Wound Healing

Wound Care Centers Offer New Opportunities

BY JEFF EVANS Senior Writer

BALTIMORE — The increasing need for wound care centers in the United States may present an opportunity for dermatologists to wed their interests in both medical and surgical dermatology, according to Dr. Robert S. Kirsner.

Wound care is at the junction of surgical and medical dermatology. To somebody with broad interests, it may be attractive because there are certain wound problems that require the internist in you and some wound problems that require the surgeon in you," said Dr. Kirsner, director of the Wound CURE (Cutaneous Ulcer Rehabilitation and Education) Center at the University of Miami.

Dermatologists can offer their expertise in wound care by directing or even opening up their own wound care clinic or by practicing or consulting part-time with a center, he said.

Some wound centers have a dermatologist who works there a half or full day per week, but typically a dermatologist is a consultant to a wound center and sees patients with dermatologic conditions such as pyoderma gangrenosum, vasculitis, or immunobullous disease, Dr. Kirsner said in an interview.

Wound care centers that include a physician may be run from a solo or group practice or based in an ambulatory center or at a hospital. Hospital-based centers may be the more "economically savvy way of doing it," Dr. Robert D. Galiano said at the annual meeting of the American Society of Plastic Surgeons.

A center can be established independently by a physician, fully staffed by an outside company, set up by an outside company that the physician then runs, or formed by a mix of these approaches. Regardless of the type of wound care center, about 35% of all hospitals now have some sort of formal wound care center, "and I

ALDARA®

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

Brief Summary of Prescribing Information See Package Insert for Full Prescribing Information

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 1.1 Actinic Keratosis Aldara Cream is indicated for the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adults.
1.2 Superficial Basal Cell Carcinoma Aldara Cream is indicated for the topical treatment of biopsyconfirmed, 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 efficacy of Aldara Cream have not been established for other types of basal cell carcinomas, including nodular and morpheaform (fibrosing or sclerosing) types. 1.3 External Genital Warts Aldara Cream is indicated for the treatment of external genital and perianal warts/condyloma acuminata in patients 12 years or older. 1.4 Limitations of Use Aldara Cream has been evaluated in children ages 2 to 12 years with molluscum contagiosum and these studies failed to demonstrate efficacy. Isee Use in Specific Populations (8.4)]. 1.5 Unevaluated Populations The safety and efficacy of Aldara Cream in immunosuppressed patients have not been established. Aldara Cream should be used with caution in patients with pre-existing autoimmune conditions. The efficacy and safety of Aldara Cream have not been established for patients with Basal Cell Nevus Syndrome or Xeroderma Pigmentosum. confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults, with a maxim

5.1 Local Inflammatory Reactions Intense local inflammatory reactions including skin weeping or erosion can occur after few applications of Aldara Cream and may require an interruption of dosing. *[see Dosage and Administration (2) and Adverse Reactions (6)]*. Aldara Cream has the potential to exacerbate inflammatory conditions of the skin, including chronic graft versus host disease. Administration of Aldara Cream is not recommended until the skin is completely healed from any previous drug or surgical treatment. 5.2 Systemic Reactions Flu-like signs and symptoms may accompany, or even precede, local inflammatory reactions and may include malaise, fever, nausea, myalgias and rigors. An interruption of dosing should be considered. *[see Adverse Reactions (6)]* **5.3 Ultraviolet Light Exposure** Exposure to dosing should be considered. *[see Adverse Reactions (6)]* **5.3 Ultraviolet Light Exposure** 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 (e.g., a 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. Aldara Cream shortened the time to skin tumor formation in an animal photoco-carcinogenicity study [see Nonclinical Toxicology (13.1)]. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Therefore, patients should minimize or avoid natural or artificial sunlight exposure. **5.4 Unevaluated Uses: Actinic Keratosis** Safety and efficacy have not been established for Aldara Cream in the treatment of actinic keratosis with repeated use is a more than one established for Aldara Cream in the treatment of actinic keratosis with repeated use, i.e., more than one treatment course in the same 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 [see Clinical 25 cm² (e.g., 5 cm X 5 cm) for the treatment of actinic keratosis has not been established [see Clinical Pharmacology (12.3)]. 5.5 Unevaluated Uses: Superficial Basal Cell Carcinoma The safety and efficacy of Aldara Cream have not been established for other types of basal cell carcinomas (BCC), including nodular and morpheaform (fibrosing or sclerosing) types. Aldara Cream is not recommended for treatment of BCC subtypes other than the superficial variant (i.e., sBCC). Patients with sBCC treated with Aldara Cream should have regular follow-up of the treatment site. [see Clinical Studies (14.2)]. The safety and efficacy of treating sBCC lesions on the face, head and anogenital area have not been established. 5.6 Unevaluated Uses: External Genital Warts Aldara Cream has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. **6.1 Clinical Trials Experience: Actinic Keratosis** The data described below reflect exposure to Aldara Cream or vehicle in 436 subjects enrolled in two double-blind, vehicle-controlled studies. Subjects applied Aldara Cream or vehicle to a 25 cm² contiguous treatment area on the face or scalp 2 times per week for 16 weeks.

