ALDARA™

[al dar' a]

(imiquimod)

Cream, 5%

For Dermatologic Use Only

Not for Ophthalmic Use

DESCRIPTION

Aldara™ is the brand name for imiquimod which is an immune response modifier. Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base consisting of isostearic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methylparaben, and propylparaben.

Chemically, imiquimod is 1-(2-methylpropyl)-1*H*-imidazo[4,5-c]quinolin-4-amine. Imiquimod has a molecular formula of $C_{14}H_{16}N_4$ and a molecular weight of 240.3

CLINICAL PHARMACOLOGY

Pharmacodynamics

Actinic Keratosis

The mechanism of action of Aldara Cream in treating actinic keratosis (AK) lesions is unknown. In a study of 18 patients with AK comparing Aldara Cream to vehicle, increases from baseline in week 2 biomarker levels were reported for CD3, CD4, CD8, CD11c, and CD68 for Aldara Cream treated patients; however, the clinical relevance of these findings is unknown.

Superficial Basal Cell Carcinoma

The mechanism of action of Aldara Cream in treating superficial basal cell carcinoma (sBCC) lesions is unknown. An open label study in six subjects with sBCC suggests that treatment with Aldara Cream may increase the infiltration of lymphocytes, dendritic cells, and macrophages into the tumor lesion; however, the clinical significance of these findings is unknown.

External Genital Warts

Imiquimod has no direct antiviral activity in cell culture. A study in 22 patients with genital/perianal warts comparing Aldara Cream and vehicle shows that Aldara Cream induces mRNA encoding cytokines including interferon-α at the treatment site. In addition HPVL1 mRNA and HPV DNA are significantly decreased following treatment. However, the clinical relevance of these findings is unknown.

Pharmacokinetics

Systemic absorption of imiquimod was observed across the affected skin of 12 patients with genital/perianal warts, with an average dose of 4.6 mg. Mean peak drug concentration of approximately 0.4 ng/mL was seen during the study. Mean urinary recoveries of imiquimod and metabolites combined over the whole course of treatment, expressed as percent of the estimated applied dose, were 0.11 and 2.41% in the males and females, respectively.

Systemic absorption of imiquimod across the affected skin of 58 patients with AK was observed with a dosing frequency of 3 applications per week for 16 weeks. Mean peak serum drug concentrations at the end of week 16 were approximately 0.1, 0.2, and 3.5 ng/mL for the applications to face (12.5 mg

imiquimod, 1 single-use packet), scalp (25 mg, 2 packets) and hands/arms (75 mg, 6 packets), respectively.

Mean Serum Imiquimod Concentration Following Administration of the Last Topical Dose During Week 16	
Amount of Aldara Cream applied	**Mean peak serum imiquimod concentration [Cmax]**
12.5 mg (1 packet)	0.1 ng/mL
25 mg (2 packets)	0.2 ng/mL
75 mg (6 packets)	3.5 ng/mL

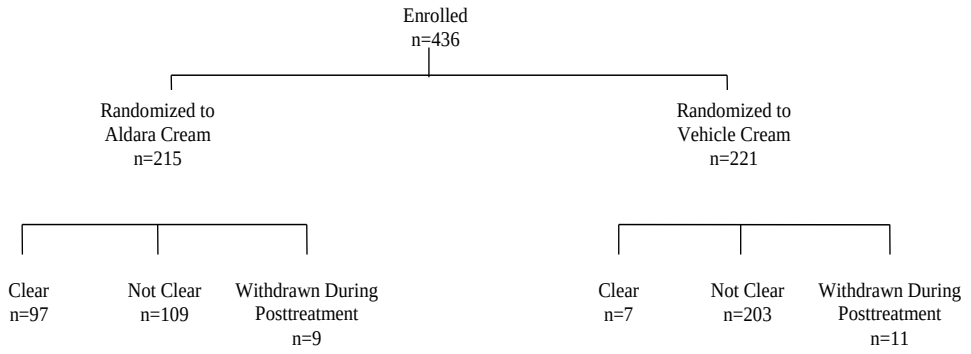
The application surface area was not controlled when more than one packet was used. Dose proportionality was not observed. However it appears that systemic exposure may be more dependent on surface area of application than amount of applied dose. The apparent half-life was approximately 10 times greater with topical dosing than the 2 hour apparent half-life seen following subcutaneous dosing, suggesting prolonged retention of drug in the skin. Mean urinary recoveries of imiquimod and metabolites combined were 0.08 and 0.15% of the applied dose in the group using 75 mg (6 packets) for males and females, respectively following 3 applications per week for 16 weeks.

CLINICAL STUDIES

Actinic Keratosis

In two double-blind, vehicle-controlled clinical studies, 436 patients with actinic keratosis (AK) were treated with Aldara Cream or vehicle cream 2 times per week for 16 weeks. Patients with 4 to 8 clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic AK lesions within a 25 cm^2 contiguous treatment area on either the face or scalp were enrolled and randomized to active or vehicle treatment. The population studied ranged from 37-88 years of age (median 66 years) and 55% had Fitzpatrick skin type I or II. All imiquimod-treated patients were Caucasians. The 25 cm^2 contiguous treatment area could be of any dimensions e.g., 5 cm x 5 cm, 3 cm by 8.3 cm, 2 cm by 12.5 cm, etc. On a scheduled dosing day, the study cream was applied to the entire treatment area prior to normal sleeping hours and left on for approximately 8 hours. Twice weekly dosing was continued for a total of 16 weeks. Eight weeks after the patient's last scheduled application of study cream, the clinical response of each patient was evaluated. The primary efficacy variable was the complete clearance rate. Complete clearance (designated below as "clear") was defined as the proportion of subjects at the 8-week post-treatment visit with no (zero) clinically visible AK lesions in the treatment area. Complete clearance included clearance of all baseline lesions, as well as any new or subclinical AK lesions which appeared during therapy. Patient outcomes are shown in the figure below.

Patient Accountability - Combined Phase III Studies
2X/Week Application



Complete and partial clearance rates are shown in the table below. The partial clearance rate was defined as the percentage of patients in whom 75% or more baseline AK lesions were cleared.

