips and nostrils should be avoided.

Imiquimod cream is not recommended for the treatment of SK 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 imiquimod cream in immunocompromised patients. .

The safety and efficacy of imiquimod cream in the re-treatment of residual solar keratoses has not been established. There are limited data of imiquimod cream on recurrence of SK (see **CLINICAL TRIALS**). No data are available on re-treating solar 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 imiquimod cream (see sBCC below). During treatment, sub-clinical SK lesions may become apparent in the treatment area and may subsequently resolve (see **CLINICAL TRIALS**). There are inadequate data to support the use of imiquimod cream on the hands and arms, and therefore it should not be used in these areas. Imiquimod cream should not be used in an area greater than 25 cm^2 due to the potential to cause local skin reactions (see **ADVERSE EFFECTS**).

Superficial Basal Cell Carcinoma

The diagnosis of superficial BCC should be confirmed by biopsy or specialist opinion before starting treatment and the patient should be carefully followed up after treatment to ensure that the tumour has been eradicated. The safety and efficacy of imiquimod cream have not been established for other types of basal cell carcinomas (BCC), including nodular and morpheaform (fibrosing or sclerosing) types.

Imiquimod cream is not recommended for treatment of BCC sub-types other than the superficial variant (i.e. sBCC).

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

Exposure to sunlight (including sunlamps) should be avoided or minimised during use of imiquimod cream because of concern for heightened sunburn susceptibility. Patients should be warned to use protective clothing when using imiquimod cream. Patients with sunburn should be advised not to use imiquimod cream until fully recovered. Patients who may have considerable sun exposure (e.g. due to their occupation), and those patients with inherent sensitivity to sunlight should exercise caution using imiquimod cream. Phototoxicity has not been adequately assessed. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Despite the absence of observed phototoxicity in humans (see **ADVERSE EFFECTS**), imiquimod cream shortened the time to skin tumour formation in an animal photo-carcinogenicity study (see **PRECAUTIONS**, Carcinogenicity, Mutagenesis and Impairment of Fertility). Therefore it is prudent for patients to minimise or avoid natural or artificial sunlight exposure.

In a limited number of patients the histological clearance rate for tumours >7.25 cm^2 (n=17) was lower (65%) than that for tumours (n=49) ranging from 2 – 7.25 cm^2 in size (90%) (see **CLINICAL TRIALS**). imiquimod cream has not been evaluated for locally recurrent superficial BCC or after initial treatment has failed.

Data on the safety of treating multiple sBCC lesions simultaneously in an individual patient is limited to one clinical study (n=67) in which the maximum number of lesions was six (see **CLINICAL TRIALS**). While no new safety issues emerged with the higher doses administered in this study, close monitoring of such patients is advised.

There is no experience in treating basal cell carcinoma associated with xeroderma pigmentosum, Gorlin's syndrome or immunosuppressive therapy.

No clinical experience exists with the use of imiquimod cream in immunocompromised patients.

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

External Genital / Perianal Warts

Imiquimod cream should not be used to treat urethral, intra-vaginal, cervical, rectal, or intra-anal warts due to the unknown local tolerance and potential systemic absorption. Imiquimod cream has not been evaluated for the treatment of warts in these locations.

Special care should be taken if applying imiquimod cream 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.

Treatment beyond 16 weeks and repeat treatment with imiquimod cream after initial successful therapy have not been studied.

Repeat treatment with imiquimod cream is not recommended in immunocompromised patients.

The efficacy of imiquimod cream for the treatment of genital warts in patients with HIV has not been studied adequately. Limited information suggests that efficacy may be reduced in these patients. The implications for patients with impairment of the immune system for other reasons are not known.

The effect of imiquimod cream on the transmission of genital/perianal warts is unknown. Sexual (genital, anal, oral) contact should be avoided while the cream is on the skin. Imiquimod 5% cream may weaken condoms and vaginal diaphragms, therefore concurrent use with imiquimod cream is not recommended. Alternate forms of contraception should be considered.

Uncircumcised males treating 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. 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.

Imiquimod cream therapy should not be initiated in tissues where open sores or wounds exist until after

the area has healed.

Carcinogenicity, Mutagenesis, and Impairment of Fertility

Imiquimod was without effect in a bacterial gene mutation assay (Ames test), chromosome damage assays *in-vitro* and *in-vivo*, and in a cell transformation assay.

