PRODUCT MONOGRAPH

PrALDARA® P
(imiquimod) Cream, 5%

Immune response modifier

Bausch Health, Canada Inc.
2150 St-Elzear Blvd. West
Laval, Quebec
H7L 4A8

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ACTION AND CLINICAL PHARMACOLOGY

In vitro studies have demonstrated that imiquimod induces the release of interferon alpha (IFN-α) and other cytokines from human monocytes/macrophages and keratinocytes. The panel of cytokines induced varied with the cell's tissue origin. Topical in vivo application of imiquimod cream on mouse skin resulted in increased concentrations of IFN and tumor necrosis factor (TNF) compared with skin of untreated mice. The cytokine inducing properties of imiquimod may be responsible for its activity against genital/perianal warts, as imiquimod does not have a direct antiviral activity in cell cultures. The clinical relevance of these findings is, however, unknown.

Pharmacodynamics

Superficial Basal Cell Carcinoma (sBCC)
The mechanism of action of imiquimod in treating superficial basal cell carcinoma (sBCC) lesions is unknown. One clinical study in 6 subjects has suggested that imiquimod stimulates the infiltration of T-cell lymphocytes, dendritic cells, and macrophages into the basal cell carcinoma lesion.

Actinic Keratosis
The mechanism of action of imiquimod in treating actinic keratosis (AK) lesions is unknown. While the following have been observed, the clinical significance of these observations in AK is not known. In a study of 58 patients with AK treated with imiquimod 3 times per week, the response of biomarkers sensitive to imiquimod after 16 weeks of dosing increased compared to the response after the first dose. For interleukin-1 antagonist, the median concentration observed following multiple dosing was <2-fold higher than that after single dose administration, for interferon-α was α 3-fold, and for 2'5'-oligoadenylate synthetase was approximately 3-fold.

External Genital Warts
Imiquimod has no direct antiviral activity in cell culture. A study in 22 patients with genital/perianal warts comparing imiquimod and vehicle shows that imiquimod 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

Percutaneous absorption of imiquimod has been studied through intact healthy skin, the skin of genital warts, and lesions of sun damaged skin. Percutaneous absorption of [14C] imiquimod was minimal in a study involving six healthy subjects treated with a single topical application (5 mg) of [14C] imiquimod in cream formulation. No radioactivity was detected in the serum

(lower limit of quantitation is 1 ng/mL) and < 0.9% of the radiolabeled dose was excreted in the urine and feces following topical application.

Systemic absorption of imiquimod was observed across the affected skin of 12 patients with genital/perianal warts who were treated 3 times per week with sufficient 5% imiquimod cream to cover the affected wart area (average dose 4.6 mg imiquimod) for 16 weeks. Mean (median) peak drug concentrations of 0.3 (0.1) ng/mL were seen following week 16 dosing. Mean (median) urinary recoveries following the last dose of week 16, expressed as percent of the estimated applied dose, were 0.24 (0.09) and 2.52 (1.2) % of the dose for males and females, respectively, which may suggest a possible sex difference in absorption and/or excretion.

Similarly, 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 (median) peak serum drug concentrations at the end of week 16 were observed between 9 and 12 hours and were approximately 0.1 (0.1), 0.2 (0.2), and 3.5 (1.6) ng/mL for the applications to face (12.5 mg imiquimod), scalp (25 mg) and hands/arms (75 mg), respectively. The application surface area was not controlled in the scalp and hands/arms groups. Dose proportionality was not observed, although the pharmacokinetic parameters (Cmax and AUC) tended to increase with dose. It appears that systemic exposure may be more dependent on surface area of application than amount of applied dose. The apparent half-life following topical dosing was calculated as 26 hours, which is approximately 10 times greater than the 2-hour apparent half-life seen following subcutaneous dosing and suggests prolonged retention of drug in the skin. Mean (median) urinary recoveries at week 16 were 0.18 (0.14), 0.24 (0.24) and 0.12 (0.09) % of the applied dose following application to the face, scalp and hands/arms, respectively. The highest urinary recovery measured in any patient was less than 0.6% of the applied dose at week 16.

INDICATIONS AND CLINICAL USE

ALDARA P (imiquimod) cream is indicated in immunocompetent adults for the following conditions.

- Treatment of biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), otherwise amenable to simple surgical excision, in patients who, in consultation with their physician, choose not to have surgery and are willing to undergo regular follow-up. Note: Surgical excision is the usual treatment of choice for these sBCC tumors. While ALDARA P has been shown to be effective in the short-term clearance of sBCC in ~75% of cases, there are no data directly comparing ALDARA P to surgical excision.

- Treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratosis on the face or balding scalp.

- Treatment of external genital and perianal warts/condyloma acuminata.

CONTRAINDICATIONS

ALDARA P (imiquimod) cream 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

Patients with sBCC treated with ALDARA P cream are required to have regular follow-up of the treatment site because the efficacy of imiquimod in the treatment of sBCC is generally less than that with surgery and, as well, because the long-term efficacy and safety of imiquimod in the treatment of sBCC have not yet been established.

The histological diagnosis of superficial basal cell carcinoma should be established prior to treatment since ALDARA P (imiquimod) cream has not been evaluated for the treatment of 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.

ALDARA P (imiquimod) cream has not been evaluated for the treatment of sBCC on the face, head, hands or feet, and anogenital area.

The efficacy of ALDARA P in the prevention of squamous cell carcinoma (SCC) associated with AK has not been established. One subject who participated in a clinical trial of imiquimod and had complete clearance of AK lesions with imiquimod treatment developed a SCC in situ in the treatment area within 12 to 18 months of treatment (see PHARMACOLOGY, Clinical Studies).

ALDARA P 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.

Hypersensitivity reactions (urticaria) and erythema multiforme have been reported in patients receiving ALDARA P cream. Causality has not been established and no other reports of similar cases have been reported in post-marketing surveillance. ALDARA P cream should be discontinued immediately if these events occur.

Some reports of localized hypopigmentation and hyperpigmentation following use of ALDARA P cream have been received. Post-marketing reporting suggests that these skin color changes may be permanent in some patients.

