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Imiquimod (Aldara™ Cream)

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KEY WORDS

immune response-modifier; anogenital warts; human papillomavirus

Imiquimod is an immune-response modifier available as a 5% cream for treating external anogenital warts. Demonstrated to exert antiviral activity by stimulating a local immune response, imiquimod 5% cream offers an effective, nonablative alternative to current treatments.

IMIQUIMOD CREAM: INDICATION

Imiquimod (Aldara™, 3M Pharmaceuticals, St. Paul, MN) is an immune-response modifier. In the United States, it is currently indicated for the treatment of external anogenital warts. Available in a 5% cream, it is applied by the patient to the warts and adjacent skin three times a week (e.g., Monday, Wednesday, and Friday or Tuesday, Thursday, and Saturday) for up to 16 weeks until warts are gone.

STRUCTURE AND DERIVATION

Imiquimod (1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine) has a structural formula indicative of a novel compound.

MECHANISM OF ACTION

The mechanism of action of imiquimod in treating genital and perianal warts is unknown. It has no direct antiviral activity in cell culture. Studies in human peripheral blood mononuclear cells (PBMCs) suggest that imiquimod induces cytokines, including interferon- α , interleukins, and tumor necrosis factor.^{1,2} Additionally, results of a vehicle-controlled clinical trial demonstrated that application of imiquimod 5% cream induced local production of interferon and reduced the viral load

of human papillomavirus (HPV) subtypes 6 and 11.³

PHARMACOKINETICS

Minimal systemic absorption of imiquimod through intact skin occurs during treatment with topically applied imiquimod 5% cream. Clinical studies showed no quantifiable concentrations of imiquimod or metabolites in serum, and <0.9% of a single 5-mg dose was excreted in urine and feces.¹

SIDE EFFECTS AND INTERACTIONS

Imiquimod 5% cream is generally well tolerated. The most common adverse events occurred at the wart site and were mild to moderate in intensity. Discomfort was reported by fewer than 50% of patients receiving imiquimod 5% cream during clinical trials, and fewer than 2% discontinued therapy because of adverse events. The most common application-site reactions reported at least once by women were itching (32%), burning (26%), pain (8%), and soreness (3%).¹

Treatment with imiquimod 5% cream is also associated with local skin reactions, the most common of which, in female patients, were erythema (65%), erosion (31%), excoriation/flaking (18%), edema (18%), ulceration (8%), and induration (5%) at the wart site.¹ Erythema is characteristic of a local immune response.

Imiquimod 5% cream is rated Pregnancy Category B. There are no adequate and well-controlled studies of imiquimod 5% cream in pregnant women. Additionally, safety and efficacy in

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TABLE 1. Cost of treating genital warts^a

Treatment	Length of course	Average cost
Imiquimod		
Aldara™ cream	4 to 16 weeks/1 visit	\$178–\$502 ^b
Podofilox		
Condylox® solution	Up to 4 weeks/1 visit	\$132 ^b
Condylox® gel	Up to 4 weeks/1 visit	\$127 ^b
Cryotherapy	1 to 4 in-office treatments	\$209–\$871 ^c
Podophyllin	1 to 6 in-office treatments	\$138–\$574 ^c
Trichloroacetic acid	1 to 6 in-office treatments	\$138–\$574 ^c
Electrosurgery	1 in-office treatment	\$270–\$340 ^{d,e}
Laser	1 to 3 in-office treatments	\$305–\$2650 ^{d,e,f}
Surgical excision	1 in-office treatment	\$282 ^d

^aAssumes average wholesale price plus cost of office visits @ \$70 per visit.

^bMedi-Span, Inc. Prescription Pricing Guide. Indianapolis, IN, January 1998.

^cStrauss MJ, Khanna V, Koenig JD, et al.: The cost of treating genital warts. *Int J Dermatol* 35:340–348, 1996.

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^eKraus SJ, Stone KM: Management of genital infection caused by human papillomavirus. *Rev Infect Dis* 12(suppl 6):S620–S632, 1990.

^fIncludes surgeon and anesthesiologist. Hospitalization would be assumed to require an additional \$500 to \$600 per day.

patients below the age of 18 years old have not been established.

SPECTRUM OF ANTIVIRAL ACTIVITY

Imiquimod has no direct antiviral effect. Indirect antiviral activity has been demonstrated in cell culture models and in several animal infection models. In vitro induction of interferons and other cytokines was demonstrated in imiquimod-stimulated PBMC culture.² Additionally, imiquimod antiviral activity against herpes simplex virus,^{4–7} cytomegalovirus,⁸ and Rift Valley fever virus (a bunyavirus)⁹ has also been demonstrated in animal models.

CLINICAL APPLICATIONS

Imiquimod 5% cream is currently approved to treat external genital and perianal warts. The Centers for Disease Control and Prevention recommends that physicians have at least one patient-applied treatment option for the treatment of external genital and perianal warts.¹⁰ Patients apply imiquimod 5% cream at bedtime three times a week until warts are gone or for as long as 16 weeks. The treated area should be washed with mild soap and water 6 to 10 hours after application. Many patients may be clear of warts after 8 to 10 weeks or sooner.¹

Patients should be informed that new warts may develop during treatment, that the effect of imiquimod 5% cream on the transmission of genital warts is unknown, and that, because imiquimod 5% cream may weaken latex condoms and diaphragms, sexual contact should be avoided while the cream is on the skin.¹

The efficacy and safety of imiquimod 5% cream were evaluated in multicenter, double-blind, randomized, vehicle-controlled, parallel-design trials. Approximately 900 male and female patients with external genital and/or perianal warts have been evaluated in a clinical trial setting with imiquimod 5% cream.

Randomized, vehicle-controlled trials have demonstrated significantly greater wart clearance rates with imiquimod 5% cream, compared with vehicle or imiquimod 1% cream. In the largest of these trials, a phase-three trial of 311 patients, imiquimod 5% cream was significantly more effective than either imiquimod 1% cream or vehicle in clearing genital and perianal warts. Complete clearance was achieved by 72% of women and 33% of men, while $\geq 50\%$ of warts cleared in 85% of women and 70% of men in the 16-week treatment period. Of those patients whose warts cleared completely, 44% were clear by week 8 of treatment and 69% were clear by week 12.¹¹

COST

Table 1 represents the average cost of treating genital warts. Because most treatments for genital warts are in-office procedures, costs were calculated by combining the cost of the average number of office visits with the average wholesale price of treatments.

CONCLUSIONS

Imiquimod is a novel chemical compound; no chemically similar compounds are indicated for hu-

man use. The proven efficacy, minimal systemic exposure, acceptable local adverse-event profile, lack of drug-related pharmacologic effects, and low potential for overdose make imiquimod 5% cream a safe, first-line, patient-applied therapy for treating external genital and perianal warts.

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