Two-year carcinogenicity studies in Wistar rats (up to 3 mg/kg/day orally) 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. Incidences of liver tumours were increased in male mice exposed to the highest dose. Systemic exposure was not measured in the mouse dermal carcinogenicity study, although it is estimated that at the high dose the absorbed dose was greater than that in humans.

A photocarcinogenicity study in hairless albino mice showed that dermal administration of the vehicle alone enhanced the development of UVR-induced skin tumours. Dermal administration of 0.03%, 0.1% and 0.3% imiquimod in the vehicle resulted in a slight dose-related reduction in UVR-induced skin tumour development compared with the vehicle alone group. Exposure to the sun of treated skin areas should be minimised (see **PRECAUTIONS**).

Daily oral administration of imiquimod to rats at doses up to 8 times the recommended human dose on a mg/m^2 basis throughout mating, gestation, parturition and lactation demonstrated no impairment of reproduction.

Use in Pregnancy (Category B1)

Imiquimod was not teratogenic in rats dosed orally or in rabbits dosed intravenously. In rats, at a maternally toxic dose (28 times the maximum human dose on a mg/m^2 basis), reduced pup weights and delayed ossification were observed. There are no adequate and well controlled studies in pregnant women. Imiquimod cream is not recommended for use during pregnancy.

Use in Lactation

It is not known whether topically applied imiquimod is excreted in animal or human milk. No adverse effects were demonstrated in developmental studies with offspring of rats treated with imiquimod during gestation and lactation at doses up to 8 times the maximum human dose on a mg/m^2 basis. Imiquimod cream is not recommended for use during lactation as there are no data available in this population.

Use in Children

The safety and efficacy of imiquimod cream in patients below the age of 18 years have not been established. Use in this patient population is therefore not recommended.

Imiquimod cream should not be used in patients with molluscum contagiosum.

Use in Elderly

Of the 185 patients in the 5x/week treatment groups of clinical studies evaluating the treatment of sBCC with imiquimod cream, 65 patients (35%) were 65 years and older, while 25 patients (14%) were 75 years and older. No overall differences in safety or effectiveness were observed 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.

Interactions with Other Medicines

In-vitro plasma protein binding of imiquimod was in the range of 90-95% and was independent of concentrations in the therapeutic range. Although no clinical trials were performed to determine drug-drug interactions of imiquimod, an *in-vitro* plasma protein binding study demonstrated that protein binding of imiquimod was not affected by paracetamol, amoxycillin, cephalexin, chlorpromazine, cimetidine, diazepam, erythromycin, flecainide, ibuprofen, morphine, phenytoin, prednisolone, theophylline, warfarin. Therefore, co-administration of topically applied imiquimod with any of these compounds would not affect systemic safety of imiquimod nor the co-administered drugs due to competitive protein binding. Furthermore, in view of the limited systemic availability following topical administration of imiquimod, it is unlikely that drug-drug interactions will occur.

Due to its immunostimulating properties, imiquimod should by used with caution in patients who are

receiving immunosuppressive medication (see **PRECAUTIONS**).

ADVERSE EFFECTS

Dermal safety studies involving induction and challenge phases produced no evidence that imiquimod cream causes photoallergenicity or contact sensitisation in healthy skin. However, cumulative irritancy testing revealed the potential for imiquimod cream to cause irritation and in the clinical studies local site reactions (LSRs) were reported in a significant percentage of study patients. Phototoxicity testing was incomplete as wavelengths in the UVB range were not included and imiquimod cream has peak absorption in the UVB range (320 nm) of the light spectrum.

The LSRs were systematically collected at every visit and assessed and recorded separately from Adverse Events. They were only recorded as AEs if they extended beyond the surrounding area(s) (i.e. greater than 5 cm beyond the margins of the treatment area[s]). As such, the incidence of each of the pre-defined LSRs is, perhaps, higher than what might have been expected if the event had been captured based on spontaneous subject reporting or observed adverse events as the AEs.

Clinical Trial Data

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect rates observed in general practice. The adverse reaction information from clinical studies does however provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

a) General Description

Solar (Actinic) Keratosis

In the pivotal trials with 3 times per week dosing for up to 2 courses each of 4 weeks, 56% of imiquimod patients reported at least one adverse event. The most frequently reported adverse event from these trials judged probably or possibly related to imiquimod cream was application site reactions (22% of imiquimod treated patients). Some systemic adverse reactions, including myalgia (2%) were reported by imiquimod treated patients.