Table 2: Selected Adverse Reactions Occurring in >1% of Aldara-Treated Subjects and at a Greater Frequency than with Vehicle in the Combined Studies (Actinic Keratosis)

Preferred Term	Aldara Cream (n=215)	Vehicle (n=221)
Application Site Reaction	71 (33%)	32 (14%)
Upper Resp Tract Infection	33 (15%)	27 (12%)
Sinusitis	16 (7%)	14 (6%)
Headache	11 (5%)	7 (3%)
Carcinoma Squamous	8 (4%)	5 (2%)
Diarrhea	6 (3%)	2 (1%)
Eczema	4 (2%)	3 (1%)
Back Pain	3 (1%)	2 (1%)
Fatigue	3 (1%)	2 (1%)
Fibrillation Atrial	3 (1%)	2 (1%)
Infection Viral	3 (1%)	2 (1%)
Dizziness	3 (1%)	1 (<1%)
Vomiting	3 (1%)	1 (<1%)
Urinary Tract Infection	3 (1%)	1 (<1%)
Fever	3 (1%)	0 (0%
Rigors	3 (1%)	0 (0%)
Alopecia	3 (1%)	0 (0%)

Table 3: Application Site Reactions Reported by >1% of Aldara-Treated Subjects and at a Greater Frequency than with Vehicle in the Combined Studies (Actinic Keratosis)

Included Term	Aldara Cream n=215	Vehicle n=221
Itching	44 (20%)	17 (8%)
Burning	13 (6%)	4 (2%)
Bleeding	7 (3%)	1 (<1%)
Stinging	6 (3%)	2 (1%)
Pain	6 (3%)	2 (1%)
Induration	5 (2%)	3 (1%)
Tenderness	4 (2%)	3 (1%)
Irritation	4 (2%)	0 (0%)

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.

Table 4: Local Skin Reactions in the Treatment Area as Assessed by the Investigator (Actinic Keratosis)

	Aldara Cream (n=215)		vehicle (n=220)	
	All Grades*	Severe	All Grades*	Severe
Erythema	209 (97%)	38 (18%)	206 (93%)	5 (2%)
Flaking/Scaling/Dryness	199 (93%)	16 (7%)	199 (91%)	7 (3%)
Scabbing/Crusting	169 (79%)	18 (8%)	92 (42%)	4 (2%)
Edema	106 (49%)	0 (0%)	22 (10%)	0 (0%)
Erosion/Ulceration	103 (48%)	5 (2%)	20 (9%)	0 (0%)
Weeping/Exudate	45 (22%)	0 (0%)	3 (1%)	0 (0%)
Vesicles	19 (9%)	0 (0%)	2 (1%)	0 (0%)