Complete Clearance Rates (100% Lesions Cleared)

Study	Aldara Cream	Vehicle
Study A	46% (49/107)	3% (3/110)
Study B	44% (48/108)	4% (4/111)

Partial Clearance Rates (75% or More Baseline Lesions Cleared)

Study	Aldara Cream	Vehicle
Study A	60% (64/107)	10% (11/110)
Study B	58% (63/108)	14% (15/111)

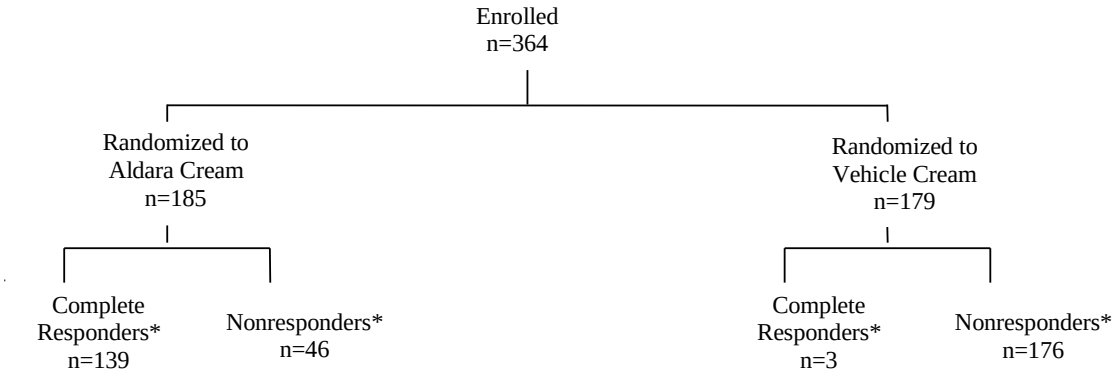
Sub-clinical AK lesions may become apparent in the treatment area during treatment with Aldara Cream. During the course of treatment, 48% (103/215) of patients experienced an increase in AK lesions relative to the number present at baseline within the treatment area. Patients with an increase in AK lesions had a similar response to those with no increase in AK lesions.

Of the 206 imiquimod subjects with both baseline and 8-week post-treatment scarring assessments, only 6 (2.9%) had a greater degree of scarring scores at 8-weeks post-treatment than at baseline.

Superficial Basal Cell Carcinoma

In two double-blind, vehicle-controlled clinical studies, 364 patients with primary superficial basal cell carcinoma (sBCC) were treated with Aldara Cream or vehicle cream 5X/week for 6 weeks. Patients with one biopsy-confirmed sBCC tumor were enrolled and randomized in a 1:1 ratio to active or vehicle treatment. Target tumors were to have a minimum area of 0.5 cm^2 and a maximum diameter of 2.0 cm (4.0 cm^2). Target tumors were not to be located within 1.0 cm of the hairline, eyes, nose, mouth, ears, on the anogenital area or on the hands or feet, or have any atypical features. On a scheduled dosing day, the study cream was applied to the target tumor and approximately 1 cm (about 1/3 inch) beyond the target tumor prior to normal sleeping hours; 5X/week dosing was continued for a total of 6 weeks. Twelve weeks after the last scheduled application of study cream, the target tumor area was clinically assessed. The entire target tumor was then excised and examined histologically for the presence of tumor.
The primary efficacy variable was the complete response rate defined as the proportion of patients with clinical (visual) and histological clearance of the sBCC lesion at 12 weeks post-treatment. The population ranged from 31-89 years of age (median 60 years) and 65% had Fitzpatrick skin type I or II. Patient outcomes are shown in the figure below.

Patient Accountability - Combined Phase III Studies



* Response measured at 12 weeks posttreatment

Of Aldara-treated patients 6% (11/178) who had both clinical and histological assessments post-treatment, and appeared to be clinically clear in Studies C and D had evidence of tumor on excision of the clinically clear treatment area.

Data on composite clearance (defined as both clinical and histological clearance) are shown in the table below.

Composite Clearance Rates at 12 Weeks Post-treatment for Superficial Basal Cell Carcinoma 5X/Week Application		
Study	**Aldara Cream**	**Vehicle Cream**
Study C	70% (66/94)	2% (2/89)
Study D	80% (73/91)	1% (1/90)
Total	75% (139/185)	2% (3/179)

An open-label 5-year study (Study E) is ongoing to assess the recurrence of sBCC treated with Aldara Cream applied once daily 5 days per week for 6 weeks. Target tumor inclusion criteria were the same as for Studies C and D as described above. At 12-weeks post-treatment, patients were clinically (no histological assessment) evaluated for evidence of persistent sBCC. Subjects with no clinical evidence of BCC entered the long-term follow-up period. At the 12 week post-treatment assessment 163/182 (90%) of the subjects enrolled had no clinical evidence of sBCC at their target site and 162 subjects entered the long-term follow-up period for up to 5 years. Two year (24 month) follow-up data are available from this study and are presented in the table below:

Estimated Clinical Clearance Rates for Superficial Basal Cell Carcinoma

Follow-up Period				
Follow-up visit after 12-week post-treatment assessment	No. of Subjects who remained clinically clear	No. of Subjects with sBCC recurrence	No. of Subjects who discontinued at this visit with no sBCC [a]	Estimated Rate of Patients who Clinically Cleared and remained Clear[b]
Month 3	153	4	5	87%
Month 6	149	4	0	85%
Month 12	143	2	4	84%
Month 24	139	4	0	79%

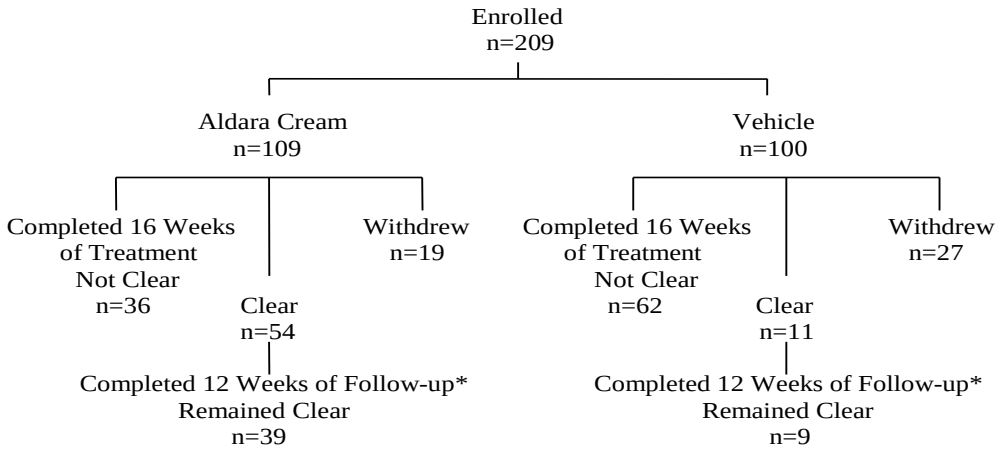
[a] Reasons for discontinuation included death, non-compliance, entry criteria violations, personal reasons, and treatment of nearby sBCC tumor.

