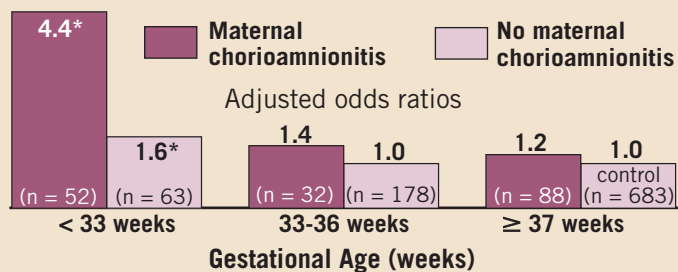


Risk of Asthma Higher in Infants Whose Mothers Had Chorioamnionitis



*Statistically significant.

Notes: Based on an average 2.2-year follow-up. Adjusted for factors including infants' age, breast-feeding, and postnatal passive smoking. Source: Dr. Kumar

Asthma in Premies May Be Linked To Chorioamnionitis in Mothers

BY MITCHEL L. ZOLER
Philadelphia Bureau

PHILADELPHIA — Children born prematurely to mothers who developed chorioamnionitis during pregnancy were about fourfold more likely to develop asthma and wheezing during the first 2 years of life, compared with term infants born to mothers without chorioamnionitis, based on data collected on nearly 1,100 children.

The finding needs to be extended by following the children to an older age and by studying other populations. If the findings are confirmed in such studies, earlier treatment and resolution of chorioamnionitis may have important implications for the future respiratory health of affected children, Dr. Rakesh Kumar said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology. "A lot of the chorioamnionitis was subclinical. We don't know if treatment will prevent the effect of

ALDARA®

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Graceway Pharmaceuticals, LLC at 1-800-328-0255 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

1 INDICATIONS AND USAGE

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 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 efficacy of Aldara Cream have not been established for other types of basal cell carcinomas, including nodular and morpheiform (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. [See 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.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

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 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 photocarcinogenicity 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, 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 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 morpheiform (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.

6 ADVERSE REACTIONS

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%)

Local skin reactions were collected independently of the adverse reaction "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.

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

Included Term	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-week post-treatment scarring assessments, 6 (2.9%) had a greater degree of scarring scores at 8-weeks post-treatment than at baseline. **6.2 Clinical Trials Experience: Superficial Basal Cell 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	Aldara Cream (n=185)	Vehicle (n=179)
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%)

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 application site reactions reported by >1% of the subjects during the 6-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)	Vehicle (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 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.

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

Included Term	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

chorioamnionitis on recurrent wheezing, but this would be an area for future study," he said in an interview.

"What was surprising was the degree of association that chorioamnionitis had with wheezing and asthma," whereas no link was seen between prematurity, chorioamnionitis, and food allergy or eczema, said Dr. Kumar, a pediatric allergy and asthma specialist at Children's Memorial Hospital and Northwestern University in Chicago. Atopy does not appear to play a role.

An alternative, physiological explanation is that chorioamnionitis produces a strong, proinflammatory response that boosts levels of various cytokines, such as

tumor necrosis factor- α , and interleukin-6 and -8. Cytokines like these may trigger premature birth, and may also lead to chronic respiratory disease in the fetus.

Results from some prior studies had shown a link between prematurity and an increased risk for asthma, but this link was not confirmed in all studies. Prior studies did not consider the underlying pathogenesis that led to premature birth, which may account for the inconsistency, Dr. Kumar said.

His analysis was based on data from children in the Boston Birth Cohort, an ongoing study at Boston Medical Center that began in 1998. Included were 771 term and 325 preterm infants who com-

pleted at least one postnatal examination. These numbers make the analysis one of the few prospective studies large enough to allow stratification of the infants in groups according to the severity of prematurity and the presence of chorioamnionitis, he noted. The average age of the children at their last follow-up visit was 2.2 years.