*Mild, Moderate, or Severe

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 subjects discontinued for local skin/application site reactions. Of the 215 subjects treated, 35 subjects (16%) on Aldara Cream and 3 of 220 subjects (1%) on vehicle cream had at least one rest period. Of these Aldara Cream subjects, 32 (91%) resumed therapy after a rest period. In the Ak studies, 22 of 678 (3.2%) of Aldara-treated subjects developed treatment site infections that required a rest period off Aldara Cream and were treated with antibiotics (19 with oral and 3 with topical). Of the 206 Aldara subjects with both baseline and 8 awaye host-treatment searting assessments. 6 (2.9%) had a greater designer of searcing scores at and 8-week post-treatment scarring assessments, 6 (2.9%) had a greater degree of scarring scores a 8-weeks post-treatment than at baseline. **6.2 Clinical Trials Experience: Superficial Basal Cel** Carcinoma The data described below reflect exposure to Aldara Cream or vehicle in 364 subjects enrolled in two double-blind, vehicle-controlled studies. Subjects applied Aldara Cream or vehicle 5 times per week for 6 weeks. The incidence of adverse reactions reported by >1% of subjects during the studies is summarized below.

Table 5: Selected Adverse Reactions Reported by >1% of Aldara-Treated Subjects and at a Greater Frequency than with Vehicle in the Combined Studies (Superficial Basal Cell Carcinoma)

Preferred Term	(n=185) N %	(n=179) N %
Application Site Reaction	52 (28%)	5 (3%)
Headache	14 (8%)	4 (2%)
Back Pain	7 (4%)	1 (<1%)
Upper Resp Tract Infection	6 (3%)	2 (1%)
Rhinitis	5 (3%)	1 (<1%)
Lymphadenopathy	5 (3%)	1 (<1%)
Fatigue	4 (2%)	2 (1%)
Sinusitis	4 (2%)	1 (<1%)
Dyspepsia	3 (2%)	2 (1%)
Coughing	3 (2%)	1 (<1%)
Fever	3 (2%)	0 (0%)
Dizziness	2 (1%)	1 (<1%)
Anxiety	2 (1%)	1 (<1%)
Pharyngitis	2 (1%)	1 (<1%)
Chest Pain	2 (1%)	0 (0%)
Nausea	2 (1%)	0 (0%)

erythema, edema, induration, erosion, flaking/scaling, scabbing/crusting, itching and burning at the application site. The incidence of application site reactions reported by >1% of the subjects during the -week treatment period is summarized in the following table.

Table 6: Application Site Reactions Reported by >1% of Aldara-Treated Subjects and at a Greater Frequency than with Vehicle in the Combined Studies (Superficial Basal Cell Carcinoma)

Included Term	Aldara Cream n=185	venicie n=179
Itching	30 (16%)	1 (1%)
Burning	11 (6%)	2 (1%)
Pain	6 (3%)	0 (0%)
Bleeding	4 (2%)	0 (0%)
Erythema	3 (2%)	0 (0%)
Papule(s)	3 (2%)	0 (0%)
Tenderness	2 (1%)	0 (0%)
Infection	2 (1%)	0 (0%)

Local skin reactions were collected independently of the adverse reaction "application site reaction" in an Educations were concern integer integer integer in the second of the second application is the real effort to provide a better picture of the specific types of local reactions that might be seen. The and severity of local skin reactions that occurred during controlled studies are shown in the following controlled studies areal studies are shown in the following controlled studies are sho

Table 7: Local Skin Reactions in the Treatment Area as Assessed by the Investigator (Superficial Basal Cell Carcinoma)

		Aldara Cream n=184		Vehicle n=178
	All Grades*	Severe	All Grades*	Severe
Erythema	184 (100%)	57 (31%)	173 (97%)	4 (2%)
Flaking/Scaling	167 (91%)	7 (4%)	135 (76%)	0 (0%)
Induration	154 (84%)	11 (6%)	94 (53%)	0 (0%)
Scabbing/Crusting	152 (83%)	35 (19%)	61 (34%)	0 (0%)
Edema	143 (78%)	13 (7%)	64 (36%)	0 (0%)
Erosion	122 (66%)	23 (13%)	25 (14%)	0 (0%)
Ulceration	73 (40%)	11 (6%)	6 (3%)	0 (0%)
Vesicles	57 (31%)	3 (2%)	4 (2%)	0 (0%)
*Mild Moderate or Severe				

think this number is only going to increase," said Dr. Galiano, who is in the process of establishing a wound care center at Northwestern Memorial Hospital in Chicago, where he is a plastic surgeon.