PRECAUTIONS

General

ALDARA P cream administration is not recommended until skin or genital/perianal tissue is healed from any previous drug or surgical treatment. ALDARA P cream has the potential to exacerbate inflammatory conditions of the skin.

Local skin reactions such as erythema, erosion, excoriation/flaking, and edema are common.

Should a severe local skin reaction occur, the cream should be removed by washing the treatment area with mild soap and water. Treatment with ALDARA P can be resumed after the skin reaction has subsided.

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

The safety of ALDARA P cream applied to areas of skin greater than 25cm2 for the treatment of actinic keratosis has not been established.

The safety and efficacy of ALDARA P cream in immunosuppressed patients have not been established.

Flu-like systemic signs and symptoms including malaise, fever, nausea, myalgias and rigors may occur. Dosing interruption may be required.

ALDARA P cream should be used with caution in patients with pre-existing autoimmune conditions. Rare reports have been received of exacerbation of autoimmune conditions in patients treated with ALDARA P.

ALDARA P cream has the potential to exacerbate inflammatory conditions of the skin, including chronic graft versus host disease.

Exposure to sunlight (including sunlamps) should be avoided or minimized during use of ALDARA P cream because of concern for heightened sunburn susceptibility. Patients should be warned to use protective clothing (hat) when using ALDARA P cream. Patients with sunburn should be advised not to use ALDARA P 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 P cream. Phototoxicity has not been adequately assessed for ALDARA P cream. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Despite the absence of observed phototoxicity in humans (see PHARMACOLOGY, Clinical Studies), ALDARA P 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.

Carcinogenicity, Mutagenesis, and Impairment of Fertility

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

In a photocarcinogenicity study in hairless mice, animals received ALDARA P cream 3 times per week at imiquimod concentrations of 0.03%, 0.1% and 0.3% and were irradiated with solar ultraviolet light for 5 days each week for 40 weeks and observed an additional 12 weeks. Vehicle cream enhanced UVR-induced skin tumour development. ALDARA P cream had no additional effect on tumour development beyond the vehicle effect (i.e., the addition of the active ingredient, imiquimod, to the vehicle cream did not result in an additional effect beyond the vehicle effect on tumour development).

Pregnancy

Imiquimod was not teratogenic in rat or rabbit teratology studies. In rats at a high maternally toxic dose (28 times human dose on a mg/m2 basis), reduced pup weights and delayed ossification were observed. However, there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

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

Use in Children

Safety and efficacy in patients below the age of 18 years have not been established.

Geriatric Use

Although no overall differences in safety or effectiveness have been observed between elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out. Of the 185 patients in the 5 times per week treatment groups of clinical studies evaluating the treatment of sBCC with ALDARA P cream, 65 patients (35%) were 65 years and older, while 25 patients (14%) were 75 years and older. Of the 215 patients in the 2 times per week clinical studies evaluating the treatment of AK lesions with ALDARA P cream, 127 patients (59%) were 65 years and older, while 60 patients (28%) 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.

DRUG INTERACTIONS

Interactions between ALDARA P cream with other drugs have not been established.

As an immune response modifier, imiquimod is not recommended for use concurrently with immunosuppressive drugs such as tacrolimus, pimecrolimus, mycophenolate mofetil, cyclosporine or methotrexate.

Concomitant use of corticosteroids with imiquimod may potentially limit efficacy.

ADVERSE REACTIONS

Superficial Basal Cell Carcinoma

The data described below reflect exposure to ALDARA P cream or vehicle in 364 patients enrolled in two double-blind, vehicle-controlled studies in which subjects with sBCC applied ALDARA P cream or vehicle to the target lesions 5X/week for 6 weeks.

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)		Vehicle 5X/Week (n = 179)	
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%)
CENTRE & 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 APPENDAGE 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 DISORDER				

LYMPHADENOPATHY	5	(2.7%)	1	(0.6%)

The most frequently reported adverse reactions were those of local skin and application site reactions including erythema, edema, induration, erosion, flaking/scaling, scabbing/crusting, itching and burning at the application site. 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. The incidence of 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		Vehicle 5X/Week	
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 incidence 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				
Local Skin Reaction	Mild/Moderate		Severe	
	ALDARA P Cream n=184	Vehicle n=178	ALDARA P 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%

Adverse events judged to be probably or possibly related to ALDARA P cream and reported by at least 1% of the patients included:

Application Site Reactions: Target Site Reactions (itching, burning, pain, tenderness, bleeding, papules, infection, pimples

Remote Site Reactions: erythema

Body as a Whole: back pain

White Cell and Resistance Disorders: lymphadenopathy.

In the sBCC studies, 23 of 1266 (1.8%) imiquimod-treated patients developed treatment site infections that were treated with antibiotics; the majority of these patients required a rest period off ALDARA P cream. In all vehicle-controlled BCC studies, the adverse event lymphadenopathy was reported in 12 (1.8%) of the 672 imiquimod-treated patients. In all phase II/III BCC trials with 5X/week imiquimod dose groups, 9 (1.7%) of 518 patients with pre- and post-treatment laboratory tests developed a α2 toxicity grade level shift from baseline to end-of-treatment in absolute lymphocyte counts.

Actinic Keratosis

The data described below reflect exposure to ALDARA P cream or vehicle in 436 patients enrolled in two double-blind, vehicle-controlled studies in which patients applied ALDARA P

cream or vehicle to a 25 cm2 contiguous treatment area on the face or balding scalp 2 times per week for 16 weeks.

In controlled clinical studies, the most frequently reported adverse reactions were those of local skin and application site reactions including erythema, flaking/scaling/dryness, scabbing/crusting, itching and burning at the application site. The adverse reactions that most frequently resulted in clinical intervention (e.g., rest periods, withdrawal from study) were local skin and application site reactions: 16% (35/215) of patients received rest periods. The average number of doses not received per patient due to rest periods was 4 doses with a range of 1 to 11 doses: 91% of patients (32/35) resumed therapy after a rest period. Overall, in the clinical studies, 2% (5/215) of patients discontinued for local skin/application site reactions and one patient discontinued due to the development of urticaria. One patient developed a bacterial infection at the treatment site.

