



BY ALAN
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UNDER MY SKIN

Good Doctors

I was flattered.

Vladimir had brought in his eczematous infant for a second opinion. No doubt he chose me

because his GP was unsure and he'd heard I'm boarded in pediatrics. Not exactly.

In fact, he had already consulted a well-known pediatric dermatologist. "I was waiting for the commuter train in Sharon," said Vladimir, "I met this Russian guy and asked him if he knew a good dermatologist."

It's nice to hear that some Russian commuter thinks I'm good. But how does he know? And what is a good doctor, anyway?

This is not an idle question. Pay for performance is our Next Big Thing. HMOs now reward hospitals for practicing better

medicine. Prodded by Medicare, professional associations are developing quality guidelines. Soon enough, patients will get lower copays for consulting better doctors.

OK, what's a better doctor?

This question is too complex for me to address in depth. I've observed, however, how hard it is to judge physician quality even when we want to, such as when referring patients to Mohs surgeons, internists, ophthalmologists, allergists, etc.

When people are referred to me, they often say things like, "Dr. Smith says you're terrific!" Since I've only seen a handful of Dr. Smith's patients and never met him, how does he know I'm terrific? Can he gauge my diagnostic acumen? Does he know my outcome data?

When I refer, I also say my colleague is swell; I want the patient to feel confident. Although I really believe the doctor is good, critical assessment forces me to con-



ALDARA™

[al dar' a]
(imiquimod)
Cream, 5%

Brief Summary of prescribing information

For Dermatologic Use Only Not for Ophthalmic Use

INDICATIONS AND USAGE Aldara Cream is indicated for the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adults. Aldara Cream is indicated for the topical treatment of biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured. The histological diagnosis of superficial basal cell carcinoma should be established prior to treatment, since safety and effectiveness of Aldara Cream have not been established for other types of basal cell carcinomas, including nodular, morpheaform (fibrosing or sclerosing) types. 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** The diagnosis of sBCC should be confirmed prior to treatment, since safety and effectiveness of Aldara Cream have not been established for 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 (i.e., sBCC). Patients with sBCC treated with Aldara Cream are recommended to have regular follow-up of the treatment site. 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 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 photocarcinogenicity study (see **Carcinogenesis, Mutagenesis, Impairment of Fertility**). Therefore, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure. **Actinic Keratosis** Safety and efficacy have not been established for Aldara Cream in the treatment of actinic keratosis with repeated use, i.e. more than one treatment course, in the same 25 cm² area. The safety of Aldara Cream applied to areas of skin greater than 25 cm² (e.g. 5 cm X 5 cm) for the treatment of actinic keratosis has not been established. **Superficial Basal Cell Carcinoma** The safety and efficacy of treating superficial basal cell carcinoma (sBCC) lesions on the face, head and anogenital area have not been established. The efficacy and safety of Aldara Cream have not been established for patients with Basal Cell Nevus Syndrome or Xeroderma Pigmentosum. **Information for Patients 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 Actinic Keratosis (AK)** 1. It is recommended that the treatment area be washed with mild soap and water 8 hours following Aldara Cream application. 2. It is common for patients to experience local skin reactions (can range from mild to severe in intensity) during treatment with Aldara Cream, and these reactions may extend beyond the application site onto the surrounding skin. Skin reactions generally decrease in intensity or resolve after cessation of Aldara Cream therapy. Potential local skin reactions include erythema, edema, vesicles, erosion/ulceration, weeping/exudate, flaking/scaling/dryness, and scabbing/crusting. Most patients using Aldara Cream for the treatment of AK experience erythema, flaking/scaling/dryness and scabbing/crusting at the application site with normal dosing. Patients may also experience application site reactions such as itching and/or burning. Local skin reactions may be of such an intensity that patients may require rest periods from treatment. Treatment with Aldara Cream can be resumed after the skin reaction has subsided, as determined by the physician. Patients should contact their physician promptly if they experience any sign or symptom at the application site that restricts or prohibits their daily activity or makes continued application of the cream difficult. 3. Because of local skin reactions, during treatment and until healed, the treatment area is likely to appear noticeably different from normal skin. The skin surrounding the treatment area may also be affected, but less intensely so. 4. Contact with the eyes, lips and nostrils should be avoided. 5. Use of sunscreen is encouraged, and patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using Aldara Cream. 6. During treatment, sub-clinical AK lesions may become apparent in the treatment area and may subsequently resolve. 7. Partially-used packets should be discarded and not reused. 8. Dosing is twice weekly for the full 16 weeks, unless otherwise directed by the physician. However, the treatment period should not be extended beyond 16 weeks due to missed doses or rest periods. **Patients Being Treated for Superficial Basal Cell Carcinoma (sBCC)** 1. It is recommended that the treatment area be washed with mild soap and water 8 hours following Aldara Cream application. 2. Most patients using Aldara Cream for the treatment of sBCC experience erythema, edema, induration, erosion, scabbing/crusting and flaking/scaling at the application site with normal dosing. These local skin reactions generally decrease in intensity or resolve after cessation of Aldara Cream therapy. Patients may also experience application site reactions such as itching and/or burning. Local skin reactions may be of such an intensity that patients may require rest periods from treatment. Treatment with Aldara Cream can be resumed after the skin reaction has subsided, as determined by the physician. 3. During treatment and until healed, affected skin is likely to appear noticeably different from normal skin. 4. It is prudent for patients to minimize or avoid exposure to natural or artificial sunlight. 5. The clinical outcome of therapy can be determined after regeneration of the treated skin, approximately 12 weeks after the end of treatment. 6. Patients should contact their physician if they experience any sign or symptom at the application site that restricts or prohibits their daily activity or makes continued application of the cream difficult. 7. Patients with sBCC treated with Aldara Cream are recommended to have regular follow-up to re-evaluate the treatment site. **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. 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 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 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. AK and sBCC are not conditions generally seen within the pediatric population. The safety and efficacy of Aldara