To determine the best course to take for Northwestern's wound care center, Dr. Galiano visited a wound care clinic at an academic medical center, a research-intensive podiatry-based center within an academic medical center, a small university-based center that was affiliated with a wound management company, and a wound care center at a large state academic medical center that also was affiliated with a management company.

During his visits, Dr. Galiano learned that most wound care centers "will be met with a high rate of skepticism. There's a feeling out there that wound centers are loss leaders and certainly not profitable." The success of centers at large academic institutions will depend on the costs of the facility, rent, and personnel; the types of wounds treated; and the role of research as an adjunct to revenue.

All of the centers that Dr. Galiano visited were well established and profitable. Such centers were also very labor intensive and left little time for other clinical activities.

Facility costs need to be shared with or underwritten by the hospital since the costs of running a center will probably not be covered by the revenues that the center itself brings in for ambulatory visits. 'You have to incorporate downstream revenue," Dr. Galiano advised.

The costs of durable medical equipment and goods, such as the best dressings, need to be controlled in some way because most academic medical centers are nonprofit and will not allow physicians to bill for the best, most expensive dressings. Arrangements could be made with another provider not affiliated with the hospital to provide those materials on-site and then bill the patient directly for them, he suggested.

The most successful centers that Dr. Galiano visited had a large volume of inpatients with chronic wounds that consisted mostly of diabetic foot ulcers, which are associated with the highest-paying diagnosis-related groups.

Dr. David L. Steed, a vascular surgeon who is director of the wound healing/limb preservation clinic at the University of Pittsburgh, handles about 4,000 patient visits per year with his colleagues. The clinic cares for venous stasis ulcers (41%), diabetic neuropathy foot ulcers (27%), ischemic ulcers (13%), pressure ulcers (10%), and other types of chronic wounds (9%).

Dr. Steed's clinic, which is not hospital based, handles all charges itself, and must break even. The clinic employs a nurse practitioner, research nurse, patient care technician, diabetes educator, and podiatrist and has one student (medical or nursing) or resident (surgery or dermatology) present at a time. Plastic and orthopedic surgeons, as well as dermatologists and diabetologists, frequently consult on cases.

'We break even in the clinic, but all the things I send to the hospital make money," he said at the meeting.

At a wound care center, it is reasonable to expect about 40% of patients to be new to the hospital and that 15% on their first



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DR. KIRSNER

visit will require hospital admission, ambulatory surgery, or angiography, Dr. Steed said. Nearly all wound center patients use radiology and laboratory services.

In another presentation, Dr. David Hurley said that he initially balked at the idea of opening a comprehensive wound care center at the hospital in which he worked as a general plastic surgeon and vice president. After the hospital opened a center without his support, he was later offered the opportunity to become its medical director.

He learned that his skepticism of wound care treatments, such as hyperbaric oxygen therapy, was unfounded. "They sent me off to a couple courses, and what I learned was that my understanding of comprehensive wound care had really stopped back with my residency training. It had not been a focus of my training," he said.

One of the things driving the interest in the development of comprehensive wound care centers is the fact that we now have a much better understanding of the biochemistry and physiology of problem wounds," he said.

Dr. Hurley spent more and more time at the center and began looking at it as a possible exit strategy from his plastic surgery practice. Three years ago, he left his medical practice to become the chief medical officer of the management company that had helped to set up the center. That company, Diversified Clinical Services, Jacksonville, Fla., partners with hospitals to manage, operate, and develop comprehensive wound care centers.

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 subjects received rest periods from study) were local skin and application site reactions; 10% (19/185) of subjects received rest periods. The average number of doses not received per subject due to rest periods was 7 doses with a range of 2 to 22 doses; 79% of subjects (15/19) resumed therapy after a rest period. Overall, in the clinical studies, 2% (4/185) of subjects discontinued for local skin/application site reactions. In the sBCC studies, 17 of 1266 (1.3%) Aldara-treated subjects developed treatment site infections that required a rest period and treatment with antibiotics. 6.3 Clinical Trials Experience: External Genital Warts In controlled clinical trials for genital warts, the most frequently reported adverse reactions were local skin and application site reactions. Some subjects also reported systemic reactions. Overall, 1.2% (4/327) of the subjects 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.