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

Body system Preferred Term	Imiquimod 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%)
CENTRE & 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	(0.0%)	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	(2.2%)
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	Imiquimod 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.

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

Event	Mild/Moderate		Severe	
	ALDARA P (n=215)	**Vehicle (n=220)**	**ALDARA P (n=215)**	**Vehicle (n=220)**
Erythema	80%	91%	18%	2%
Edema	49%	10%	0%	0%
Weeping/Exudate	21%	1%	0%	0%
Vesicles	9%	1%	0%	0%
Erosion/Ulceration	46%	9%	2%	0%
Flaking/Scaling/Dryness	85%	87%	7%	3%
Scabbing/Crusting	70%	40%	8%	2%

External Genital Warts

In controlled clinical trials, the most frequently reported adverse reactions were those of local skin and application site reactions; some patients also reported systemic reactions. These reactions were usually mild to moderate in intensity; however, severe reactions were reported with 3 times per week application. **These reactions were more frequent and more intense with daily application than with 3 times per week application**. Overall, in the 3 times per 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 (3X/Week Application)								
	Mild/Moderate				Severe			
	Females		Males		Females		Males	
	ALDARA P (n=114)	vehicle (n=99)	ALDARA P (n=156)	vehicle (n=157)	ALDARA P (n=114)	vehicle (n=99)	ALDARA P (n=156)	vehicle (n=157)
Erythema	61%	21%	54%	22%	4%	0%	4%	0%
Erosion	30%	8%	29%	6%	1%	0%	1%	0%
Excoriation / Flaking	18%	8%	25%	8%	0%	0%	1%	0%
Edema	17%	5%	12%	1%	1%	0%	0%	0%
Induration	5%	2%	7%	2%	0%	0%	0%	0%
Ulceration	5%	1%	4%	1%	3%	0%	0%	0%
Scabbing	4%	0%	13%	3%	0%	0%	0%	0%
Vesicles	3%	0%	2%	0%	0%	0%	0%	0%

Remote site skin reactions were also reported in female and male patients treated 3 times a week with ALDARA P 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 P cream reported by more than 5% of patients are listed below; also included are soreness, influenza-like symptoms and myalgia.

Adverse Events Probably or Possibly Related to ALDARA P cream (3X/Week Application)				
	Females		**Males**	
	ALDARA P (n=117)	vehicle (n=103)	ALDARA P (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[a]	11%	3%	2%	1%
SYSTEMIC REACTIONS:				
Headache	4%	3%	5%	2%
Influenza-like symptoms	3%	2%	1%	0%
Myalgia	1%	0%	1%	1%

[a] Incidences reported without regard to causality with ALDARA P cream.

Adverse events judged to be possibly or probably related to ALDARA P cream and reported by more than 1% of patients include:

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.

Post-Marketing Experience

Application Site Disorders (resulting from internal application): local skin reactions, pain and swelling, difficulty passing urine in female patients.

Rare reports have been received of either the onset or exacerbation of autoimmune conditions (including thyroiditis, multiple sclerosis, spondyloarthropathy, psoriasis, ulcerative colitis) in association with ALDARA P therapy.

The following adverse reactions have been identified during post-approval use of ALDARA P (imiquimod) Cream, 5%. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Application Site Disorders: tingling at the application site.

Body as a Whole: angioedema.

Cardiovascular: capillary leak syndrome, cardiac failure, cardiomyopathy, pulmonary edema, arrhythmias (tachycardia, atrial fibrillation, palpitations), chest pain, ischemia, myocardial infarction, syncope.

Endocrine: thyroiditis.

Gastro-Intestinal System Disorders: abdominal pain.

Hematological: decreases in red cell, white cell and platelet counts (including idiopathic thrombocytopenic purpura), lymphoma.

Hepatic: abnormal liver function.

Infections and Infestations: herpes simplex.

Musculo-Skeletal System Disorders: arthralgia.

Neuropsychiatric: agitation, cerebrovascular accident, convulsions (including febrile convulsions), depression, insomnia, multiple sclerosis aggravation, paresis, suicide.

Respiratory: dyspnea.

Urinary System Disorders: proteinuria.

Skin and Appendages: exfoliative dermatitis, erythema multiforme, hyperpigmentation, hypertrophic scar.

Vascular: Henoch-Schoenlein purpura syndrome.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage of ALDARA P (imiquimod) cream in humans is unlikely due to minimal percutaneous absorption. Animal studies reveal a rabbit dermal lethal imiquimod dose of greater than 5000 mg/kg. Persistent topical overdosing of ALDARA P cream could result in severe local skin reactions.

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.

DOSAGE AND ADMINISTRATION

The application frequency for ALDARA P (imiquimod) cream is different for each indication.

Superficial Basal Cell Carcinoma

ALDARA P cream is to be applied to a biopsy-confirmed sBCC 5 times per week, prior to normal sleeping hours, and left on the skin for approximately 8 hours. The treatment area should include a 1 cm margin of skin around the tumour. The amount of cream to be applied depends upon the diameter of the target sBCC (see table below)

Patient Dosing Guide		
Target Tumour 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

Before applying the cream, the patient should wash the treatment area with mild soap and water and allow the area to dry thoroughly. The cream should be applied to cover the treatment area, including one centimetre of skin surrounding the tumour, and should be rubbed into the treatment area until the cream is no longer visible. Caution subjects to avoid contacting the cream in or near the eyes. Approximately 8 hours after applying ALDARA P, 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 P cream once per day, Monday through Friday, prior to sleeping hours.

ALDARA P 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. However, the treatment period should not be extended beyond 6 weeks due to missed doses or rest periods.

The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of ALDARA P cream therapy. Hand washing before and after cream application is recommended. The application site is not to be occluded.

A follow-up visit at approximately 12 weeks post-treatment to assess the treatment site for clinical clearance is appropriate. Early clinical clearance cannot be adequately assessed until resolution of local skin reactions. If there is clinical evidence of persistent tumour at the 12-week post-treatment visit, a biopsy or other alternative intervention should be considered; the safety of and efficacy of a repeat course of ALDARA P 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.