Patient reported adverse reactions from 252 patients treated with imiquimod cream in vehicle controlled phase III clinical studies for solar keratosis are presented below. These adverse events are considered at least possibly causally related to treatment with imiquimod.

Superficial Basal Cell Carcinoma

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.

Patient reported adverse reactions from 185 patients treated with imiquimod cream in placebo controlled phase III clinical studies for superficial basal cell carcinoma are presented below. These adverse events are considered at least possibly causally related to treatment with imiquimod.

External Genital Warts

In the pivotal trials with 3 times a week dosing, the most frequently reported adverse drug reactions judged to be probably or possibly related to imiquimod cream treatment were application site reactions at the wart treatment site (33.7% of imiquimod treated patients). Some systemic adverse reactions, including headache (2.1%), influenza-like symptoms (0.3%), and myalgia (1.4%) were also reported.

Patient reported adverse reactions from 2292 patients treated with imiquimod cream in placebo controlled and open clinical studies are presented below. These adverse events are considered at least possibly causally related to treatment with imiquimod.

b) Tabular Listing of Adverse Events

Adverse events are listed in the following table in CIOMS frequency categories: Very common (greater than 10%), Common (1% - 10%), Uncommon (0.1% - 1%).

Lower frequencies from clinical trials are not reported here.

Table 7:

	External Genital Warts		Superficial Basal Cell Carcinoma		Actinic Keratosis	
	Imiquimod 3x/wk, 16wks	**Vehicle**	**Imiquimod 5x/wk, 6wks**	**Vehicle**	**Imiquimod 3x/wk, 4 or 8wks**	**Vehicle**
	N = 2292	N = 261	N = 185	N = 179	N = 252	N = 253
Blood & Lymphatic System Disorders						
Lymphadenopathy	0.2%		1.6%		0.4%	
Ear & Labyrinth Disorders						
Tinnitus	0.1%					
Eye Disorders						
Conjunctival irritation					0.4%	
Eyelid Oedema					0.4%	
Gastrointestinal Disorders						
Abdominal pain	0.3%					
Diarrhoea	0.3%				0.8%	
Dry mouth			0.5%			
Nausea	1.1%	1.1%	0.5%		1.2%	
Rectal disorder	0.1%					
Rectal tenesmum	0.1%					
Vomiting	0.2%					
General Disorders & Administration Site Conditions						
Application Site Disorders: Target Site						
Bleeding		1.1%	2.2%		0.4%	0.4%
Burning	16.1%*	7.7%	6.5%	1.1%	5.2%	0.8%
Dermatitis					0.4%	
Discharge			0.5%		0.4%	
Erythema			1.6%		1.2%	
Hyperaestheisa					0.8%	
Hypopigmentation	1.1%*					
Inflammation			0.5%			
Irritation	1.8%*	1.5%	1.1%		1.6%	0.4%
Oedema			0.5%		0.4%	
Pain	4.4%*	1.1%	4.3%		3.2%	1.2%
Papules			1.6%		0.4%	
Paraesthesia			1.1%	1.7%	0.8%	0.4%
Pruritis/Itching	26.4%*	14.2%	16.8%	0.6%	13.9%	0.8%
Rash	1.1%*		1.1%			
Reaction					2.4%	
Scabbing			0.5%		0.4%	
Scar					0.4%	
Sensitive	1.1%*					
Skin breakdown			0.5%			
Sore	1.1%*					
Stinging sensation	1.1%*					
Swelling			0.5%		0.4%	