The analysis adjusted for several infant and maternal variables, including breastfeeding, postnatal passive smoking, maternal smoking during pregnancy, and maternal educational status. Infants born at less than 33 weeks' gestation to mothers who had chorioamnionitis were 4.0-fold more likely to wheeze and 4.4-fold more likely to

have asthma, compared with infants born at 37 weeks or beyond to mothers without chorioamnionitis. (See graph.) Both differences were highly statistically significant. In contrast, infants born before 33 weeks to mothers without chorioamnionitis were 2.7-fold more likely to wheeze (a significant difference), but were no more likely to have asthma than were term infants.

"One of the major issues in our study was that our primary outcome was recurrent wheezing of early childhood. We also evaluated physician-diagnosed asthma, but this is a bit less clear of a diagnosis at a young age. We will continue to follow these children [until] they are 6 years of age to see if the effects of chorioamnionitis on physician-diagnosed asthma will truly equate to persistent asthma by the time the children are older," Dr. Kumar said.

The associations were even stronger in infants born to African American mothers, about 62% of the study cohort. In this subgroup, infants born at less than 33 weeks to mothers with chorioamnionitis were 5.4-fold more likely to have wheezing and 5.2-fold more likely to have asthma than infants born at term to black mothers without chorioamnionitis. Both differences were highly significant. Again, infants born at less than 33 weeks to mothers without chorioamnionitis were 3.8-fold more likely to wheeze, but did not have a significantly increased risk for developing asthma. ■

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. 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)

	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	38 (32%)	21 (20%)	34 (22%)	16 (10%)
Burning	30 (26%)	12 (12%)	14 (9%)	8 (5%)
Pain	9 (8%)	2 (2%)	3 (2%)	1 (1%)
Soreness	3 (3%)	0 (0%)	0 (0%)	1 (1%)
Fungal Infection*	13 (11%)	3 (3%)	3 (2%)	1 (1%)
Systemic Reactions:				
Headache	5 (4%)	3 (3%)	8 (5%)	3 (2%)
Influenza-like symptoms	4 (3%)	2 (2%)	2 (1%)	0 (0%)
Myalgia	1 (1%)	0 (0%)	2 (1%)	1 (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 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, suicide. **Respiratory:** dyspnea. **Urinary System Disorders:** proteinuria. **Skin and Appendages:** exfoliative dermatitis, erythema multiforme, hyperpigmentation. **Vascular:** Henoch-Schönlein 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 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 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 (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. **8.3 Nursing Mothers** It is not known whether imiquimod is excreted in human milk following use of Aldara Cream. Because many drugs are excreted 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 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 the dose applied, either 1, 2 or 3 packets per dose, based on the size of the treatment area and the subject's 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*10⁹/L and the median absolute neutrophil count decreased by 1.42*10⁹/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 (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.

10 OVERDOSAGE

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.

13 NONCLINICAL TOXICOLOGY

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 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 phototoxicity 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.

Rx Only

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Breast-Feeding May Protect vs. Type 2 Diabetes

Breast-fed babies may be protected against developing type 2 diabetes during childhood, regardless of ethnicity, according to results from an adjunct study to the ongoing SEARCH for Diabetes in Youth study.

The dramatic increase in type 2 diabetes in youth has inspired researchers to identify behaviors that might prevent both obesity and type 2 diabetes, wrote Elizabeth J. Mayer-Davis, Ph.D., of the University of South Carolina, Columbia, and her colleagues.

Their case-control study, conducted at two of the SEARCH for Diabetes in Youth study sites, included 80 participants aged 10-21 years with type 2 diabetes and 167 age-matched controls (Diabetes Care 2008; 31:470-5).

Overall, the prevalence of breast-feeding for any length of time was significantly lower among youth with type 2 diabetes, compared with controls (31% vs. 64%).

When the study population was divided into three ethnic groups, the prevalence of breast-feeding was lower among black youth with type 2 diabetes than among controls (20% vs. 27%), although this difference was not statistically significant. But the difference remained significant among Hispanics (50% vs. 84%), and among non-Hispanic whites (39% vs. 78%).

The researchers noted previous evidence that a lower prevalence of breast-feeding among blacks, compared with other ethnicities, might be a confounding variable.

—Heidi Splette