ALDARA P cream is packaged in a pump that contains 7.5g of the cream. Each complete actuation of the pump delivers 235 mg of the cream. No more than one sixth of the amount delivered by a full actuation of the pump of ALDARA P cream (or) should be applied to the treatment area at each application. Remaining cream from a full actuation of the pump should be discarded. Partially used pump should be discarded at end of treatment period.

Actinic Keratosis

ALDARA P cream is to be applied 2 times per week to a defined treatment area on the face or scalp no larger than 25 cm^2, 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. 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. Following the treatment period, cream should be removed by washing the area with mild soap and water. Examples of two times per week application schedules are Monday and Thursday, or Tuesday and Friday prior to sleeping hours.

ALDARA P cream treatment should continue for 16 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. However, the treatment period should not be extended beyond 16 weeks due to missed doses or rest periods.

The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of ALDARA P cream therapy. Hand washing before and after cream

application is recommended.

ALDARA P cream is packaged in a pump which contains 7.5g of cream. No more the amount delivered by one full actuation of the pump, 235 mg of ALDARA P cream should be applied to the treatment area at each application. The application site is not to be occluded.

External Genital Warts

ALDARA P (imiquimod) cream is to be applied 3 times per week, prior to normal sleeping hours, and left on the skin for 6-10 hours. 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 P 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 due to 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 P cream therapy. Hand washing before and after cream application is recommended.

ALDARA P cream is packaged in a pump, which contains 7.5 g of cream total, with each actuation of the pump delivering 235 mg cream. Each full actuation of the pump contains sufficient cream to cover a wart area of up to 20 cm^2; use of excessive amounts of cream should be avoided. Patients self-administer ALDARA P cream by applying the cream to external genital and/or 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.

PHARMACEUTICAL INFORMATION

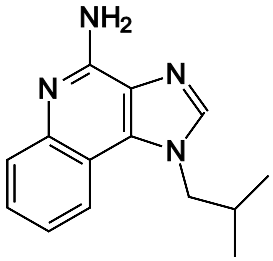
Drug Substance:

Common name: Imiquimod (USAN, INN)

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

CAS number: 99011-02-6

Structural formula:



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

Molecular weight: 240.3 g/mol

Physical Form: Crystalline solid that varies in colour from white to off-white or buff. The compound has no odour.

Solubility: Practically insoluble in most common organic solvents and in aqueous systems except at extremely low pH conditions. It can be made soluble to the extent of at least 100 mg/mL in methanol (as a salt) upon the addition of a few drops of hydrochloric or acetic acid. Soluble in fatty acids such as oleic acid and isostearic acid.

pKa Value: The ionization constant for imiquimod was determined by ultraviolet (UV) spectroscopy and pH-solubility to be about 7.5.

Melting point: 297-299˚C with sublimation.

Composition
Each gram of ALDARA P 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.

Stability and storage recommendations:
Store between 15-25°C. Avoid freezing.

AVAILABILITY OF DOSAGE FORMS

ALDARA P (imiquimod) cream is supplied as a pump that contains 7.5 g of the cream. Each full actuation of the pump delivers 235 mg of cream.

INFORMATION FOR THE CONSUMER

Please read this before using ALDARA P cream and talk to your doctor, the nurse or your pharmacist if you have any questions about how to use ALDARA P.

1. What is ALDARA P Cream?

ALDARA P cream is the brand name for imiquimod cream. ALDARA P cream is used in immunocompetent adults to treat the following conditions:

- Biopsy-confirmed, primary Superficial Basal Cell Carcinoma (sBCC) located on the trunk (excluding external genital and perianal skin), neck, or extremities (excluding hands and feet).
- Actinic Keratosis (AK)
- External Genital/Perianal Warts (EGW) caused by the human papillomavirus (HPV).

ALDARA P cream can only be used if a doctor prescribes it for you.

ALDARA P cream should only be used on the skin.

ALDARA P cream is manufactured for Bausch Health, Canada Inc. It is an off-white cream containing 50 mg of imiquimod per gram.

2. What other ingredients are in ALDARA P Cream?

ALDARA P cream also contains:
Isostearic Acid, Cetyl Alcohol, Stearyl Alcohol, White Petrolatum, Polysorbate 60, Sorbitan Monostearate, Glycerin, Xanthan Gum, Purified Water, Benzyl Alcohol, Methylparaben, and Propylparaben.

3. What packages is ALDARA P Cream sold in?

ALDARA P cream is available as a pump that contains 7.5 g of the cream and delivers 235 mg of the cream per actuation.

4. How does ALDARA P Cream work?

ALDARA P cream is an immune response modifier. ALDARA P cream is a medicine that works by stimulating your body's own immune response.

5. What should I tell my doctor before using ALDARA P Cream?

Allergies

- Tell your doctor if you have ever had any unusual or allergic reaction to ALDARA P

cream.
- Tell your doctor or the nurse or pharmacist if you have any allergies.

Pregnancy
- Tell your doctor if you are planning to become pregnant.
- Tell your doctor if you are pregnant (about to have a baby).
- Tell your doctor if you are breast-feeding your baby.

ALDARA P cream should not be used while pregnant or breast-feeding unless your doctor tells you to.

Previous treatment
Tell your doctor and pharmacist of any other treatment you have had for your Superficial Basal Cell Carcinoma, Actinic Keratosis or External Genital/Perianal Warts including:
- any prescription and over-the-counter drugs you have used.
- any other non-drug treatments you have had for your condition for example, freezing or surgery.

Other Medical Conditions
The safety and efficacy of ALDARA P cream in immunosuppressed patients has not been established. Tell your doctor about any other medical conditions that you may have before using ALDARA P cream, such as pre-existing auto-immune conditions.

6. How do I use ALDARA P Cream?
Put ALDARA P cream on before you go to sleep for the night.

Do not put bandages or wraps or covers on top of the cream.

Only use ALDARA P cream as instructed by your doctor.

Step 1: Wash your hands.

Step 2: Wash the area where you are going to put the cream with mild soap and water.

Step 3: Dry the area well.

Step 4: Remove the cap from the pump (before using the pump for the first time, remove the cap and prime the pump by pressing the top of the pump all the way down, one or more times as needed, until the product appears. Discard this portion of the product).