Table 8: Local Skin Reactions in the Treatment Area as Assessed by the Investigator (External Genital Warts)

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

*Mild, Moderate, or Severe

Remote site skin reactions were also reported. 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%). Selected adverse reactions judged to be probably or possibly related to Aldara Cream are listed below

Table 9: Selected Treatment Related Reactions (External Genital Warts)

Idara Cream n=117	Vehicle n=103	Aldara Cream n=156	Vehicle n=158
00 (000)			
38 (32%)	21 (20%)	34 (22%)	16 (10%)
30 (26%)	12 (12%)	14 (9%)	8 (5%)
9 (8%)	2 (2%)	3 (2%)	1 (1%)
3 (3%)	0 (0%)	0 (0%)	1 (1%)
13 (11%)	3 (3%)	3 (2%)	1 (1%)
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5 (4%)	3 (3%)	8 (5%)	3 (2%)
4 (3%)	2 (2%)		0 (0%)
1 (1%)	0 (0%)	2 (1%)	1 (1%)
	30 (26%) 9 (8%) 3 (3%) 13 (11%) 5 (4%) 4 (3%) 1 (1%)	30 (26%) 12 (12%) 9 (8%) 2 (2%) 3 (3%) 0 (0%) 13 (11%) 3 (3%) 5 (4%) 3 (3%) 4 (3%) 2 (2%)	30 (26%) 12 (12%) 14 (9%) 9 (8%) 2 (2%) 3 (2%) 3 (3%) 0 (0%) 0 (0%) 13 (11%) 3 (3%) 3 (2%) 5 (4%) 3 (3%) 8 (5%) 4 (3%) 2 (2%) 2 (1%) 1 (1%) 0 (0%) 2 (1%)

^{*}Incidences reported without regard to causality with Aldara Cream

Adverse reactions judged to be possibly or probably related to Aldara Cream and reported by more than 1% of subjects included: Application Site Disorders: 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, 6.4 Clinical Trials Experience: Dermal Safety Studies Provocative repeat insult patch test 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 photoallergenicity or contact sensitization in healthy skin; however, cumulative irritancy testing revealed the potential for Aldara Cream to cause irritation, and application site reactions were reported in the clinical studies [see Adverse Reactions (6)]. 6.5 Postmarketing Experience 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 (including idiopathic thrombocytopenic purpura), lymphoma Hepatic: abnormal liver function Neuropsychiatric: agitation, cerebrovascular accident, convulsions (including febrile convulsions), depression, insomnia, multiple sclerosis aggravation, paresis, convulsions (including febrile convulsions), depression, insomnia, multiple sclerosis aggravation, paresis, suicide. Respiratory: dyspnea. Urinary System Disorders: proteinuria. Skin and Appendages: exfoliative dermatitis, erythema multiforme, hyperpigmentation. Vascular: Henoch-Schonlein purpura syndrome

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Pregnancy Category C: 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 co exposure with increased dose of Aldara Cream was noted in the clinical pharmacokinetic study conducted in actinic keratosis subjects [see Clinical Pharmacology (12.3)]. 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 a daily dose comparisons for the proproductive topical power studies described in this label. Systemic were based on daily dose comparisons for the reproductive toxicology studies described in this label. 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 (MOTX 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 embryofetal development studies were conducted in rats and rabbits. Oral doses of 1, 5 and 20 mg/kg/day