[b] Estimated rate of patients who clinically cleared and remained clear are estimated based on the time to event analysis employing the life table method beginning with the rate of clinical clearance at 12 weeks post-treatment.

External Genital Warts

In a double-blind, placebo-controlled clinical study, 209 otherwise healthy patients 18 years of age and older with genital/perianal warts were treated with Aldara Cream or vehicle control 3X/week for a maximum of 16 weeks. The median baseline wart area was 69 mm^2 (range 8 to 5525 mm^2). Patient accountability is shown in the figure below.

Patient Accountability - Study 1004-IMIQ
3X/Week Application



*The other patients were either lost to follow-up or experienced recurrences.

Data on complete clearance are listed in the table below. The median time to complete wart clearance was 10 weeks.

Complete Clearance Rates - Study 1004-IMIQ

Treatment	Patients with Complete Clearance of Warts	Patients Without Follow-up	Patients with Warts Remaining at Week 16
Overall			
Aldara Cream (n =109)	50%	17%	33%
Vehicle (n =100)	11%	27%	62%
Females			
Aldara Cream (n =46)	72%	11%	17%
Vehicle (n =40)	20%	33%	48%
Males			
Aldara Cream (n =63)	33%	22%	44%
Vehicle (n =60)	5%	23%	72%

INDICATIONS AND USAGE

Aldara Cream is indicated for the treatment of external genital and perianal warts/condyloma acumunata in adult patients. For the treatment of actinic keratoses in adults with normal immune systems.

Aldara Cream is indicated for the topical treatment of biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured. The histological diagnosis of superficial basal cell carcinoma should be established prior to treatment , since safety and effectiveness of Aldara Cream have not been established for other types of basal cell carcinomas, including nodular, morpheaform (fibrosing or sclerosing) types.

CONTRAINDICATIONS

This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity to any of its ingredients is noted.

Warnings
The diagnosis of sBCC should be confirmed prior to treatment, since safety and effectiveness of Aldara Cream have not been established for other types of basal cell carcinomas, including nodular, morpheaform (fibrosing or sclerosing) types and is not recommended for treatment of BCC subtypes other than the superficial variant (i.e., sBCC). Patients with sBCC treated with Aldara Cream are recommended to have regular follow-up of the treatment site. See table of Estimated Clinical Clearance Rates for Superficial Basal Cell Carcinoma in the CLINICAL STUDIES section.

Aldara Cream has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease and is not recommended for these conditions.

Precautions

General

The safety and efficacy of Aldara Cream in immunosuppressed patients have not been established.

Aldara Cream administration is not recommended until the skin is completely healed from any previous drug or surgical treatment.

Aldara Cream has the potential to exacerbate inflammatory conditions of the skin.

Exposure to sunlight (including sunlamps) should be avoided or minimized during use of Aldara Cream because of concern for heightened sunburn susceptibility. Patients should be warned to use protective clothing (hat) when using Aldara Cream. Patients with sunburn should be advised not to use Aldara 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 when using Aldara Cream. Phototoxicity has not been adequately assessed for Aldara Cream. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Despite the absence of observed phototoxicity in humans *(see ADVERSE REACTIONS)*, Aldara Cream shortened the time to skin tumor formation in an animal photoco-carcinogenicity study *(see Carcinogenesis, Mutagenesis, Impairment of Fertility)*. Therefore, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure.

Actinic Keratosis

Safety and efficacy have not been established for Aldara Cream in the treatment of actinic keratosis with repeated use, i.e. more than one treatment course, in the same 25 cm^2 area.The safety of Aldara Cream applied to areas of skin greater than 25 cm^2 (e.g. 5 cm X 5 cm) for the treatment of actinic keratosis has not been established (*see CLINICAL PHARMACOLOGY; Pharmacokinetics section* regarding systemic absorption).

SUPERFICIAL BASAL CELL CARCINOMA

The safety and efficacy of treating superficial basal cell carcinoma (sBCC) lesions on the face, head and anogenital area have not been established.

The efficacy and safety of Aldara Cream have not been established for patients with Basal Cell Nevus Syndrome or Xeroderma Pigmentosum.

Information for Patients

General Information

Patients using Aldara Cream should receive the following information and instructions:

1. This medication is to be used as directed by a physician. It is for external use only. Eye contact should be avoided.

2. The treatment area should not be bandaged or otherwise covered or wrapped as to be occlusive.

3. Some reports have been received of localized hypopigmentation and hyperpigmentation following Aldara Cream use. Follow-up information suggests that these skin color changes may be permanent in some patients.

Patients Being Treated for Actinic Keratosis (AK)

1. It is recommended that the treatment area be washed with mild soap and water 8 hours following Aldara Cream application.

2. It is common for patients to experience local skin reactions (can range from mild to severe in intensity) during treatment with Aldara Cream, and these reactions may extend beyond the application site onto the surrounding skin. Skin reactions generally decrease in intensity or resolve after cessation of Aldara Cream therapy. Potential local skin reactions include erythema, edema, vesicles, erosion/ulceration, weeping/exudate, flaking/scaling/dryness, and scabbing/crusting. Most patients using Aldara Cream for the treatment of AK experience erythema, flaking/scaling/dryness and scabbing/crusting at the application site with normal dosing. Patients may also experience application site reactions such as itching and/or burning.

Local skin reactions may be of such an intensity that patients may require rest periods from treatment. Treatment with Aldara Cream can be resumed after the skin reaction has subsided, as determined by the physician. Patients should contact their physician promptly if they experience any sign or symptom at the application site that restricts or prohibits their daily activity or makes continued application of the cream difficult.

3. Because of local skin reactions, during treatment and until healed, the treatment area is likely to appear noticeably different from normal skin. The skin surrounding the treatment area may also be affected, but less intensely so.