Step 5: Squeeze ALDARA P cream onto your fingertip.

Step 6: Put a thin layer of cream on the area shown to you by your doctor or the nurse.

Step 7: Rub a thin layer of cream in until you cannot see it.

Step 8: Replace cap on the pump.

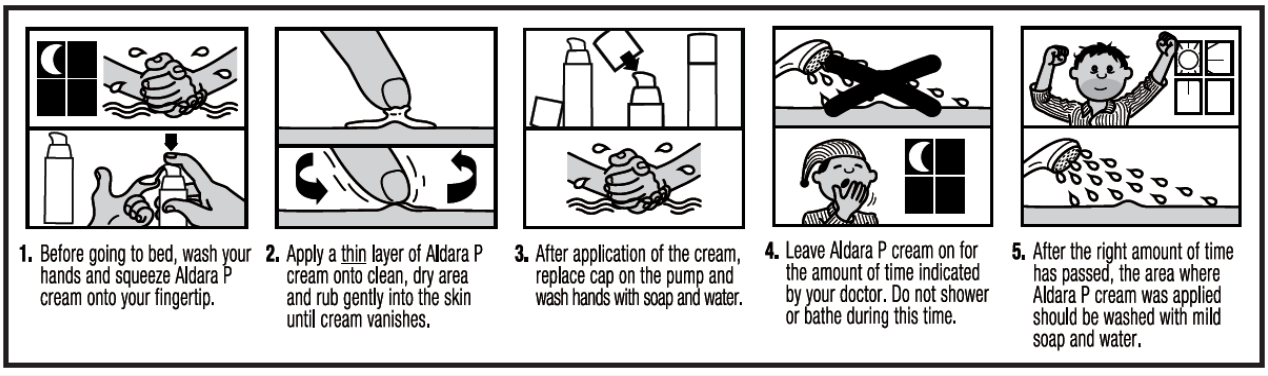
Step 9: Wash your hands with soap and water.

Step 10: a) For external genital/perianal warts, leave the cream on for 6 to 10 hours.
b) For superficial basal cell carcinoma or actinic keratosis, leave the cream on for approximately 8 hours.
Do not shower or bathe during this time.

Step 11: a) For external genital/perianal warts, after 6 to 10 hours wash the area where the cream was applied with mild soap and water.
b) For superficial basal cell carcinoma or actinic keratosis, after 8 hours wash the area where the cream was applied with mild soap and water.

- Sufficient cream should be applied to cover the treatment area, including one centimetre of skin surrounding the tumour, for superficial basal cell carcinoma. One-sixth of the amount delivered by one full actuation of the pump can treat a tumour with a maximum diameter of 2.0 cm, for superficial basal cell carcinoma.
- The amount delivered by one full actuation of the pump can treat a maximum area of 25cm2, for actinic keratosis.
- The amount delivered by one full actuation of the pump, can treat a maximum area of 20cm2, for external genital/perianal warts.

How to use ALDARA P in pump



7. When should I use ALDARA P Cream?

Superficial Basal Cell Carcinoma (sBCC)

- Use ALDARA P cream 5 times per week for a maximum or 6 weeks, or as directed by

your doctor.
- An example of 5 times per week application schedule is: Monday, Tuesday, Wednesday, Thursday and Friday.

Actinic Keratosis (AK)

- Use ALDARA P cream 2 times per week for a total of 16 weeks, or as directed by your doctor.
- Examples of 2 times per week application schedules are: Monday and Thursday OR Tuesday and Friday

External Genital and Perianal Warts (EGW)

- Use ALDARA P cream 3 times per week for a maximum of 16 weeks, or the length of time directed by your doctor (maximum of 16 weeks). Some patients clear their warts after 4 weeks of therapy; however, some may require up to 16 weeks of therapy.
- Examples of 3 times per week application schedules are: Monday, Wednesday, Friday OR Tuesday, Thursday, Saturday

8. What do I do if I forget to apply ALDARA P Cream?

If you miss a dose of ALDARA P cream, wait until the next night to apply it.

9. What should I be careful of when I use ALDARA P Cream?

- Only use on the affected area of your skin.
- Use this cream the way your doctor showed you.
- Do not rub cream in your eyes, lips or nostrils.
- If you get cream in your eyes, wash your eyes out with abundant amounts of water.
- Don’t use this cream in your vagina. 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.
- Wear a hat, long sleeves and use sunscreen if you must be out in the sun.
- Avoid natural or artificial sunlight, for example tanning salons, as much as possible.

10. What can I expect from ALDARA P Cream?

- Results vary from person to person.
- For best results with ALDARA P cream, follow your doctor's instructions closely.

11. What side effects might I expect to see or feel?

Some people who use ALDARA P cream see the area where the cream was applied get lighter or darker. Sometimes the change in the colour of the skin is permanent.

It is common for patients using ALDARA P cream to experience local skin reactions such as redness, wearing away of the skin, flaking, dryness, itching, burning, crusting or scabbing, and swelling at the site of application or surrounding areas. This may be a sign that the cream is working. These local skin reactions may get better over time while using the cream or will go away after stopping the cream. Most skin reactions are mild to moderate. Severe skin reactions should be reported to your doctor. If you have questions regarding treatment or local skin reactions, please talk to your doctor.

- While you are using the cream, your skin may look red. This is due to the drug's effects and is common in most patients.
- Some red spots might appear in the area where you are putting the cream. This is normal and not unusual.
- The way the area of skin where the warts or actinic keratosis lesions are may look red during the time you are using ALDARA P cream. Cover the wart area when you put the cream on.

12. What if I have a severe skin reaction?

Should a severe skin reaction occur, do not apply any more ALDARA P cream on your skin until you have talked to your doctor. Remove the cream by washing with mild soap and water. Treatment with ALDARA P cream can usually resume as directed by your doctor.

13. When should I call my doctor?

- Call your doctor if the area where you are applying the cream is so sore or uncomfortable that you are not able to put the cream on the area or you cannot do your normal daily activities.
- Call your doctor if flu-like symptoms (fatigue, fever, muscle and joint pain, chills) develop after beginning treatment with ALDARA P.