	External Genital Warts		Superficial Basal Cell Carcinoma		Actinic Keratosis	
	Imiquimod 3x/wk, 16wks	**Vehicle**	**Imiquimod 5x/wk, 6wks**	**Vehicle**	**Imiquimod 3x/wk, 16wks**	**Vehicle**
	N = 2292	N = 261	N = 185	N = 179	N = 2292	N = 261
General Disorders & Administration Site Conditions						
Application Site Disorders: Target Site						
Tenderness	4.0%*	1.1%	1.1%			
Ulcer					0.4%	
Vesicles			0.5%		0.8%	
Warmth					0.4%	0.4%
Application Site Disorders: Remote Site						
Burning	2.2%*					
Erythema			1.6%			
Itching/Pruritus	4.4%*	1.9%				
Pain	2.2%*					
Tenderness	1.1%*					
Asthenia	0.2%				0.8%	
Discomfort					0.8%	
Fatigue	1.2%		2.2%^	1.1%	1.2%	
Inflammation					0.4%	
Influenza like illness	0.3%		0.5%			
Lethargy			0.5%			
Malaise	0.2%					
Pain	0.3%			0.6%		
Pyrexia/Fever	0.8%	1.5%	1.6%^		0.4%	
Rigors	0.1%	0.4%			0.8%	
Infections & Infestations						
Bacteria infection	0.1%					
Fungal infection	0.1%					
Genital Candidiasis	0.2%					
Herpes Simplex	0.3%					
Infection	1.4%		1.1%		0.8%	
Influenza					0.4%	
Pustules			1.1%		0.4%	
Rhinitis					0.4%	
Upper respiratory tract infection	0.1%					
Vaginitis	0.2%					
Vulvitis	0.1%					
Metabolism & Nutrition Disorders						
Anorexia	0.2%				1.2%	
Musculoskeletal & Connective Tissue Disorders						
Arthralgia	0.2%	0.4%			1.2%	
Back pain	0.2%		1.1%			
Myalgia	1.4%	0.4%			2.0%	
Pain in extremity					0.4%	

	External Genital Warts		Superficial Basal Cell Carcinoma		Actinic Keratosis	
	Imiquimod 3x/wk, 16wks	**Vehicle**	**Imiquimod 5x/wk, 6wks**	**Vehicle**	**Imiquimod 3x/wk, 16wks**	**Vehicle**
	N = 2292	N = 261	N = 185	N = 179	N = 2292	N = 261
Nervous System Disorders						
Dizziness	0.3%					
Headache	2.1%	2.3%	7.6%^	2.2%	1.6%	0.4%
Migraine	0.1%					
Paraesthesia	0.4%	0.4%				
Somnolence	0.1%					
Psychiatric Disorders						
Depression	0.1%				0.8%	
Insomnia	0.2%	0.4%				
Irritability			0.5%			
Renal & Urinary Disorders						
Dysuria	0.4%					
Reproductive System & Breast Disorders						
Dyspareunia	0.1%					
Erectile dysfunction	0.1%					
Genital pain male	0.2%					
Penile disorder	0.2%					
Uterovaginal prolapsed	0.1%					
Vaginal pain	0.1%					
Vaginitis atrophic	0.1%					
Vulval disorder	0.1%					
Respiratory, Thoracic & Mediastinal Disorders						
Nasal congestion					0.4%	
Pharyngitis	0.1%	0.4%				
Pharyngo laryngeal pain					0.4%	
Rhinitis	0.1%	0.4%				
Skin & Subcutaneous Tissue Disorders						
Actinic keratosis					0.4%	
Dermatitis	0.2%		0.5%			
Eczema	0.1%					
Erthema					0.8%	
Face oedema					0.4%	
Folliculitis	0.1%					
Pruritus	0.5%	0.4%				
Rash	0.1%	0.4%				0.4%
Rash erythematous	0.1%					
Skin ulcer					0.4%	
Sweating increased	0.1%					
Urticaria	0.1%	0.4%				
Vascular Disorders						
Flushing	0.1%	0.8%				

^ Incidences reported without regard to causality with imiquimod cream

* AEs reported from 273 patients

c) Frequently Occurring Adverse Events

Solar (Actinic) Keratosis

In clinical trials of imiquimod cream 3x weekly for 4 or 8 weeks 56% of imiquimod patients reported at least one adverse event. The most frequently occurring application site reactions were itching at the target site (14%) and burning at the target site (5%). Severe erythema (24%) and severe scabbing and crusting (20%) were very common. Local skin reactions, such as erythema, are probably an extension of the pharmacological effect of imiquimod cream. See **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS** for information on rest periods.

Skin infections during treatment with imiquimod have been observed. While serious sequelae have not resulted, the possibility of infection in broken skin should always be considered.

Table 8:

Most Intense Local Skin Reactions in the Treatment Area Overall (Investigator Assessment) for the Treatment of Solar Keratosis

Type of Reaction	Intensity	Imiquimod 3x Week	Vehicle 3x Week
		N = 252	N = 253
Erythema	Mild	20.6%	56.9%
	Moderate	51.2%	19.8%
	Severe	23.8%	-
Edema	Mild	36.9%	5.1%
	Moderate	17.5%	1.6%
	Severe	3.6%	-
Vesicles	Mild	17.9%	0.4%
	Moderate	5.9%	-
	Severe	1.2%	-
Erosion / Ulceration	Mild	26.6%	9.1%
	Moderate	25%	2.0%
	Severe	6.3%	0.4%
Weeping / Exudate	Mild	22.6%	2.0%
	Moderate	17.9%	0.4%
	Severe	3.6%	0.4%
Flaking / Scaling / Dryness	Mild	47.2%	54.2%
	Moderate	38.9%	19.8%
	Severe	7.1%	0.4%
Scabbing / Crusting	Mild	24.6%	31.6%
	Moderate	37.7%	6.3%
	Severe	20.2%	0.8%

These LSRs peaked at 4 weeks. Their incidence during the second course of treatment was generally lower than during the first course.