4. Contact with the eyes, lips and nostrils should be avoided.

5. Use of sunscreen is encouraged, and patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using Aldara Cream.

6. During treatment, sub-clinical AK lesions may become apparent in the treatment area and may subsequently resolve.

7. Partially-used packets should be discarded and not reused.

8. Dosing is twice weekly for the full 16 weeks, unless otherwise directed by the physician. However, the treatment period should not be extended beyond 16 weeks due to missed doses or rest periods.

Patients Being Treated for Superficial Basal Cell Carcinoma (sBCC)

1. It is recommended that the treatment area be washed with mild soap and water 8 hours following Aldara Cream application.

2. Most patients using Aldara Cream for the treatment of sBCC experience erythema, edema, induration, erosion, scabbing/crusting and flaking/scaling at the application site with normal dosing. These local skin reactions generally decrease in intensity or resolve after cessation of Aldara Cream therapy. Patients may also experience application site reactions such as itching and/or burning. Local skin reactions may be of such an intensity that patients may require rest periods from treatment. Treatment with Aldara Cream can be resumed after the skin reaction has subsided, as determined by the physician.

3. During treatment and until healed, affected skin is likely to appear noticeably different from normal skin.
4. It is prudent for patients to minimize or avoid exposure to natural or artificial sunlight.

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

6. Patients should contact their physician if they experience any sign or symptom at the application site that restricts or prohibits their daily activity or makes continued application of the cream difficult.

7. Patients with sBCC treated with Aldara Cream are recommended to have regular follow-up to re-evaluate the treatment site.

Patients Being Treated for External Genital Warts

1. It is recommended that the treatment area be washed with mild soap and water 6-10 hours following Aldara Cream application.

2. It is common for patients to experience local skin reactions such as erythema, erosion, excoriation/flaking, and edema at the site of application or surrounding areas. Most skin reactions are mild to moderate. Severe skin reactions can occur and should be promptly reported to the prescribing physician. Should severe local skin reaction occur, the cream should be removed by washing the treatment area with mild soap and water. Treatment with Aldara Cream can be resumed after the skin reaction has subsided.

3. Sexual (genital, anal, oral) contact should be avoided while the cream is on the skin.

4. Application of Aldara Cream in the vagina is considered internal and should be avoided. Female patients should take special care if applying the cream at the opening of the vagina because local skin reactions on the delicate moist surfaces can result in pain or swelling, and may cause difficulty in passing urine.

5. Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.

6. Patients should be aware that new warts may develop during therapy, as Aldara Cream is not a cure.

7. The effect of Aldara Cream on the transmission of genital/perianal warts is unknown.

8. Aldara Cream may weaken condoms and vaginal diaphragms, therefore concurrent use is not recommended.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Note: The Maximum Recommended Human Dose (MRHD) was set at 2 packets per treatment of Aldara Cream (25 mg imiquimod) for the animal multiple of human exposure ratios presented in this label. If higher doses than 2 packets of Aldara Cream are used clinically, then the animal multiple of human exposure would be reduced for that dose. A non-proportional increase in systemic exposure with increased dose of Aldara Cream was noted in the clinical pharmacokinetic study conducted in actinic keratosis subjects (*see Pharmacokinetics*). The AUC after topical application of 6 packets of Aldara Cream was 8 fold greater than the AUC after topical application of 2 packets of Aldara Cream in actinic keratosis subjects. Therefore, if a dose of 6 packets per treatment of Aldara Cream was topically administered to an individual, then the animal multiple of human exposure would be either 1/3 of the value provided in the label (based on body surface area comparisons) or 1/8 of the value provided in the label (based on AUC comparisons). The animal multiples of human exposure calculations were based on weekly dose comparisons for the carcinogenicity studies described in this label. The animal multiples of human exposure calculations were based on daily dose comparisons for the reproductive toxicology studies described in this label.

In an oral (gavage) rat carcinogenicity study, imiquimod was administered to Wistar rats on a 2X/week (up to 6 mg/kg/day) or daily (3 mg/kg/day) dosing schedule for 24 months. No treatment related tumors were noted in the oral rat carcinogenicity study up to the highest doses tested in this study of 6 mg/kg administered 2X/week in female rats (87X MRHD based on weekly AUC comparisons), 4 mg/kg administered 2X/week in male rats (75X MRHD based on weekly AUC comparisons) or 3 mg/kg administered 7X/week to male and female rats (153X MRHD based on weekly AUC comparisons).

In a dermal mouse carcinogenicity study, imiquimod cream (up to 5 mg/kg/application imiquimod or 0.3% imiquimod cream) was applied to the backs of mice 3X/week for 24 months. A statistically significant increase in the incidence of liver adenomas and carcinomas was noted in high dose male mice compared to control male mice (251X MRHD based on weekly AUC comparisons). An increased number of skin papillomas was observed in vehicle cream control group animals at the treated site only. The quantitative composition of the vehicle cream used in the dermal mouse carcinogenicity study is the same as the vehicle cream used for Aldara Cream, minus the active moiety (imiquimod).

In a 52-week dermal photoco-carcinogenicity study, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing (3X/week; 40 weeks of treatment followed by 12 weeks of observation) with concurrent exposure to UV radiation (5 days per week) with the Aldara Cream vehicle alone. No additional effect on tumor development beyond the vehicle effect was noted with the addition of the active ingredient, imiquimod, to the vehicle cream.

Imiquimod revealed no evidence of mutagenic or clastogenic potential based on the results of five in vitro genotoxicity tests (Ames assay, mouse lymphoma L5178Y assay, Chinese hamster ovary cell chromosome aberration assay, human lymphocyte chromosome aberration assay and SHE cell

transformation assay) and three in vivo genotoxicity tests (rat and hamster bone marrow cytogenetics assay and a mouse dominant lethal test).

Daily oral administration of imiquimod to rats, throughout mating, gestation, parturition and lactation, demonstrated no effects on growth, fertility or reproduction, at doses up to 87X MRHD based on AUC comparisons.

Pregnancy
Pregnancy Category C:

Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 1, 5 and 20 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. In the presence of maternal toxicity, fetal effects noted at 20 mg/kg/day [8X MRHD based on body surface area (BSA) comparisons] included increased resorptions, decreased fetal body weights, delays in skeletal ossification, bent limb bones, and two fetuses in one litter (2 of 1567 fetuses) demonstrated exencephaly, protruding tongues and low-set ears. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 5 mg/kg/day (55X MRHD based on AUC comparisons).