cede that my evidence is thin. What, after all, do I really know about this doctor?

- ▶ Patients say his staff is nice.
- ▶ She sends prompt referral letters.
- ▶ He'll see an emergency right away.
- ▶ I once met her in the hall, and she seemed personable.

Such criteria imply something about my colleagues' characters and managerial skills but not much about competence. Is the internist a sharp diagnostician? Would she nail kala-azar if it came her way? How would I know? Because the people I send her mostly need routine physicals, does it matter? I guess the Mohs guy has good technique—he sends pictures of gapping

wounds and neat stitching. But is he better or worse than anybody else? I must admit I'm in no position to judge.

If doctors aren't too clever at recognizing quality, patients are perhaps worse. At times, most of us learn about truly terrible physicians who miss basic diagnoses, treat patients with casual contempt, do surgery beyond their ability, or biopsy anything that moves. They're still in practice because most of their patients are still breathing. And many of these doctors have one striking thing in common:

They are wildly successful. Their patients swear by them.

In other pursuits, gauging quality is fair-

ly straightforward: gardening, auto repair, taxidermy. Defining excellence in medical care is a bit subtler, for reasons too numerous to list. Soon, however, we're going to have to do it anyway, because those who pay our bills want value for their money. And they say value means "quality care."

So they've started with dramatic procedures with easily measured outcomes, like mortality rates for transplants. For the rest of us, they want process data: how often doctors measure hemoglobin A_{1c} in people with diabetes or prescribe steroid inhalers to asthma patients, and so on. Good process may turn out to produce good outcome, or it may not. Either way,

we're going to have to both do the right thing and—most crucial—report that we did it. If we don't, the counters will be displeased and our efforts won't count.

Will this make us better doctors? Consider: Everyone agrees that a good doctor assesses whether isotretinoin patients understand precautions. The iPLEDGE program forces us to click the box, "In my opinion, this patient understands and is capable of complying with the requirements of the iPLEDGE program." Does forcing us to click this box make us better?

Years of struggle with PCP referrals, OSHA, CLIA, and E/M codes make one realize the futility of debating bureaucratic imperatives. Soon we'll have more boxes to click, along with online physician-quality tables for patients to peruse.

But many will still find their way to excellence the old-fashioned way.

Like Eddie, who has a rare and debilitating neuropathy. "I'm seeing Dr. Lariat over at St. Anselm's," he says.

"I hear he's tops," I reply. "How'd you find him?"