14. Are there any special things to know about the use of ALDARA P cream for Superficial Basal Cell Carcinoma?

- About 80% of the subjects tested in clinical trials had effective treatment.
- About 12 weeks after you finish using ALDARA P cream, your doctor will need to check the area that was treated to make sure that the skin cancer is gone. Superficial basal cell carcinoma can come back. The chances of it coming back are higher as time passes. It is very important to have regular follow-up visits with your doctor to check the area to make sure your skin cancer has not come back. Ask your doctor how often you should have your skin check.

15. Are there any special things to know about the use of ALDARA P cream for Actinic Keratosis?

- Patients should be aware that new actinic keratosis lesions may develop during treatment with ALDARA P cream. These lesions may resolve during the treatment period. Even though initial actinic keratosis lesions may clear with treatment, new actinic keratosis lesions may develop in the future and require further treatment. ALDARA P cream is not a cure, since actinic keratosis is considered to be a chronic skin condition.

16. Are there any special things to know about the use of ALDARA P cream for External Genital/Perianal Warts?

- In most patients, warts disappear in 8 to 12 weeks. However, some patients get rid of their warts in 4 weeks and others take up to 16 weeks. Patients should be aware that new warts may develop during therapy. However, ALDARA P cream is not a cure, as the virus that causes genital/perianal warts can also be present in normal looking skin. ALDARA P cream may not be able to clear virus infection in some of these cases.
- It is not known whether ALDARA P cream has any effect on transmission of the warts. For your own health and health of others, it is important to practice safer sex. Talk to your doctor about safer sex practices.
- ALDARA P CREAM MAY WEAKEN CONDOMS AND VAGINAL DIAPHRAGMS. AN ALTERNATE FORM OF CONTRACEPTION (BIRTH CONTROL) SHOULD BE USED WHILE USING ALDARA P CREAM.
- Some women who put ALDARA P cream at the opening of the vagina have pain or swelling. Sometimes this makes it hard to urinate (go to the washroom or toilet).
- **Uncircumcised male** - If you use the ALDARA P cream to treat warts under the penis' foreskin, you should pull back the foreskin and clean the area each morning.
- **Sexual contact** - Sexual (genital, anal, oral) contact should be avoided while the cream is on the skin. The effect of ALDARA P cream on the transmission of genital warts is unknown.

17. How should I store ALDARA P Cream?

- Keep out of reach of children. Store at 15-25°C
- Keep away from heat. Do not store near the shower or cooking area of the kitchen.
- Do not freeze.

PHARMACOLOGY

Pharmacodynamics

Imiquimod is an immune response modifier that is not a nucleoside analogue. Saturable binding studies suggest a membrane receptor for imiquimod exists on responding cells. In vitro studies have demonstrated that imiquimod induces the production of IFN and other cytokines from a variety of human and animal cells. In addition, cytokines were produced following dermal application and oral administration in various laboratory animals and in human studies following oral administration of imiquimod. In animal models imiquimod is an effective antiviral and antitumor agent whose activity is principally due to induction of alpha interferon, but other cytokines are also involved. Imiquimod induced a local immune response and a decrease in HPV-DNA for genotypes 6 and 11 in patients treating external genital/perianal warts. The immune response was characterized by significant increases in mRNA for IFN-α, 2'5'-oligoadenylate synthetase and IFN-γ in wart tissue. Although these data suggest a sequence of immunologic events initiated by imiquimod therapy, the cause of wart regression seen with imiquimod therapy has not been established.

In vitro studies using isolated guinea pig myocardium, showed stimulation with tachyphylaxis development after multiple doses. Moderate to marked inhibition of agonist-induced contractions was observed in isolated guinea pig tracheal strips. Intravenous administration of a bolus dose of imiquimod caused CNS and cardiac stimulation in dogs. Little activity was found in inflammatory rat models. Some local anaesthetic activity, slight effect on locomotor, and slight effect on hexobarbital induced sleep time were observed in the mouse.

Pharmacokinetics and Metabolism

Animal and human dermal pharmacokinetic results indicate that minimal, if any, systemic absorption occurs following dermal application of imiquimod cream. Imiquimod was not quantifiable in the serum of rats dosed topically three times per week at 5 mg/kg for 4 weeks; low levels of metabolite were quantifiable after the last, but not after the first dose. In guinea pigs, after a single large (21 mg/kg) topical dose of [14C] imiquimod as a 5% cream, only low concentrations of imiquimod were quantifiable in plasma.

Oral ADME (absorption, distribution, metabolism, elimination) studies in laboratory animals, revealed extensive biotransformation followed by both urinary and biliary excretion of metabolites. Tissue distribution is rapid with clearance after 2 to 3 days with the exception of pigmented tissues - skin and uveal tract of the eye. No evidence of ocular toxicity was found in six-month oral rat and monkey imiquimod toxicity studies conducted at high daily doses.

Percutaneous absorption of 5% imiquimod cream following topical application for 8 12 hours was observed across the intact skin of healthy subjects and the affected skin of subjects with either genital warts or AK. In subjects with AK, urinary recovery less than 0.6% of the applied dose was seen. Because of this low percutaneus absorption, serum levels of imiquimod and metabolites were low or undetectable in these subjects.

Clinical Studies

The results of phase 1 dermal safety studies in healthy volunteers produced evidence that ALDARA P cream causes irritation in healthy and to a lesser extent sun damaged skin and no evidence that it causes photoirritation, phototoxicity, photoallergenicity or contact sensitization in healthy skin. However, phototoxicity testing was incomplete as wavelengths in the UVB range were not included and ALDARA P cream has peak absorption in the UVB range (320 nm) of the light spectrum.

Superficial Basal Cell Carcinoma

In two double-blind, vehicle-controlled clinical studies, 364 patients with a biopsy confirmed primary sBCC tumours were treated with ALDARA P or vehicle cream 5X/week for 6 weeks. Target tumours were to have a minimum area of 0.5 cm2 and a maximum diameter of 2.0 cm. Tumours within 1 cm of the hairline, eyes, nose, mouth and ears, on the anogenital area or on the hands or feet, or having any atypical features were excluded. Twelve weeks after the last scheduled application of study cream, the clinical response of the target tumour was evaluated. Following the clinical assessment, the entire target tumour area was excised and examined histologically for the presence of tumour.