Intravenous doses of 0.5, 1 and 2 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6 – 18) to pregnant female rabbits. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 2 mg/kg/day (1.5X MRHD based on BSA comparisons), the highest dose evaluated in this study, or 1 mg/kg/day (407X MRHD based on AUC comparisons).

A combined fertility and peri- and post-natal development study was conducted in rats. Oral doses of 1, 1.5, 3 and 6 mg/kg/day imiquimod were administered to male rats from 70 days prior to mating through the mating period and to female rats from 14 days prior to mating through parturition and lactation. No effects on growth, fertility, reproduction or post-natal development were noted at doses up to 6 mg/kg/day (87X MRHD based on AUC comparisons), the highest dose evaluated in this study. In the absence of maternal toxicity, bent limb bones were noted in the F1 fetuses at a dose of 6 mg/kg/day (87X MRHD based on AUC comparisons). This fetal effect was also noted in the oral rat embryofetal development study conducted with imiquimod. No treatment related effects on teratogenicity were noted at 3 mg/kg/day (41X MRHD based on AUC comparisons).

There are no adequate and well-controlled studies in pregnant women. Aldara Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether topically applied imiquimod is excreted in breast milk.

Pediatric Use

Safety and efficacy in patients with external genital/perianal warts below the age of 12 years have not been established.

AK and sBCC are not conditions generally seen within the pediatric population. The safety and efficacy of Aldara Cream for AK or sBCC in patients less than 18 years of age have not been established.

Geriatric Use

Of the 215 patients in the 2X/week clinical studies evaluating the treatment of AK lesions with Aldara Cream, 127 patients (59%) were 65 years and older, while 60 patients (28%) were 75 years and older. Of the 185 patients in the 5X/week treatment groups of clinical studies evaluating the treatment of sBCC with Aldara 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 responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

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

Actinic Keratosis

The data described below reflect exposure to Aldara Cream or vehicle in 436 patients enrolled in two double-blind, vehicle-controlled, 2X/week studies. Patients applied Aldara Cream or vehicle to a 25 cm^2 contiguous treatment area on the face or scalp 2X/week for 16 weeks.

Summary of All Adverse Events Reported by > 1% of Patients in the Combined 2X/ Week Studies

Body System Preferred Term	Imiq 2X/Week (n= 215)	Vehicle 2X/Week (n= 221)
APPLICATION SITE DISORDERS		
APPLICATION SITE REACTION	71 (33.0%)	32 (14.5%)
BODY AS A WHOLE - GENERAL DISORDERS		
BACK PAIN	3 (1.4%)	2 (0.9%)
FATIGUE	3 (1.4%)	2 (0.9%)
FEVER	3 (1.4%)	0 (0.0%)
HEADACHE	11 (5.1%)	7 (3.2%)
HERNIA NOS	4 (1.9%)	1 (0.5%)
INFLUENZA- LIKE SYMPTOMS	4 (1.9%)	4 (1.8%)
PAIN	3 (1.4%)	3 (1.4%)
RIGORS	3 (1.4%)	0 (0.0%)
CARDIOVASCULAR DISORDERS, GENERAL		
CHEST PAIN	1 (0.5%)	4 (1.8%)
HYPERTENSION	3 (1.4%)	5 (2.3%)
CENTR & PERIPH NERVOUS SYSTEM DISORDERS		
DIZZINESS	3 (1.4%)	1 (0.5%)
GASTRO- INTESTINAL SYSTEM DISORDERS		
DIARRHOEA	6 (2.8%)	2 (0.9%)
DYSPEPSIA	6 (2.8%)	4 (1.8%)
GASTROESOPHAGEAL REFLUX	3 (1.4%)	3 (1.4%)
NAUSEA	3 (1.4%)	3 (1.4%)
VOMITING	3 (1.4%)	1 (0.5%)
HEART RATE AND RHYTHM DISORDERS		
FIBRILLATION ATRIAL	3 (1.4%)	2 (0.9%)
METABOLIC AND NUTRITIONAL DISORDERS		
HYPERCHOLESTEROLAEMIA	4 (1.9%)	0 (0.0%)
MUSCULO- SKELETAL SYSTEM DISORDERS		
ARTHRALGIA	2 (0.9%)	4 (1.8%)
ARTHRITIS	2 (0.9%)	3 (1.4%)
MYALGIA	3 (1.4%)	3 (1.4%)
SKELETAL PAIN	1 (0.5%)	3 (1.4%)
NEOPLASM		
BASAL CELL CARCINOMA	5 (2.3%)	5 (2.3%)
CARCINOMA SQUAMOUS	8 (3.7%)	5 (2.3%)
RESISTANCE MECHANISM DISORDERS	9 (4.2%)	11 (5.0%)
HERPES SIMPLEX	4 (1.9%)	4 (1.8%)
INFECTION VIRAL	3 (1.4%)	2 (0.9%)
RESPIRATORY SYSTEM DISORDERS		
BRONCHITIS	2 (0.9%)	3 (1.4%)
COUGHING	6 (2.8%)	10 (4.5%)
PHARYNGITIS	4 (1.9%)	4 (1.8%)

PULMONARY CONGESTION	1 (0.5%)	3 (1.4%)
RHINITIS	7 (3.3%)	8 (3.6%)
SINUSITIS	16 (7.4%)	14 (6.3%)
UPPER RESP TRACT INFECTION	33 (15.3%)	27 (12.2%)
SECONDARY TERMS		
ABRASION NOS	7 (3.3%)	5 (2.3%)
CYST NOS	0 (0.0%)	4 (1.8%)
INFLICTED INJURY	19 (8.8%)	21 (9.5%)
POST- OPERATIVE PAIN	3 (1.4%)	4 (1.8%)
SKIN AND APPENDAGES DISORDERS	47 (21.9%)	42 (19.0%)
ALOPECIA	3 (1.4%)	0 (0.0%)
DERMATITIS	3 (1.4%)	7 (3.2%)
ECZEMA	4 (1.9%)	3 (1.4%)
HYPERKERATOSIS	19 (8.8%)	12 (5.4%)
PHOTOSENSITIVITY REACTION	2 (0.9%)	4 (1.8%)
PRURITUS	2 (0.9%)	3 (1.4%)
RASH	5 (2.3%)	5 (2.3%)
SKIN DISORDER	6 (2.8%)	7 (3.2%)
VERRUCA	1 (0.5%)	3 (1.4%)
URINARY SYSTEM DISORDERS	8 (3.7%)	10 (4.5%)
URINARY TRACT INFECTION	3 (1.4%)	1 (0.5%)
VISION DISORDERS		
CONJUNCTIVITIS	1 (0.5%)	3 (1.4%)
EYE ABNORMALITY	4 (1.9%)	1 (0.5%)
EYE INFECTION	0 (0.0%)	3 (1.4%)

