TEXT OF THE LABELING FOR THE DRUG

Revised Package Insert

ALDARA™

[al dar' a]

(imiquimod)

Cream, 5%

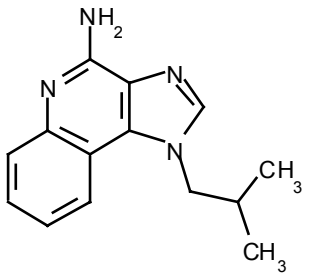
For Dermatologic Use Only -

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. Its structural formula is:



CLINICAL PHARMACOLOGY

Pharmacodynamics

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-∝ 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.

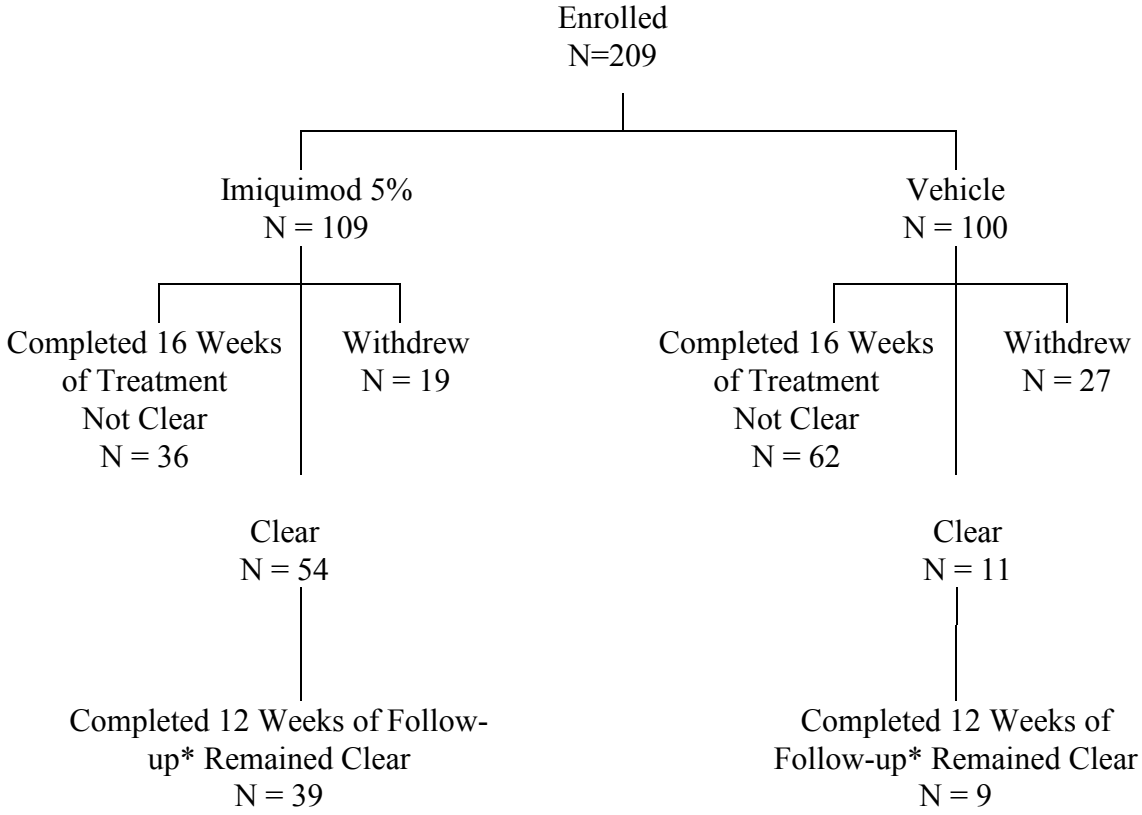
Pharmacokinetics

Percutaneous absorption of [^{14}C] imiquimod was minimal in a study involving 6 healthy subjects treated with a single topical application (5 mg) of [^{14}C] imiquimod cream formulation. No radioactivity was detected in the serum (lower limit of quantitation: 1 ng/mL) and < 0.9% of the radiolabelled dose was excreted in the urine and feces following topical application.