Superficial Basal Cell Carcinoma

Investigators of the placebo controlled clinical trials were required to evaluate protocol mandated clinical signs (skin reactions). These protocol-mandated clinical sign assessments indicate that severe erythema (31%) severe erosions (13%) and severe scabbing and crusting (19%) were very common in these trials with imiquimod cream applied 5x weekly. Local skin reactions, such as erythema, are probably an extension of the pharmacological effect of imiquimod cream.

The data described below reflect exposure to 5x/week imiquimod cream for 6 weeks or vehicle in 364 patients enrolled in two double-blind, vehicle-controlled studies. The population ranged from 31 to 89 years of age (median 60 years) and 65% had Fitzpatrick skin types I or II. The incidence and severity of local skin reactions that occurred during controlled studies is shown in the following table:

Table 9:

Local Skin Reactions in the Treatment Area as Assessed by the Investigator over the Entire Study Period

Type of Reaction	Mild / Moderate		Severe	
	Imiquimod Cream (n=184)	Vehicle (n=178)	Imiquimod Cream (n=184)	Vehicle (n=178)
Oedema	71%	36%	7%	0%
Erosion	54%	14%	13%	0%
Erythema	69%	95%	31%	2%
Flaking/Scaling	87%	76%	4%	0%
Induration	78%	53%	6%	0%
Scabbing/Crusting	64%	34%	19%	0%
Ulceration	34%	3%	6%	0%
Vesicles	29%	2%	2%	0%

External Genital / Perianal Warts

In controlled clinical trials the most frequently observed adverse events were local inflammatory skin reactions, which may be due to the pharmacological response of the body's immune system to imiquimod. These reactions were usually mild to moderate in intensity, although some were severe. Overall, in clinical studies applying imiquimod cream three times per week, 1.2% (4/327) of patients discontinued treatment due to local skin/application site reactions.

To accurately report the incidence of the local skin reactions among patients in placebo-controlled studies of imiquimod cream applied 3x/week for 16 weeks, the investigators were requested to specifically assess erythema, oedema, induration, vesicles, erosion, ulceration, excoriation/flaking, and scabbing at the wart site and remote sites (defined as skin areas other than where study cream was applied). The incidence of these local skin reactions assessed by the investigator during the entire study period are summarised below:

Table 10:

Local Skin Reactions as Assessed by the Investigator over the Entire Study Period

Type of Reaction	Mild / Moderate	Severe
	Imiquimod 5% (n=270)	Vehicle (n=256)
At wart site		
Erythema	60.7%	21.5%
Oedema	14.4%	2.3%
Induration	6.3%	2.0%
Vesicles	2.2%	0.0%
Erosion	30.4%	7.0%
Ulceration	5.9%	0.8%
Excoriation/Flaking	22.6%	7.8%
Scabbing	8.9%	1.6%
At remote site		
Erythema	44.1%	9.8%
Oedema	7.8%	0.8%
Induration	2.6%	1.2%
Vesicles	1.5%	0.4%
Erosion	15.6%	3.9%
Ulceration	5.9%	1.6%
Excoriation/Flaking	15.9%	2.3%
Scabbing	6.3%	0.4%

d) Adverse Events Applicable to all Indications

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

Clinical studies investigating the use of imiquimod for the treatment of solar 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.

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.

Rare cases of remote site dermatological 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.

In clinical studies, psoriasis was recorded as a pre-existing condition in 24 imiquimod subjects. Of those, an exacerbation of psoriasis causally related to imiquimod was reported in 6 subjects.

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 is to be applied to the affected area prior to normal sleeping hours and should be left on the skin for approximately 8 hours (6-10 hours). The cream should be rubbed in until it is no longer visible. Following the treatment period the cream should be removed by washing the treated area with mild soap and water. During the 6-10 hours treatment period showering or bathing should be avoided. Hand washing before and after cream application is recommended.