Summary of All Application Site Reactions Reported by > 1% of Patients in the Combined 2X/ Week Studies

Included Term	Imiq 2X/Week (n= 215)	Vehicle 2X/Week (n= 221)
BLEEDING AT TARGET SITE	7 (3.3%)	1 (0.5%)
BURNING AT REMOTE SITE	4 (1.9%)	0 (0.0%)
BURNING AT TARGET SITE	12 (5.6%)	4 (1.8%)
INDURATION AT REMOTE SITE	3 (1.4%)	0 (0.0%)
INDURATION AT TARGET SITE	5 (2.3%)	3 (1.4%)
IRRITATION AT REMOTE SITE	3 (1.4%)	0 (0.0%)
ITCHING AT REMOTE SITE	7 (3.3%)	3 (1.4%)
ITCHING AT TARGET SITE	44 (20.5%)	15 (6.8%)
PAIN AT TARGET SITE	5 (2.3%)	2 (0.9%)
STINGING AT TARGET SITE	6 (2.8%)	2 (0.9%)
TENDERNESS AT TARGET SITE	4 (1.9%)	3 (1.4%)

Local skin reactions were collected independently of the adverse event "application site reaction" in an effort to provide a better picture of the specific types of local reactions that might be seen. The most frequently reported local skin reactions were erythema, flaking/scaling/dryness, and scabbing/crusting. The prevalence and severity of local skin reactions that occurred during controlled studies are shown in the following table.

Local Skin Reactions in the Treatment Area as Assessed by the Investigator (Percentage of Patients) 2X/Week Application

	Mild/Moderate/Severe		Severe	
	Aldara Cream n=215	Vehicle n=220	Aldara Cream n=215	Vehicle n=220
Erythema	209 (97%)	206 (93%)	38 (18%)	5 (2%)
Edema	106 (49%)	22 (10%)	0 (0%)	0 (0%)
Weeping/Exudate	45 (22%)	3 (1%)	0 (0%)	0 (0%)

Vesicles	19 (9%)	2 (1%)	0 (0%)	0 (0%)
Erosion/Ulceration	103 (48%)	20 (9%)	5 (2%)	0 (0%)
Flaking/Scaling/Dryness	199 (93%)	199 (91%)	16 (7%)	7 (3%)
Scabbing/Crusting	169 (79%)	92 (42%)	18 (8%)	4 (2%)

The adverse reactions that most frequently resulted in clinical intervention (e.g., rest periods, withdrawal from study) were local skin and application site reactions. Overall, in the clinical studies, 2% (5/215) of patients discontinued for local skin/application site reactions. Of the 215 patients treated, 35 patients (16%) on Aldara Cream and 3 of 220 patients (1%) on vehicle cream had at least one rest period. Of these Aldara Cream patients, 32 (91%) resumed therapy after a rest period.

In the AK studies, 22 of 678 imiquimod treated patients developed treatment site infections that required a rest period off Aldara Cream and were treated with antibiotics (19 with oral and 3 with topical).

Superficial Basal Cell Carcinoma

The data described below reflect exposure to Aldara Cream or vehicle in 364 patients enrolled in two double-blind, vehicle-controlled, 5X/week studies. Patients applied Aldara Cream or vehicle 5X/week for 6 weeks. The incidence of adverse events reported by > 1% of subjects during the 6 week treatment period is summarized below.

Summary of All Adverse Events Reported by > 1% of Patients in the Combined 5X/ Week Studies

Body System Preferred Term	**Imiquimod 5x/Week (n= 185) N %**	**Vehicle 5x/Week (n= 179) N %**
APPLICATION SITE DISORDERS		
APPLICATION SITE REACTION	52 (28.1%)	5 (2.8%)
BODY AS A WHOLE - GENERAL DISORDERS		
ALLERGY AGGRAVATED	2 (1.1%)	1 (0.6%)
BACK PAIN	7 (3.8%)	1 (0.6%)
CHEST PAIN	2 (1.1%)	0 (0.0%)
FATIGUE	4 (2.2%)	2 (1.1%)
FEVER	3 (1.6%)	0 (0.0%)
PAIN	3 (1.6%)	2 (1.1%)
CARDIOVASCULAR DISORDERS, GENERAL		
HYPERTENSION	5 (2.7%)	1 (0.6%)
CENTR & PERIPH NERVOUS SYSTEM DISORDERS		
DIZZINESS	2 (1.1%)	1 (0.6%)
HEADACHE	14 (7.6%)	4 (2.2%)
GASTRO- INTESTINAL SYSTEM DISORDERS		
ABDOMINAL PAIN	1 (0.5%)	2 (1.1%)
DIARRHOEA	1 (0.5%)	2 (1.1%)
DYSPEPSIA	3 (1.6%)	2 (1.1%)
GASTRO- INTESTINAL DISORDER NOS	1 (0.5%)	2 (1.1%)
NAUSEA	2 (1.1%)	0 (0.0%)
TOOTH DISORDER	0 (0.0%)	2 (1.1%)
METABOLIC AND NUTRITIONAL DISORDERS		
GOUT	2 (1.1%)	0 (0.0%)
MUSCULO-SKELETAL SYSTEM DISORDERS		
SKELETAL PAIN	3 (1.6%)	2 (1.1%)
PSYCHIATRIC DISORDERS		
ANXIETY	2 (1.1%)	1 (0.6%)
RESISTANCE MECHANISM DISORDERS		
INFECTION	1 (0.5%)	3 (1.7%)
INFECTION FUNGAL	2 (1.1%)	2 (1.1%)