CLINICAL STUDIES

In a double-blind, placebo-controlled clinical trial, 209 otherwise healthy patients 18 years of age and older with genital/perianal warts were treated with Aldara 5% 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.

1004-IMIQ Patient Accountability



* 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.

CLEARANCE - STUDY 1004

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

INDICATIONS AND USAGE

Aldara 5% cream is indicated for the treatment of external genital and perianal warts/condyloma acuminata in individuals 12 years old and above.

CONTRAINDICATIONS

None known

WARNINGS

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

Local skin reactions such as erythema, erosion, excoriation/flaking, and edema are common. 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. There is no clinical experience with Aldara cream therapy immediately following the treatment of genital/perianal warts with other cutaneously applied drugs; therefore, Aldara cream administration is not recommended until genital/perianal tissue is healed from any previous drug or surgical treatment. Aldara has the potential to exacerbate inflammatory conditions of the skin.

Information for Patients

Patients using Aldara 5% cream should receive the following information and instructions. The effect of Aldara 5% cream on the transmission of genital/perianal warts is unknown. Aldara 5% cream may weaken condoms and vaginal diaphragms. Therefore, concurrent use is not recommended.

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. Sexual (genital, anal, oral) contact should be avoided while the cream is on the skin.
4. It is recommended that 6-10 hours following Aldara 5% cream application the treatment area be washed with mild soap and water.
5. 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 reported promptly to the prescribing physician.
6. 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.

7. Some reports have been received of localized hypopigmentation and hyperpigmentation following Aldara use. Follow-up information suggests that these skin color changes may be permanent in some patients.
8. Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.
9. Patients should be aware that new warts may develop during therapy, as Aldara is not a cure.

Carcinogenicity, Mutagenesis, and Impairment of Fertility

Rodent carcinogenicity data are not available. Imiquimod was without effect in a series of eight different 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. Daily oral administration of imiquimod to rats, at doses up to 8 times the recommended human dose on a mg/m^2 basis throughout mating, gestation, parturition and lactation, demonstrated no impairment of reproduction.

Pregnancy

Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women. Imiquimod was not found to be teratogenic in rat or rabbit teratology studies. In rats at a high maternally toxic dose (28 times human dose on a mg/m^2 basis), reduced pup weights and delayed ossification were observed. In developmental studies with offspring of pregnant rats treated with imiquimod (8 times human dose), no adverse effects were demonstrated.

Nursing Mothers

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

Pediatric Use

Safety and efficacy in patients below the age of 12 years have not been established.

ADVERSE REACTIONS

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 3X/week application. **These reactions were more frequent and more intense with daily application than with 3X/week application.** 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.

3X/WEEK APPLICATION
WART SITE REACTION AS ASSESSED BY INVESTIGATOR

	MILD/MODERATE				**SEVERE**			
	FEMALES		**MALES**		**FEMALES**		**MALES**	
	5% Imiquimod N=114	Vehicle N=99	5% Imiquimod N=156	Vehicle N=157	5% Imiquimod N=114	Vehicle N=99	5% Imiquimod 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 3X/week with imiquimod 5% 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 reported by more than 5% of patients are listed below; also included are soreness, influenza-like symptoms and myalgia.

	3X/WEEK APPLICATION			
	FEMALES		MALES	
	5% Imiquimod (n=117)	Vehicle (n=103)	5% Imiquimod (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.

Adverse events judged to be possibly or probably related to Aldara 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.

OVERDOSAGE

Overdosage of Aldara 5% cream in humans is unlikely due to minimal percutaneous absorption. Animal studies reveal a rabbit dermal lethal imiquimod dose of greater than 1600 mg/m^2. Persistent topical overdosing of Aldara 5% 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

Aldara 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 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 therapy. Handwashing before and after cream application is recommended. Aldara 5% 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. 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.

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.
Rx only.