"Funny," says Eddie. "My brother-in-law Dave has box seats at Fenway. Turns out that the guy in the next box is a neurologist at MBH. When Dave tells him what I've got, the guy says, 'Neuropathy? He's gotta see Lariat over at St. Anselm's. He's the best!'"

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LETTERS

No Place for E-Mail in Medical Practice

Two academic physicians (presumably salaried and not financially docked for unremunerated patient care) slug it out on the topic of physician communication with patients via e-mail. ("Should physicians communicate with patients via e-mail?" Point-Counterpoint, July 2006, p. 17).

Since both are on the same side of the fence on this issue, I feel some obligation to communicate my point of view, to wit, there is no place whatsoever for e-mail in medical practice. It is a waste of time, a serious potential breach of confidentiality (just assume that anything in electronic form can be posted anywhere in a nanosecond, because it can, and often is), and a giant black hole of potential misunderstanding and unmet expectations. And we don't get paid for it.

Medicine is drowning in inappropriate technology. E-mail will not rescue it.

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LETTERS

Letters in response to articles in SKIN & ALLERGY NEWS and its supplements should include your name and address, affiliation, and conflicts of interest in regard to the topic discussed. Letters may be edited for space and clarity.

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Cream for AK or sBCC in patients less than 18 years of age have not been established. **Geriatric Use** Of the 215 patients in the 2X/week clinical studies evaluating the treatment of AK lesions with Aldara Cream, 127 patients (59%) were 65 years and older, while 60 patients (28%) were 75 years and older. Of the 185 patients in the 5X/week treatment groups of clinical studies evaluating the treatment of sBCC with Aldara Cream, 65 patients (35%) were 65 years and older, while 25 patients (14%) 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, but greater sensitivity of some older individuals cannot be ruled out. **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 photolability 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. **Actinic Keratosis** The data described below reflect exposure to Aldara Cream or vehicle in 436 patients enrolled in two double-blind, vehicle-controlled, 2X/week studies. Patients applied Aldara Cream or vehicle to a 25 cm² contiguous treatment area on the face or scalp 2X/week for 16 weeks. **Summary of All Adverse Events Reported by >1% of Patients in the Combined 2X/ Week Studies** [Body System Imiq 2X/Week Preferred Term (n=215) and Vehicle 2X/Week Preferred Term (n=221)]: **APPLICATION SITE DISORDERS:** APPLICATION SITE REACTION 71 (33.0%) and 32 (14.5%). **BODY AS A WHOLE - GENERAL DISORDERS:** BACK PAIN 3 (1.4%) and 2 (0.9%); FATIGUE 3 (1.4%) and 2 (0.9%); FEVER 3 (1.4%) and 0 (0.0%); HEADACHE 11 (5.1%) and 7 (3.2%); HERNIA NOS 4 (1.9%) and 1 (0.5%); INFLUENZA-LIKE SYMPTOMS 4 (1.9%) and 4 (1.8%); PAIN 3 (1.4%) and 3 (1.4%); RIGORS 