Local skin reactions (erythema) at the treatment area are common. These reactions may be due to the pharmacological response of the body's immune system to imiquimod. In clinical studies in patients with sBCC the histological clearance following imiquimod therapy was statistically ($p<0.001$) higher (91%) in patients with moderate to severe local skin reactions compared to those patients who experienced no or mild skin reactions (54%). Similarly there was a significant association between the intensity of local skin reactions (e.g. erythema) seen during the treatment period and complete clearance of solar (actinic) keratosis. 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 cessation of imiquimod cream therapy. Treatment may resume once the reaction subsides. In patients requiring a rest period during treatment with imiquimod it is not necessary to make up the missed doses or to prolong the duration of imiquimod therapy.

APO-Imiquimod cream is provided in single use sachets. A new sachet should be opened for each treatment, and cream from a previously opened sachet should not be used.

The dosing frequency of APO-Imiquimod cream for the treatment of sBCC is different to that for the treatment of solar keratosis and external genital warts.

Solar (Actinic) Keratosis

APO-Imiquimod cream is to be applied to a treatment area no larger than 25 cm^2. The recommended dose per application is one sachet. Treatment should be initiated and monitored by a physician using either of the following two dosage regimens.

Cyclical

APO-Imiquimod cream may 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 SKs should be assessed. If any lesions persist, treatment should be repeated for another four 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 (see **PRECAUTIONS**).

Continuous

APO-Imiquimod cream may be applied 3 times per week (example: Monday, Wednesday and Friday) for up to 16 weeks. The treatment period should not be extended beyond 16 weeks due to missed doses or rest periods.

Superficial Basal Cell Carcinoma

APO-Imiquimod cream is to be applied once daily for 5 consecutive days per week and the 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 that includes 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.

Ten percent (19/185) of patients treated with 5x/week imiquimod therapy for the treatment of sBCC received rest periods. The median time for rest periods was 4 weeks with a range of 1 to 6 weeks after the initiation of therapy. The average number of doses not received per patient due to rest periods was 7 doses with a range of 2 to 22 doses. There was higher histological clearance in patients treated with imiquimod 5x/week for 6 weeks who had taken a rest period during treatment (89%) compared to those who did not take a rest period from dosing (81%). No statistically significant difference in the effect of rest periods was noted.

External Genital / Perianal Warts

APO-Imiquimod cream is to be applied once per day three times per week. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday; or Tuesday, Thursday, Saturday. Treatment should continue until there is total clearance of the genital/perianal warts or for a maximum of 16 weeks. A thin layer of APO-Imiquimod cream is to be applied to the wart area. Each sachet contains sufficient cream to cover a wart area of up to 20 cm^2; use of excessive amounts of cream should be avoided. The application site is not to be occluded. Non-occlusive dressings such as cotton gauze or cotton underwear may be used in the management of skin reactions.

OVERDOSAGE

Overdose of imiquimod 5% cream in humans is unlikely due to minimal percutaneous absorption. Animal studies reveal a rabbit dermal lethal imiquimod dose of greater than 1600 mg/m^2 (5000 mg/kg). Persistent topical overdosing of imiquimod 5% cream could result in severe local skin reactions. These usually subside within 2 weeks of imiquimod discontinuation.

Following ingestion of a single 200 mg oral imiquimod dose (corresponds to the content of approximately 16 sachets), nausea, emesis, headache and fever can occur. The most clinically serious adverse event reported following multiple oral imiquimod doses of > 200 mg was hypotension, which resolved following oral or intravenous fluid administration.

Contact the Poisons Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

APO-Imiquimod 50 mg/g (5% w/w) cream: white, soft cream.

Single-use foil sachet containing 250 mg cream. In boxes of 1*, 3*, 6, 12 and 30* sachets:
AUST R 168101.

* Not all strengths, pack types and/or pack sizes may be available.

APO-Imiquimod cream is intended for topical administration. Each 250 mg single-use sachet contains 12.5 mg imiquimod, as the active ingredient. In addition, the solution contains the following inactive ingredients: isostearic acid, benzyl alcohol, cetyl alcohol, stearyl alcohol, soft white paraffin, sorbitan monostearate, polysorbate 60, xanthan gum, glycerol, methyl hydroxybenzoate, propyl hydroxybenzoate and purified water.

Store below 25°C. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

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POISONS SCHEDULE OF THE MEDICINE

S4 : Prescription Only Medicine.

Date of TGA approval : 8 March 2011

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