The primary efficacy variable was the complete response rate defined as the proportion of patients with clinical (visual) and histological clearance of the sBCC target lesion at 12 weeks post-treatment.

The study population ranged from 31 to 89 years of age (median 60 years) and 65% had Fitzpatrick skin type I or II. Data on composite clearance (defined as both clinical and histological clearance) and on histological clearance are shown in the table below.

Clearance Rates at 12 Weeks Post-Treatment for Superficial Basal Cell Carcinoma

Study	Endpoint	ALDARA P cream	Vehicle cream
1393- IMIQ	Composite Clearance	70% (66/94)	2% (2/89)
	Histological Clearance	78% (73/94)	6% (5/89)
1408- IMIQ	Composite Clearance	80% (73/91)	1% (1/90)
	Histological Clearance	87% (79/91)	1% (1/90)
Pooled Results	Composite Clearance	75% (139/185)	2% (3/179)
	Histological Clearance	82% (152/185)	3% (6/179)

There was a statistically significant observed association between the composite clearance rate and the most intense assessment of erythema, erosion and scabbing/crusting made over the course of the study by the investigator.

One non-controlled five-year long-term follow-up study was conducted to assess the recurrence

of sBCC treated with ALDARA P cream applied once daily, 5 times per week, for 6 weeks. Target tumour inclusion criteria were the same as for the short-term sBCC studies described above. Efficacy assessment was done solely by clinical evaluation (i.e., no histological assessment). At 12 weeks post-treatment, patients were assessed for evidence of persistent sBCC. Subjects with no clinical evidence of sBCC entered the long-term follow-up period. The initial 12-week post-treatment clearance rate was 90% (163/182) and 162 subjects entered the long-term follow-up period for up to 5 years.

As of the 60-month visit of the follow-up period, a total of 18 subjects have had clinical evidence of sBCC recurrence at the target tumour site. For the 162 subjects who achieved initial clearance and entered the follow-up period, the estimated non-recurrence rate at Month 60 was 87% by life table method. The highest incidence of recurrences was seen during the first 12 months of long-term follow-up with the rate of recurrences decreasing in subsequent years. For all treated patients (N=182), the estimate of achieving initial clearance and remaining clear over the duration of the 5-year follow-up period was 78%.

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] (N=182)
Month 3	153	4	5	87%
Month 6	149	4	0	85%
Month 12	143	2	4	84%
Month 24	138	4	1	82%
Month 36	136	0	2	82%
Month 48	127	2	7	80%
Month 60	125	2	---	78%

a. Reasons for discontinuation included death, non-compliance, and personal reasons.
b. Estimated rate of 182 patients who clinically cleared and remained clear was determined by multiplying the initial clearance rate at 12 weeks post-treatment (0.90) by the estimated non-recurrence rate using life table time to event analyses for those who achieved clearance during the 5-year long term follow-up beginning after the 12-week post-treatment visit.

Actinic Keratosis

In two double-blind, vehicle-controlled clinical studies, 436 patients with AK on the head were treated with ALDARA P 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 cm2 contiguous treatment area on either face or balding scalp 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 the entire 25 cm2 treatment area prior to normal sleeping hours and left on for approximately 8 hours; twice weekly dosing 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 complete clearance. Complete clearance (designated below as "clear") was defined as a count of zero AK lesions at 8 weeks post-treatment. A secondary efficacy variable was partial clearance, defined as the percentage of patients in whom 75% or more baseline AK lesions were cleared.

The study populations included patients ranging in age from 37 to 88 years (median 66 years) and 55% had Fitzpatrick skin type I or II. All imiquimod-treated patients were Caucasians. A total of 9 patients in the imiquimod treatment group and 11 in the vehicle treatment group withdrew from the post-treatment 8-week assessment phase of the two studies. Complete and partial clearance rates are shown in the table below.

Rates (100% Lesions Cleared)					
Study	**ALDARA P Cream**	**Vehicle**	**p-value**	**Difference in Complete Clearance Rates**	**95% Confidence Interval for the Difference**
1444-IMIQ	46% (49/107)	3% (3/110)	<0.0001	43%	(33%, 53%)
1446-IMIQ	44% (48/108)	4% (4/111)	<0.0001	41%	(31%, 51%)

Partial Clearance Rates (75% or More Lesions Cleared)					
Study	**ALDARA P Cream**	**Vehicle**	**p-value**	**Difference in Partial Clearance Rates**	**95% Confidence Interval for the Difference**
1444-IMIQ	60% (64/107)	10% (11/110)	<0.0001	50%	(39%, 61%)
1446-IMIQ	58% (63/108)	14% (15/111)	<0.0001	45%	(34%, 56%)

There was a statistically significant observed association between the complete clearance rate and the most intense assessment of erythema made over the course of the study by the investigator.

During treatment with ALDARA P cream, sub-clinical AK lesions in the treatment area may appear. 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.

Actinic keratoses may recur in patients whose lesions initially appear clinically to have completely cleared after completion of imiquimod treatment. In an observational follow-up study, the subset of subjects who experienced complete clearance of their AK lesions at the 8-week post-treatment visit in the above two randomized trials were re-evaluated 12-18 months after the post-treatment visit. A total of 104 of the original 436 patients experienced complete clearance and were thus eligible for this study: 97 of the 215 (45%) initially randomized to imiquimod and 7 of the 221 (3%) randomized to vehicle. Of these 104 eligible subjects, 57 participated in the study. During a median follow-up period of 16 months, 42.6% (23/54) of the imiquimod-treated subjects and 33.3% (1/3) of the vehicle-treated subjects had a recurrence of AK within the original treatment area (i.e., the estimated sustained clearance rate [rate of subjects who clinically cleared and remained clear] for subjects in the original two randomized trials was 26% for the imiquimod treatment group and 2% for the vehicle treatment group). In addition, one patient, who had received imiquimod 3X/week for the treatment of AK lesions in another clinical trial (not described above) and who had complete clinical clearance of lesions at the 8-week post-treatment visit, developed a squamous cell carcinoma in situ in the treatment area which was excised prior to re-evaluation at the 12-18-month follow-up visit.