3 (1.4%) and 0 (0.0%). **CARDIOVASCULAR DISORDERS, GENERAL:** CHEST PAIN 1 (0.5%) and 4 (1.8%); HYPERTENSION 3 (1.4%) and 5 (2.3%). **CENTR & PERIPH NERVOUS SYSTEM DISORDERS:** DIZZINESS 3 (1.4%) and 1 (0.5%). **GASTRO-INTESTINAL SYSTEM DISORDERS:** DIARRHEA 6 (2.8%) and 2 (0.9%); DYSPEPSIA 6 (2.8%) and 4 (1.8%); GASTROESOPHAGEAL REFLUX 3 (1.4%) and 3 (1.4%); NAUSEA 3 (1.4%) and 3 (1.4%); VOMITING 3 (1.4%) and 1 (0.5%). **HEART RATE AND RHYTHM DISORDERS:** FIBRILLATION ATRIAL 3 (1.4%) and 2 (0.9%); METABOLIC AND NUTRITIONAL DISORDERS: HYPERCHOLESTEROLEMIA 4 (1.9%) and 0 (0.0%). **MUSCULO-SKELETAL SYSTEM DISORDERS:** ARTHRALGIA 2 (0.9%) and 4 (1.8%); ARTHRITIS 2 (0.9%) and 3 (1.4%); MYALGIA 3 (1.4%) and 3 (1.4%); SKELETAL PAIN 1 (0.5%) and 3 (1.4%). **NEOPLASM:** BASAL CELL CARCINOMA 5 (2.3%) and 5 (2.3%); CARCINOMA SQUAMOUS 8 (3.7%) and 5 (2.3%). **RESISTANCE MECHANISM DISORDERS:** 9 (4.2%) and 11 (5.0%); HERPES SIMPLEX 4 (1.9%) and 4 (1.8%); INFECTION VIRAL 3 (1.4%) and 0 (0.0%). **RESPIRATORY SYSTEM DISORDERS:** BRONCHITIS 2 (0.9%) and 3 (1.4%); COUGHING 6 (2.8%) and 10 (4.5%); PHARYNGITIS 4 (1.9%) and 4 (1.8%); PULMONARY CONGESTION 1 (0.5%) and 3 (1.4%); RHINITIS 7 (3.3%) and 8 (3.6%); SINUSITIS 16 (7.4%) and 14 (6.3%); UPPER RESP TRACT INFECTION 33 (15.3%) and 27 (12.2%). **SECONDARY TERMS:** ABRASION NOS 7 (3.3%) and 5 (2.3%); CYST NOS 0 (0.0%) and 4 (1.8%); INFLICTED INJURY 19 (8.8%) and 21 (9.5%); POST-OPERATIVE PAIN 3 (1.4%) and 4 (1.8%). **SKIN AND APPENDAGES DISORDERS:** 47 (21.9%) and 42 (19.0%); ALOPECIA 3 (1.4%) and 0 (0.0%); DERMATITIS 3 (1.4%) and 7 (3.2%); ECZEMA 4 (1.9%) and 3 (1.4%); HYPERKERATOSIS 19 (8.8%) and 12 (5.4%); PHOTSENSITIVITY REACTION 2 (0.9%) and 4 (1.8%); PRURITUS 2 (0.9%) and 3 (1.4%); RASH 5 (2.3%) and 5 (2.3%); SKIN DISORDER 6 (2.8%) and 7 (3.2%); VERRUCA 1 (0.5%) and 3 (1.4%). **URINARY SYSTEM DISORDERS:** 8 (3.7%) and 10 (4.5%); URINARY TRACT INFECTION 3 (1.4%) and 1 (0.5%). **VISION DISORDERS:** CONJUNCTIVITIS 1 (0.5%) and 3 (1.4%); EYE ABNORMALITY 4 (1.9%) and 1 (0.5%); EYE INFECTION 0 (0.0%) and 3 (1.4%). **Summary of All Application Site Reactions Reported by >1% of Patients in the Combined 2X/ Week Studies** [Imiq 2X/Week Included Term (n=215) and Vehicle 2X/Week Included Term (n=221)]: **BLEEDING AT TARGET SITE** 7 (3.3%) and 1 (0.5%). **BURNING AT REMOTE SITE** 4 (1.9%) and 0 (0.0%). **BURNING AT TARGET SITE** 12 (5.6%) and 4 (1.8%). **INDURATION AT REMOTE SITE** 3 (1.4%) and 0 (0.0%). **INDURATION AT TARGET SITE** 5 (2.3%) and 3 (1.4%). **IRRITATION AT REMOTE SITE** 3 (1.4%) and 0 (0.0%). **ITCHING AT REMOTE SITE** 7 (3.3%) and 3 (1.4%). **ITCHING AT TARGET SITE** 44 (20.5%) and 15 (6.8%). **PAIN AT TARGET SITE** 5 (2.3%) and 2 (0.9%). **STINGING AT TARGET SITE** 6 (2.8%) and 2 (0.9%). **TENDERNESS AT TARGET SITE** 4 (1.9%) and 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. **Local Skin Reactions in the Treatment Area as Assessed by the Investigator (Percentage of Patients) 2X/Week Application [Mild/Moderate/Severe Aldara Cream (n=215), Vehicle (n=220) and Severe Aldara Cream (n=215), Vehicle (n=220)]:** Erythema 209 (97%), 206 (93%) and 38 (18%), 5 (2%). Edema 106 (49%), 22 (10%) and 0 (0%), 0 (0%). Weeping/Exudate 45 (22%), 3 (1%) and 0 (0%), 0 (0%). Vesicles 19 (9%), 2 (1%) and 0 (0%), 0 (0%). Erosion/Ulceration 103 (48%), 20 (9%) and 5 (2%), 0 (0%). Flaking/Scaling/Dryness 199 (93%), 199 (91%) and 16 (7%), 7 (3%). Scabbing/Crusting 169 (79%), 92 (42%) and 18 (8%), 4 (2%). The adverse reactions that most frequently resulted in clinical intervention (e.g., rest periods, withdrawal from study) were local skin and application site reactions. Overall, in the clinical studies, 2% (5/215) of patients discontinued for local skin/application site reactions. Of the 215 patients treated, 35 patients (16%) on Aldara Cream and 3 of 220 patients (1%) on vehicle cream had at least one rest period. Of these Aldara Cream patients, 32 (91%) resumed therapy after a rest period. In the AK studies, 22 of 678 imiquimod treated patients developed treatment site infections that required a rest period off Aldara Cream and were treated with antibiotics (19 with oral and 3 with topical). **Superficial Basal Cell Carcinoma** The data described below reflect exposure to Aldara Cream or vehicle in 364 patients enrolled in two double-blind, vehicle-controlled, 5X/week studies. Patients applied Aldara Cream or vehicle 5X/week for 6 weeks. The incidence of adverse events reported by >1% of subjects during the 6 week treatment period is summarized below. **Summary of All Adverse Events Reported by >1% of Patients in the Combined 5X/ Week Studies** [Body System Imiquimod 5X/Week Preferred Term (n=185) and Vehicle 5X/Week Preferred Term (n=179)]: **APPLICATION SITE DISORDERS:** APPLICATION SITE REACTION 52 (28.1%) and 5 (2.8%). **BODY AS A WHOLE - GENERAL DISORDERS:** ALLERGY AGGRAVATED 2 (1.1%) and 1 (0.6%); BACK PAIN 7 (3.8%) and 1 (0.6%); CHEST PAIN 2 (1.1%) and 0 (0.0%); FATIGUE 4 (2.2%) and 2 (1.1%); FEVER 3 (1.6%) and 0 (0.0%); PAIN 3 (1.6%) and 2 (1.1%). **CARDIOVASCULAR DISORDERS, GENERAL:** HYPERTENSION 5 (2.7%) and 1 (0.6%). **CENTR & PERIPH NERVOUS SYSTEM DISORDERS:** DIZZINESS 2 (1.1%) and 1 (0.6%); HEADACHE 14 (7.6%) and 4 (2.2%). **GASTRO-INTESTINAL SYSTEM DISORDERS:** ABDOMINAL PAIN 1 (0.5%) and 2 (1.1%); DIARRHEA 1 (0.5%) and 2 (1.1%); DYSPEPSIA 3 (1.6%) and 2 (1.1%); GASTRO-INTESTINAL DISORDER NOS 1 (0.5%) and 2 (1.1%); NAUSEA 2 (1.1%) and 0 (0.0%); TOOTH DISORDER 0 (0.0%) and 2 (1.1%). **METABOLIC AND NUTRITIONAL DISORDERS:** GOUT 2 (1.1%) and 0 (0.0%). **MUSCULO-SKELETAL SYSTEM DISORDERS:** SKELETAL PAIN 3 (1.6%) and 2 (1.1%). **PSYCHIATRIC DISORDERS:** ANXIETY 2 (1.1%) and 1 (0.6%). **RESISTANCE MECHANISM DISORDERS:** INFECTION 1 (0.5%) and 3 (1.7%); INFECTION FUNGAL 2 (1.1%) and 2 (1.1%). **RESPIRATORY SYSTEM DISORDERS:** COUGHING 3 (1.6%) and 1 (0.6%); PHARYNGITIS 2 (1.1%) and 1 (0.6%); RHINITIS 5 (2.7%) and 1 (0.6%); SINUSITIS 4 (2.2%) and 1 (0.6%); UPPER RESP TRACT INFECTION 6 (3.2%) and 2 (1.1%). **SECONDARY TERMS:** INFLICTED INJURY 3 (1.6%) and 3 (1.7%); PROCEDURAL SITE REACTION 2 (1.1%) and 3 (1.7%). **SKIN AND APPENDAGES DISORDERS:** HYPERKERATOSIS 3 (1.6%) and 2 (1.1%); RASH 3 (1.6%) and 1 (0.6%); SKIN DISORDER 