RESPIRATORY SYSTEM DISORDERS		
COUGHING	3 (1.6%)	1 (0.6%)
PHARYNGITIS	2 (1.1%)	1 (0.6%)
RHINITIS	5 (2.7%)	1 (0.6%)
SINUSITIS	4 (2.2%)	1 (0.6%)
UPPER RESP TRACT INFECTION	6 (3.2%)	2 (1.1%)
SECONDARY TERMS		
INFLICTED INJURY	3 (1.6%)	3 (1.7%)
PROCEDURAL SITE REACTION	2 (1.1%)	3 (1.7%)
SKIN AND APPENDAGES DISORDERS		
HYPERKERATOSIS	3 (1.6%)	2 (1.1%)
RASH	3 (1.6%)	1 (0.6%)
SKIN DISORDER	1 (0.5%)	3 (1.7%)
WHITE CELL AND RES DISORDERS		
LYMPHADENOPATHY	5 (2.7%)	1 (0.6%)

In controlled clinical studies, the most frequently reported adverse reactions were local skin and application site reactions including erythema, edema, induration, erosion, flaking/scaling, scabbing/crusting, itching and burning at the application site. The incidence of the application site reactions reported by > 1% of the subjects during the 6 week treatment period is summarized in the table below.

Summary of All Application Site Reactions Reported by > 1% of Patients in the Combined 5X/ Week Studies

Included Term	**Imiquimod 5x/ Week (n= 185) N %**	**Vehicle 5x/ Week (n= 179) N %**
ITCHING AT TARGET SITE	30 (16.2%)	1 (0.6%)
BURNING AT TARGET SITE	11 (5.9%)	2 (1.1%)
PAIN AT TARGET SITE	6 (3.2%)	0 (0.0%)
TENDERNESS AT TARGET SITE	2 (1.1%)	0 (0.0%)
ERYTHEMA AT REMOTE SITE	3 (1.6%)	0 (0.0%)
PAPULE(S) AT TARGET SITE	3 (1.6%)	0 (0.0%)
BLEEDING AT TARGET SITE	4 (2.2%)	0 (0.0%)
TINGLING AT TARGET SITE	1 (0.5%)	2 (1.1%)
INFECTION AT TARGET SITE	2 (1.1%)	0 (0.0%)

Local skin reactions were collected independently of the adverse event "application site reaction" in an effort to provide a better picture of the specific types of local reactions that might be seen. The prevalence and severity of local skin reactions that occurred during controlled studies are shown in the following table.

Most Intense Local Skin Reactions in the Treatment Area as Assessed by the Investigator (Percentage of Patients) 5X/Week Application

	Mild/Moderate		**Severe**	
	Aldara Cream n=184	Vehicle n=178	Aldara Cream n=184	Vehicle n=178
Edema	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%

The adverse reactions that most frequently resulted in clinical intervention (e.g., rest periods, withdrawal from study) were local skin and application site reactions; 10% (19/185) of patients received rest periods. The average number of doses not received per patient due to rest periods was 7 doses with a range of 2 to 22 doses; 79% of patients (15/19) resumed therapy after a rest period. Overall, in the clinical studies, 2% (4/185) of patients discontinued for local skin/application site reactions.

In the sBCC studies, 17 of 1266 (1.3%) imiquimod-treated patients developed treatment site infections that required a rest period off Aldara Cream and were treated with antibiotics.

External Genital Warts

In controlled clinical trials for genital warts, the most frequently reported adverse reactions were local skin and application site reactions.
These reactions were usually mild to moderate in intensity; however, severe reactions were reported with 3X/week application. **These reactions were more frequent and more intense with daily application than with 3X/week application.** Some patients also reported systemic reactions. Overall, in the 3X/week application clinical studies, 1.2% (4/327) of the patients discontinued due to local skin/application site reactions. The incidence and severity of local skin reactions during controlled clinical trials are shown in the following table.

Wart Site Reaction as Assessed by Investigator (Percentage of Patients)
3X/Week Application

	Mild/Moderate/Severe				**Severe**			
	Females		**Males**		**Females**		**Males**	
	Aldara Cream n=114	Vehicle n=99	Aldara Cream n=156	Vehicle n=157	Aldara Cream n=114	Vehicle n=99	Aldara Cream n=156	Vehicle n=157
Erythema	74 (65%)	21 (21%)	90 (58%)	34 (22%)	4 (4%)	0 (0%)	6 (4%)	0 (0%)
Erosion	35 (31%)	8 (8%)	47 (30%)	10 (6%)	1 (1%)	0 (0%)	2 (1%)	0 (0%)
Excoriation/ Flaking	21 (18%)	8 (8%)	40 (26%)	12 (8%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Edema	20 (18%)	5 (5%)	19 (12%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Induration	6 (5%)	2 (2%)	11 (7%)	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ulceration	9 (8%)	1 (1%)	7 (4%)	1 (1%)	3 (3%)	0 (0%)	0 (0%)	0 (0%)
Scabbing	4 (4%)	0 (0%)	20 (13%)	4 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Vesicles	3 (3%)	0 (0%)	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Remote site skin reactions were also reported in female and male patients treated 3X/week with Aldara Cream. The severe remote site skin reactions reported for females were erythema (3%), ulceration (2%), and edema (1%); and for males, erosion (2%), and erythema, edema, induration, and excoriation/flaking (each 1%).

Adverse events judged to be probably or possibly related to Aldara Cream reported by more than 5% of patients are listed below; also included are soreness, influenza-like symptoms and myalgia.

3X/Week Application

	Females		Males	
	Aldara Cream n=117	Vehicle n=103	Aldara Cream n=156	Vehicle n=158
Application Site Disorders:				
Application Site Reactions				
Wart Site:				
Itching	32%	20%	22%	10%
Burning	26%	12%	9%	5%
Pain	8%	2%	2%	1%
Soreness	3%	0%	0%	1%
Fungal Infection*	11%	3%	2%	1%
Systemic Reactions:				
Headache	4%	3%	5%	2%
Influenza-like symptoms	3%	2%	1%	0%
Myalgia	1%	0%	1%	1%

* Incidences reported without regard to causality with Aldara Cream.

Adverse events judged to be possibly or probably related to Aldara Cream and reported by more than 1% of patients included: **Application Site Disorders: Wart Site Reactions** (burning, hypopigmentation, irritation, itching, pain, rash, sensitivity, soreness, stinging, tenderness); **Remote Site Reactions** (bleeding, burning, itching, pain, tenderness, tinea cruris); **Body as a Whole:** fatigue, fever, influenza-like symptoms; **Central and Peripheral Nervous System Disorders:** headache; **Gastro-Intestinal System Disorders:** diarrhea; **Musculo-Skeletal System Disorders:** myalgia.

