

Staph Found in 11% of Vaginal-Rectal Specimens

BY TIMOTHY F. KIRN
Sacramento Bureau

SAN FRANCISCO — *Staphylococcus aureus* was carried in the vaginal-rectal area in 11% of screened pregnant women at a Camden, N.J., hospital, according to a study presented at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

The investigators took vaginal-rectal specimens collected from pregnant

women being screened for group B streptococcus from June 2005 until March 2006 and cultured them for *S. aureus*.

Of 353 women screened, 39 (11%) were colonized with staphylococcus; 7 of the 39 (2%) were methicillin-resistant strains, said Dr. Henry Fraimow of Cooper University Hospital in Camden. Five of the seven MRSA isolates contained the Panton-Valentine leukocidin virulence gene.

All seven were susceptible to clindamycin and levofloxacin.

The study could help to explain why in Camden generally half of *S. aureus* abscesses occur below the waist, and why Camden nurseries have had outbreaks of neonatal *S. aureus* infections, Dr. Fraimow said at the conference, which was sponsored by the American Society for Microbiology.

"This is higher than reported rates of vaginal colonization with staph aureus, most [studies] of which were done in the 1980s during some of the toxic shock syn-

drome outbreaks," he said. "There hasn't been a lot of good recent data."

One other recent study that looked at vaginal colonization found a higher rate of carriage, 18%, but a lower rate of methicillin resistance, 0.5%, he added.

Dr. Fraimow and his colleagues also found much more carriage in the summer months than during the rest of the year. They found that 14% of the specimens collected between June and September were colonized, compared with only 7% of those collected between October and March.

"We also conclude that all reservoirs for this organism must be considered when looking at strategies such as decolonization to prevent recurrent infections," Dr. Fraimow said. ■

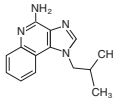


ALDARA™
[al dar' a]
(imiquimod)
Cream, 5%
For Dermatologic Use Only
Not for Ophthalmic Use

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 emulsifying cream base consisting of stearic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monooleate, glycerin, xanthan gum, purified water, benzyl alcohol, methylparaben, and propylparaben.

Chemically, imiquimod is 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine. Imiquimod has a molecular formula of C₁₇H₁₈N₄ and a molecular weight of 340.3. Its structural formula is:



CLINICAL PHARMACOLOGY

Pharmacodynamics

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 HPV11 mRNA and HPV DNA are significantly decreased following treatment. However, the clinical relevance of these findings is unknown.

INDICATIONS AND USAGE

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

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

Aldara Cream has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma virus 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, including chronic graft versus host disease.

Aldara Cream should be used with caution in patients with pre-existing autoimmune conditions.

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

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 photochemical mechanisms. Despite the absence of observed phototoxicity in humans (see ADVERSE REACTIONS), Aldara Cream shortened the time to skin tumor formation in an animal photocarcinogenicity study (see Carcinogenesis, Mutagenesis, Impairment of Fertility). Therefore, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure.

General Information

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

- This medication is to be used as directed by a physician. It is for external use only. Eye contact should be avoided.
- The treatment area should not be bandaged or otherwise covered or wrapped as to be occlusive.
- 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 External Genital Warts

- It is recommended that the treatment area be washed with mild soap and water 6-10 hours following Aldara Cream application.
- It is common for pain, itching, and edema to occur 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.
- Sexual (genital, anal, oral) contact should be avoided while the cream is on the skin.
- 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.
- Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.
- Patients should be aware that new warts may develop during therapy, as Aldara Cream is not a cure.
- The effect of Aldara Cream on the transmission of genital/perianal warts is unknown.
- 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 2X/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 photocarcinogenicity 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 cytogenetic tests (rat 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 (57X MRHD based on AUC 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 cenecephaly, protruding tongues and low-set ears. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 5 mg/kg/day (98X 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 (115X 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 2 mg/kg/day (115X 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 fetality 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.