F1 fetuses at a dose of 6 mg/kg/day (87X MRHD based on AUC comparisons). This fetal effect was also F1 fetuses at a dose of 6 mg/kg/day (87K MRHD based on AUC comparisons). This fetal effect was also noted in the oral ratembryofetal 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. 8.3 Nursing Mothers It is not known whether imiquimod is excreted in human milk following use of Aldara Cream. Because many drugs are exreted in human milk, caution should be exercised when Aldara Cream is administered to nursing women. 8.4 Pediatric Use AK and sBCC are not conditions generally seen within the pediatric population. The safety and efficacy of Aldara Cream for AK or sBCC in patients less than 18 years of age have not been established. Safety and efficacy in patients with external genital/perianal warts below the age of 12 years have not been established. Aldara Cream was evaluated in two randomized, vehicle-controlled, double-blind trials involving 702 pediatric subjects with molluscum contagiosum (MC) (470 exposed to Aldara; median age 5 years, range 2-12 years). Subjects applied Aldara Cream or vehicle 3 times weekly for up to 16 weeks. Complete clearance (no MC) Subjects applied Aldara Cream or vehicle 3 times weekly for up to 16 weeks. Complete clearance (no MC lesions) was assessed at Week 18. In Study 1, the complete clearance rate was 24% (52/217) in the Aldara Cream group compared with 26% (28/106) in the vehicle group. In Study 2, the clearance rates were 24% (60/253) in the Aldara Cream group compared with 28% (35/126) in the vehicle group. These studies failed to demonstrate efficacy. Similar to the studies conducted in adults, the most frequently reported adverse reaction from 2 studies in children with molluscum contagiosum was application site reaction. Adverse events which occurred more frequently in Aldara-treated subjects compared with vehicle-treated subjects generally resembled those seen in studies in indications approved for adults and also included otitis media (5% Aldara vs. 3% vehicle) and conjunctivitis (3% Aldara vs. 2% vehicle). Erythema was the most frequently reported local skin reaction. Severe local skin reactions reported by Aldara-treated subjects in the pediatric studies included erythema (28%), edema (8%), scabbing/crusting (5%), flaking/scaling (5%), erosion (2%) and weeping/exudate (2%). Systemic absorption of imiquimod across the affected skin of 22 subjects aged 2 to 12 years with extensive MC involving at least 10% of the total body surface area was observed after single and multiple doses at a dosing frequency of 3 applications per week for 4 weeks. The investigator determined Subjects applied Aldara Cream or vehicle 3 times weekly for up to 16 weeks. Complete clearance (no MC and multiple doses at a dosing frequency of 3 applications per week for 4 weeks. The investigator determined the dose applied, either 1, 2 or 3 packets per dose, based on the size of the treatment area and the subjects weight. The overall median peak serum drug concentrations at the end of week 4 was between 0.26 and 1.06 ng/mL except in a 2-year old female who was administered 2 packets of study drug per dose, had a C_{max} of 9.66 ng/mL after multiple dosing. Children aged 2-5 years received doses of 12.5 mg (one packet) or 25 mg (two packets) of imiquimod and had median multiple-dose peak serum drug levels of approximately 0.2 or 0.5 ng/mL, respectively. Children aged 6-12 years received doses of 12.5 mg, 25 mg, or 37.5 mg (three packets) and had median multiple dose serum drug levels of approximately 0.1, 0.15, or 0.3 ng/mL, respectively. Among the 20 subjects with evaluable laboratory assessments, the median WBC count decreased by 1.4*10°/L and the median absolute neutrophil count decreased by 1.4*2*10°/L 8.5 Geriatric Use Of the 215 subjects treated with Aldara Cream in the AK clinical studies, 127 subjects (59%) were 65 years and older, while 60 subjects treated with Aldara Cream in the SBCC and multiple doses at a dosing frequency of 3 applications per week for 4 weeks. The investigator determined while 60 subjects (28%) were 75 years and older. Of the 185 subjects treated with Aldara Cream in the sBCC clinical studies, 65 subjects (35%) were 65 years and older, while 25 subjects (14%) were 75 years and older, No overall differences in safety or effectiveness were observed between these subjects and younger subjects. No other clinical experience has identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

highest dose evaluated in this study. In the absence of maternal toxicity, bent limb bones were noted in the

10 OVERDOSAGE

Topical overdosing of Aldara Cream could result in an increased incidence of severe local skin reactions and inspirate overtosing or Natia a forest count reaction as 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis. Mutagenesis. Impairment of Fertility In an oral (gavage) rat carcinogenicity study. 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility 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 dreat male mice. 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 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 photoco-carcinogenicity 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 additions defect 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. to 87X MRHD based on ALIC comparisons



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