1 (0.5%) and 3 (1.7%). **WHITE CELL AND RES DISORDERS:** LYMPHADENOPATHY 5 (2.7%) and 1 (0.6%). In controlled clinical studies, the most frequently reported adverse reactions were local skin and application site reactions including erythema, edema, induration, erosion, flaking/scaling, scabbing/crusting, itching and burning at the application site. The incidence of the 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** [Imiquimod 5X/ Week Included Term (n=185) and Vehicle 5X/ Week Included Term (n=179)]: **ITCHING AT TARGET SITE** 30 (16.2%) and 1 (0.6%). **BURNING AT TARGET SITE** 11 (5.9%) and 2 (1.1%). **PAIN AT TARGET SITE** 6 (3.2%) and 0 (0.0%). **TENDERNESS AT TARGET SITE** 2 (1.1%) and 0 (0.0%). **ERYTHEMA AT REMOTE SITE** 3 (1.6%) and 0 (0.0%). **PAPULE (S) AT TARGET SITE** 3 (1.6%) and 0 (0.0%). **BLEEDING AT TARGET SITE** 4 (2.2%) and 0 (0.0%). **TINGLING AT TARGET SITE** 1 (0.5%) and 2 (1.1%). **INFECTION AT TARGET SITE** 2 (1.1%) and 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 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) 5X/Week Application [Mild/Moderate Aldara Cream (n=184), Vehicle (n=178) and Severe Aldara Cream (n=184) Vehicle (n=178)]:** Edema 71%, 36% and 7%, 0%. Erosion 54%, 14% and 13%, 0%. Erythema 69%, 95% and 31%, 2%. Flaking/Scaling 87%, 76% and 4%, 0%. Induration 78%, 53% and 6%, 0%. Scabbing/Crusting 64%, 34% and 19%, 0%. Ulceration 34%, 3% and 6%, 0%. Vesicles 29%, 2% and 2%, 0%. 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. In the sBCC studies, 17 of 1266 (1.3%) imiquimod-treated patients developed treatment site infections that required a rest period off Aldara Cream and were treated with antibiotics. **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 Females Aldara Cream (n=114), Vehicle (n=99); Males Aldara Cream (n=114), Vehicle (n=157) and Severe Females Aldara Cream (n=114), Vehicle (n=99); Males Aldara Cream (n=156), Vehicle (n=157)]:** Erythema 74 (65%), 21 (21%); 90 (58%), 34 (22%) and 4 (4%), 0 (0%); 6 (4%), 0 (0%). Erosion 35 (31%), 8 (8%); 47 (30%), 10 (6%) and 1 (1%), 0 (0%); 2 (1%), 0 (0%). Excoriation/Flaking 21 (18%), 8 (8%); 40 (26%), 12 (8%) and 0 (0%), 0 (0%); 1 (1%), 0 (0%). Edema 20 (18%), 5 (5%); 19 (12%), 1 (1%) and 1 (1%), 0 (0%); 0 (0%), 0 (0%). Induration 6 (5%), 2 (2%); 11 (7%), 3 (2%) and 0 (0%), 0 (0%); 0 (0%), 0 (0%). Ulceration 9 (8%), 1 (1%); 7 (4%), 1 (1%) and 3 (3%), 0 (0%); 0 (0%), 0 (0%). Scabbing 4 (4%), 0 (0%); 20 (13%), 4 (3%) and 0 (0%), 0 (0%); 0 (0%), 0 (0%). Vesicles 3 (3%), 0 (0%); 3 (2%), 0 (0%) and 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 Aldara Cream (n=117), Vehicle (n=103) and Males Aldara Cream (n=156), Vehicle (n=158)]:** Application Site Disorders: Application Site Reactions **Wart Site:** Itching 32%, 20% and 22%, 10%. Burning 26%, 12% and 9%, 5%. Pain 8%, 2% and 2%, 1%. Soreness 3%, 0% and 0%, 1%. Fungal Infection* 11%, 3% and 2%, 1%. Systemic Reactions: Headache 4%, 3% and 5%, 2%. Influenza-like symptoms 3%, 2% and 1%, 0%. Myalgia 1%, 0% and 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.

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