External Genital Warts

In a double-blind placebo-controlled clinical trial, 209 otherwise healthy patients 18 years of age and older with histologically-confirmed genital/perianal warts were treated with ALDARA P cream or placebo cream 3 times a week for a maximum of 16 weeks. The median baseline wart area was 69 mm2 (range 8 to 5525 mm2). ALDARA P cream was proven safe and effective for the treatment of genital and perianal warts (see following table). The ALDARA P cream group had wart clearance rates that were significantly greater than the placebo control. The percentage of patients achieving total clearance of their genital and perianal warts was 72% for females and 33% for males. Visible reduction in wart area occurred as early as 2 weeks and the median time to total wart clearance was 10 weeks; however, some patients required 16 weeks of therapy. Significantly more ALDARA P cream patients than the placebo patients achieved > 50% reduction in their baseline wart area (85% versus 38% in females, and 70% versus 22% in males, respectively). Six to nineteen percent of the cleared patients experienced a recurrence of their warts during the 12-week follow-up period.

Clearance and Recurrence Rates
3X/Week - Study 1004

Patient group	Treatment Group	Total Clearance [a]		Recurrence Rate [b]	
all patients	ALDARA P Cream placebo	50% 11%	(54/109) (11/100)	13% 10%	(6/45) (1/10)
females	ALDARA P Cream placebo	72% 20%	(33/46) (8/40)	19% 14%	(5/27) (1/7)
males	ALDARA P Cream placebo	33% 5%	(21/63) (3/60)	6% 0%	(1/18) (0/3)

a. Intent-to-treat analysis.
b. Patients with total clearance who had recurrence of baseline/target warts during the 12-week follow-up period.

TOXICOLOGY

Acute Toxicity

Acute dermal toxicity studies in rabbits with unformulated imiquimod under occlusion did not reveal any toxic effects at very high dose levels - 5000 mg/kg. When administered orally, intraperitoneally, subcutaneously or intravenously, single dose studies revealed that imiquimod produced central nervous system (CNS) stimulation and convulsions at lethal doses. However, signs of CNS toxicity did not occur when animals were given lower repeat doses (100 mg/kg or lower).

Species	**Route**	**LD_{50} (mg/kg)**
Mouse	oral	403
	intraperitoneal	879
Rat	oral	1665
	intraperitoneal	763
	subcutaneous	≈ 20
Rabbit	dermal	> 5000
Monkey	oral	> 200
	intravenous infusion	≈ 8
	intravenous bolus	> 6

Irritation/Sensitization Studies

Skin irritation studies in rabbits showed that imiquimod was non-irritating when dosed unformulated at 500 mg or formulated up to 250 mg per site. Unformulated imiquimod produced mild or no eye irritation in rabbits when applied unformulated at 100 mg/eye or formulated up to 5 mg/eye. Formulated imiquimod was not irritating to rat or rabbit vaginal tract when applied every other day for 10 days at 10 and 50 mg/dose respectively. Dermal sensitization studies in guinea pigs showed that the 5% imiquimod cream was not a dermal sensitizer. Comparison of the dermal reaction to imiquimod cream in animal species (rat, mouse, rabbit) with clinical study results, reveals that mouse and rabbit results are comparable to humans. The more severe dermal irritation seen in the rat is not predictive of human response.

Long-Term Toxicity
Two repeat dose dermal toxicity studies in rats showed a compound related but non-dose related dermal irritation. A dose-related decrease in body weight of male rats was also observed. No systemic toxicity was found at doses up to 5 mg/kg three days per week for 4 weeks or at doses up to 2.5 mg/kg three days per week for 16 weeks.

The adverse effects observed for the high doses (10-30 mg/kg) in repeat dose oral toxicity studies in rats and monkeys could be related to exaggerated pharmacological effects of excessive cytokines induction and lymphoid stimulation: reduced body weight gains, anaemia, serum protein changes and death. High repeat daily doses of imiquimod did not produce necrosis in any organ; the compound is not cytotoxic. Recovery animals demonstrated that the adverse effects were readily reversible. An oral no adverse effect level of 3 mg/kg/day was determined in both rats and monkeys dosed daily for 6 months.

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

In a photocarcinogenicity study in hairless mice, animals received ALDARA P cream 3 times per week at imiquimod concentrations of 0.03%, 0.1% and 0.3% and were irradiated with solar ultraviolet light for 5 days each week for 40 weeks and observed an additional 12 weeks. Vehicle cream enhanced UVR-induced skin tumour development. ALDARA P cream had no additional effect on tumour development beyond the vehicle effect (i.e., the addition of the active ingredient, imiquimod, to the vehicle cream did not result in an additional effect beyond the vehicle effect on tumour development).

Mutagenicity
Imiquimod was without effect in a series of eight mutagenicity assays including Ames, mouse lymphoma, CHO chromosome aberration, human lymphocyte chromosome aberration, SHE cell transformation, rat and hamster bone marrow cytogenetics, and mouse dominant lethal test.

Reproduction and Teratology
Teratology studies in rats and rabbits dosed at 1-20 mg/kg orally and at 0.5-2.0 mg/kg intravenously, did not reveal any teratogenic effects. The high doses in both studies produced some adverse effects in the dams related to maternal toxicity. The maternal toxicity was reflected in the high dose pups: reduced pup weights and delayed ossification in the rat. A radiolabel intravenous study in pregnant rabbits dosed at 1 mg/kg between day 6 to 18 of gestation for a total of 13 doses, showed radiolabel in the uteri, placenta, amniotic fluid and fetuses with no preferential concentration in the conceptus.

In a rat general reproduction study which utilized daily oral doses of 1.5-6.0 mg/kg, drug-related toxicity was observed at the high dose in the F0 generation with no adverse reproductive effects. Reversible ossification defects were observed in pups at the high dose. No effects were observed in growth, development, behaviour, learning/memory or reproduction of second generation.
Daily oral administration of imiquimod to rats, at doses up to 8 times recommended human dose on a mg/m2 basis throughout mating, gestation, parturition and lactation, demonstrated no impairment of reproduction.

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