ADVERSE REACTIONS

Healthcare providers and patients may contact 3M or FDA's Medwatch to report adverse reactions by calling 1-800-814-1795 or 1-800-FDA-1088, or on the internet at <http://www.fda.gov/medwatch>.

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.

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	n=99	n=156	n=157
Vehicle	n=114	n=99	n=156	n=157
Erythema	74 (65%)	21 (21%)	90 (58%)	34 (22%)
Erosion	35 (31%)	8 (8%)	47 (30%)	1 (1%)
Excoriation/Flaking	21 (18%)	8 (8%)	40 (26%)	12 (8%)
Edema	20 (18%)	5 (5%)	19 (12%)	1 (1%)
Induration	6 (5%)	2 (2%)	11 (7%)	3 (2%)
Ulceration	9 (8%)	1 (1%)	7 (4%)	3 (3%)
Scabbing	4 (4%)	0 (0%)	20 (13%)	4 (3%)
Vesicles	3 (3%)	0 (0%)	3 (2%)	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	Vehicle	Aldara Cream	Vehicle
	n=117	n=103	n=156	n=158
Application Site Disorders:				
Application Site Reactions:				
Wart Site:				
Itching	32%	20%	22%	10%
Burning	26%	12%	9%	5%
Pain	8%	2%	2%	0%
Soreness	3%	0%	0%	1%
Systemic Reactions:				
Headache	4%	3%	5%	2%
Influenza-like symptoms	3%	2%	1%	0%
Myalgia	1%	0%	1%	1%
*Incidence 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, itea 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.

POSTMARKETING ADVERSE EVENTS

The following adverse reactions have been identified during post-approval use of Aldara Cream. 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.

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. **Hematological:** decreases in red cell, white cell and platelet counts. **Hepatic:** abnormal liver function. **Neuropsychiatric:** agitation, cerebrovascular accident, convulsions, depression, insomnia, multiple sclerosis aggravation, paresis, suicide. **Respiratory:** dyspnea. **Urinary System Disorders:** proteinuria. **Skin and Appendages:** exfoliative dermatitis.

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.

DOSE AND ADMINISTRATION

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 treatment 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 cm²; use of excessive amounts of cream should be avoided.

Keep out of reach of children.

Rx only

Distributed by:

3M Pharmaceuticals

Northridge, CA 91324

July 2004 662800

3M

3M Pharmaceuticals

275-3W-01 3M Center

St. Paul, MN 55144-1000

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Printed in U.S.A.

AL-9605K

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Study Challenges Breast-Feeding as IQ Boost for Kids

Breast-feeding has little or no effect on children's later intelligence, according to the largest study ever to address this question.

The influence of breast-feeding on cognitive ability has been debated for more than 70 years, with multiple potentially confounding factors having been identified. These include socioeconomic status, birth weight, maternal history of smoking, maternal and paternal education, and race or ethnicity. Maternal intelligence, however, has largely been overlooked as a potential confounder in studies investigating the effects of breast-feeding, according to Geoff Der, a statistician at the Medical Research Council's Social and Public Health Sciences Unit in Glasgow, Scotland.

Analyzing data from 5,475 children and their mothers in the population-based U.S. national longitudinal survey of youth that began in 1979, Mr. Der and his colleagues found that if maternal intelligence was not included as a potential confounder, breast-feeding did appear to exert beneficial effects on children's intelligence, adding approximately 4 points. However, when maternal intelligence was included in the analysis, breast-feeding was associated with an increase of less than half a point (BMJ 2006 Oct. 4 [doi:10.1136/bmj.38978.699583.55]). Previous studies' not having considered maternal intelligence was "surprising given the heritability of intelligence," he observed.

The researchers also determined that an increase of 15 points in maternal intelligence more than doubled the likelihood that the child would be breast-fed. They furthermore observed that mothers who breast-fed tended to be older and more educated, and to provide a more stimulating home environment.

Despite the lack of association with children's intelligence, breast-feeding remains important for overall growth and development, Mr. Der noted.

—Nancy Walsh