OVERDOSAGE

Persistent topical overdosing of Aldara Cream could result in an increased incidence of severe local skin reactions and may increase the risk for systemic reactions. The most clinically serious adverse event reported following multiple oral imiquimod doses of >200 mg (equivalent to imiquimod content of >16 packets) was hypotension, which resolved following oral or intravenous fluid administration.

DOSAGE AND ADMINISTRATION

The application frequency for Aldara Cream is different for each indication.

Actinic Keratosis

Aldara Cream is to be applied 2 times per week for 16 weeks to a defined treatment area on the face or scalp (but not both concurrently). The treatment area should be one contiguous area of approximately 25 cm^2 (e.g., 5 cm x 5 cm). Imiquimod cream should be applied to the entire treatment area (e.g., the forehead, scalp, or one cheek).

Aldara Cream is packaged in single-use packets, with 12 packets supplied per box. Patients should be prescribed no more than 3 boxes (36 packets) for the 16 week treatment period. Unused packets should be discarded. Partially-used packets should be discarded and not reused. Before applying the cream, the patient should wash the treatment area with mild soap and water and allow the area to dry thoroughly (at least 10 minutes). The patient should apply no more than one packet of Aldara Cream to the contiguous treatment area at each application. **Aldara Cream is applied prior to normal sleeping hours, and left on the skin for approximately 8 hours, after which time the cream should be removed by washing the area with mild soap and water.** The cream should be rubbed into the treatment area until the cream is no longer visible. Contact with the eyes, lips and nostrils should be avoided. Examples of two times per week application schedules are Monday and Thursday, or Tuesday and Friday prior to sleeping hours**. Aldara Cream treatment should continue for the full 16 weeks. However, the treatment period should not be extended beyond 16 weeks due to missed doses or rest periods.** Local skin reactions in the treatment area are common. Patients should contact their physician if they experience any sign or symptom in the treatment area that restricts or prohibits their daily activity or makes continued

application of the cream difficult. A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of Aldara Cream therapy. Handwashing before and after cream application is recommended.

Lesions that do not respond to therapy should be carefully re-evaluated and management reconsidered.

Superficial Basal Cell Carcinoma

Aldara Cream is to be applied 5 times per week for 6 weeks to a biopsy-confirmed superficial basal cell carcinoma. The target tumor should have a maximum diameter of no more than 2 cm and be located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet). The treatment area should include a 1 cm margin of skin around the tumor**.**

Target Tumor Diameter	Size of Cream Droplet to be Used (diameter)	Approximate Amount of Cream to be Used
0.5 to < 1.0 cm	**4 mm**	**10 mg**
≥ 1.0 to < 1.5 cm	**5 mm**	**25 mg**
≥ 1.5 to 2.0 cm	**7 mm**	**40 mg**

Aldara Cream is packaged in single-use packets, with 12 packets supplied per box. Patients should be prescribed no more than 3 boxes (36 packets) for the 6 week treatment period. Unused packets should be discarded. Partially-used packets should be discarded and not reused.

Aldara Cream is to be applied 5 times per week, prior to normal sleeping hours, and left on the skin for approximately 8 hours. Before applying the cream, the patient should wash the treatment area with mild soap and water and allow the area to dry thoroughly. Sufficient cream should be applied to cover the treatment area, including one centimeter of skin surrounding the tumor. The cream should be rubbed into the treatment area until the cream is no longer visible. Eye contact should be avoided. Following the treatment period, cream should be removed by washing the area with mild soap and water. An example of a 5 times per week application schedule is to apply Aldara Cream, once per day, Monday through Friday, prior to sleeping hours. **Aldara Cream treatment should continue for 6 weeks.** Local skin reactions in the treatment area are common. Patients should contact their physician if they experience any sign or symptom in the treatment area that restricts or prohibits their daily activity or makes continued application of the cream difficult. A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of Aldara Cream therapy. Handwashing before and after cream application is recommended.

Early clinical clearance cannot be adequately assessed until resolution of local skin reactions. It is appropriate to have the first follow-up visit at approximately 12 weeks post-treatment to assess the treatment site for clinical clearance. Local skin reactions or other findings (e.g. infection) may require that a patient be seen sooner than the 12 week post-treatment visit. If there is clinical evidence of persistent tumor at the 12 week post-treatment assessment, a biopsy or other alternative intervention should be considered; the safety and efficacy of a repeat course of Aldara Cream treatment have not been established. If any suspicious lesion arises in the treatment area at any time after 12 weeks, the patient should seek a medical evaluation. See table of Estimated Clinical Clearance Rates for Superficial Basal Cell Carcinoma in the CLINICAL STUDIES section.

External Genital Warts

Aldara Cream is to be applied 3 times per week, prior to normal sleeping hours, and left on the skin for 6-10 hours. Patients should be instructed to apply Aldara Cream to external genital/perianal warts. A thin layer is applied to the wart area and rubbed in until the cream is no longer visible. The application site is not to be occluded. Following the treatment period cream should be removed by washing the treated area with mild soap and water. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday; or Tuesday, Thursday, Saturday application prior to sleeping hours. Aldara Cream treatment should continue until there is total clearance of the genital/perianal warts or for a maximum of 16 weeks. Local skin reactions (erythema) at the treatment site are common. A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. Treatment

may resume once the reaction subsides. Non-occlusive dressings such as cotton gauze or cotton underwear may be used in the management of skin reactions. The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of Aldara Cream therapy. Handwashing before and after cream application is recommended. Aldara Cream is packaged in single-use packets which contain sufficient cream to cover a wart area of up to 20 cm^2; use of excessive amounts of cream should be avoided.

HOW SUPPLIED

Aldara (imiquimod) Cream, 5%, is supplied in single-use packets which contain 250 mg of the cream.
Available as: box of 12 packets NDC 0089-0610-12.

Store below 25°C (77°F).
Avoid freezing.

Keep out of reach of children.

Rx only

Manufactured by
3M HEALTH Care Limited
Loughborough LE11 1EP England

Imported by
Pharmateam Marketing 2000 L td.
P.O. Box 405 Jerusalem 91003

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