

# Complication Rate 41% in ART Pregnancy Study

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WASHINGTON — Complications including gestational diabetes, placenta previa, and hypertension occurred in 41% of assisted reproductive technology pregnancies, based on data from 293 pregnancies.

"Increased fetal and maternal surveillance is warranted in these pregnancies," wrote Dr. Elena China and colleagues from the Centro de Asistencia a la Repro-

ducción Humana de Canarias S.L., Santa Cruz de Tenerife, Spain, in a poster presented at the annual meeting of the American Society for Reproductive Medicine.

To determine the nature and incidence of adverse events for assisted reproductive technology (ART) pregnancies, as well as the effect of increasing maternal age, the researchers analyzed the rates of preexisting maternal conditions, pregnancy complications, labor and delivery complications, and perinatal outcomes in pregnancies

from 1,056 cycles of in vitro fertilization with intracytoplasmic sperm injection.

Preexisting maternal conditions were noted in 15% of the women, and the incidence increased consistently from 10% in women under 31 years to 28% in women over 40 years. Gestational diabetes occurred in 18% overall (16% of singleton and 25% of twin pregnancies). But no age-related increases in rates of gestational diabetes or pregnancy-induced hypertension were seen.

As for labor and delivery complications,

the overall incidence of premature labor was 13%, and the rate for twin pregnancies was double the rate for singleton pregnancies (20% vs. 10%). The average overall cesarean section rate was 49%, with an average of 40% in singleton pregnancies and an average of 77% for twin pregnancies.

Low birth weights occurred in 30% of the infants overall (11% of singletons, 51% of twins). Very low birth weights occurred in 4.5% of the infants overall (2% of singletons and 7% of twins). ■

## 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](http://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 cm<sup>2</sup> (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 cm<sup>2</sup> 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-week 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