Low-Dose Estrogens Effective for Hot Flashes

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Senior Writer

WASHINGTON — A 0.45-mg daily dose of synthetic conjugated estrogens-A improves moderate to severe menopausal vasomotor symptoms, compared with placebo, according to data presented at the annual meeting of the American College of Obstetricians and Gynecologists.

The results indicate that postmenopausal women who start estrogen therapy at a low dose may be able to gain the efficacy of higher-dose treatments while having minimal side effects, Dr. James A. Simon of George Washington University in Washington and Dr. Sam S. Miller of the SAM Clinical Research Center in San Antonio wrote in a poster presented at the ACOG meeting.

At week 12 of therapy, nearly 38% of patients taking synthetic conjugated estrogens-A (SCE-A) reported no moderate to severe vasomotor symptoms vs. 7.8% of patients taking placebo, according to the researchers. In addition, the 0.45-mg daily dose of SCE-A reduced the mean weekly frequency of moderate to severe vasomotor symptoms by 67.8 from a baseline of 95.9 at 12 weeks, compared with a mean drop of 42.9 among placebo patients from the same baseline score.

The multicenter, double-blind trial included postmenopausal women, with or without a uterus, who had experienced at least 60 moderate to severe vasomotor symptoms per week. A total of 104 patients were randomized to receive either the 0.45-mg dose of SCE-A or placebo daily for 12 weeks. Approximately 91% of the patients taking SCE-A and 67% of the patients taking placebo completed the full 12 weeks of the study.

The subjects were asked to keep a daily diary of the frequency and severity of their symptoms. Patients also had vital signs, body weight, and adverse events evaluated during six office visits. The investigators assessed the safety and tolerability of the treatment through standard laboratory evaluations at screening and at week 12 of the study.

The research was supported by Duramed Research Inc. of Bala Cynwyd, Pa., which markets SCE-A under the trade name Cenestin. Duramed is a wholly owned subsidiary of Barr Pharmaceuticals. Cenestin 0.45 mg was approved by the Food and Drug Administration in 2004 for the treatment of moderate to severe vasomotor symptoms. The patients recruited for the study were healthy women ages 30-80 years who had experienced spontaneous amenorrhea for 12 months before screening or had a bilateral oophorectomy, with or without hysterectomy, at least 6 weeks before screening.

Patients taking SCE-A had a greater reduction in frequency of symptoms starting at week 2 and reaching statistical significance from week 3 on. The drug also resulted in greater reduction in severity of symptoms at week 2, reaching statistical significance from week 5 on. ■

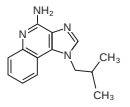
Aldara Cream, 5% (imiquimod)

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

External Genital Warts

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

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 viral disease and is not recommended for these conditions.

PRECAUTIONS

General

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

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

Aldara Cream has the potential to exacerbate inflammatory conditions of the skin, 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 phototoxic mechanisms. Despite the absence of observed phototoxicity in humans (*see ADVERSE REACTIONS*), Aldara Cream shortened the time to skin tumor formation in an animal photococarcinogenicity 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:
1. This medication is to be used as directed by a physician. It is for external use only. Eye contact should be avoided.
2. The treatment area should not be bandaged or otherwise covered or wrapped as to be occlusive.
3. Some reports have been received of localized hypopigmentation and hyperpigmentation following Aldara Cream use. Follow-up information suggests that these skin color changes may be permanent in some patients.

Patients Being Treated for External Genital Warts

1. It is recommended that the treatment area be washed with mild soap and water 6-10 hours following Aldara Cream application.
2. It is common for patients to experience local skin reactions such as erythema, erosion, excoriation/flaking, and edema at the site of application or surrounding areas. Most skin reactions are mild to moderate. Severe skin reactions can occur and should be promptly reported to the prescribing physician. Should severe local skin reaction occur, the cream should be removed by washing the treatment area with mild soap and water. Treatment with Aldara Cream can be resumed after the skin reaction has subsided.
3. Sexual (genital, anal, oral) contact should be avoided while the cream is on the skin.
4. Application of Aldara Cream in the vagina is considered internal and should be avoided. Female patients should take special care if applying the cream at the opening of the vagina because local skin reactions on the delicate moist surfaces can result in pain or swelling, and may cause difficulty in passing urine.
5. Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.
6. Patients should be aware that new warts may develop during therapy, as Aldara Cream is not a cure.
7. The effect of Aldara Cream on the transmission of genital/perianal warts is unknown.
8. Aldara Cream may weaken condoms and vaginal diaphragms, therefore concurrent use is not recommended.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

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

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

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

Imiquimod revealed no evidence of mutagenic or clastogenic potential based on the results of five in vitro genotoxicity tests (Ames assay, mouse lymphoma L5178Y assay, Chinese hamster ovary cell chromosome aberration assay, human lymphocyte chromosome aberration assay and SHE cell transformation assay) and three in vivo genotoxicity tests (rat and hamster bone marrow cytogenetics assay and a mouse dominant lethal test).

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

Pregnancy

Pregnancy Category C:
Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 1, 5 and 20 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. In the presence of maternal toxicity, fetal effects noted at 20 mg/kg/day [577X 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 exencephaly, 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 (1.5X MRHD based on BSA comparisons), the highest dose evaluated in this study, or 1 mg/kg/day (407X MRHD based on AUC comparisons).

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

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

Nursing Mothers

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

Pediatric Use

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

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

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

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

3X/Week Application

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

*Incidences reported without regard to causality with Aldara Cream.

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

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.

DOSAGE 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 treated area with mild soap and water. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday; or Tuesday, Thursday, Saturday application prior to sleeping hours. Aldara Cream treatment should continue until there is total clearance of the genital/perianal warts or for a maximum of 16 weeks. Local skin reactions (erythema) at the treatment site are common. A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. Treatment may resume once the reaction subsides. Non-occlusive dressings such as cotton gauze or cotton underwear may be used in the management of skin reactions. The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of Aldara Cream therapy. Handwashing before and after cream application is recommended. Aldara Cream is packaged in single-use packets which contain sufficient cream to cover a wart area of up to 20 cm^2; use of excessive amounts of cream should be avoided.

Keep out of reach of children.
Rx only

Distributed by:
3M Pharmaceuticals
Northridge, CA 91324
July 2004 662800

3M
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275-3W-01 3M Center
St. Paul, MN 55144-1000

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Nonhormonal Tx For Hot Flashes Rated Not So Hot

Despite avid interest in finding nonhormonal therapies for menopausal hot flashes, most alternative treatments have demonstrated only limited efficacy, and their safety remains in question, according to a systematic review of the literature.

Dr. Heidi D. Nelson and her associates at Oregon Health and Science University, Portland, compared all randomized, placebo-controlled trials of nonhormonal treatments for hot flashes with the efficacy and adverse effects of agents other than estrogens, progestins, progesterone, or androgens (JAMA 2006;295:2057-71).

A metaanalysis was conducted using 24 of 43 selected studies. Overall, there was some evidence that selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), clonidine, and gabapentin reduce the severity and frequency of hot flashes. However, none of these agents approached the effectiveness of hormone therapy, Dr. Nelson and her associated noted.

The evidence for soy isoflavone extracts was contradictory, "even among the largest and highest quality trials," they noted. There was no evidence to support the efficacy of red clover isoflavone extracts.

—Mary Ann Moon