



BY ALAN ROCKOFF, M.D.

## UNDER MY SKIN

# All in the Family

“But nobody in my family has it!”

That’s a common reaction patients have when told their condition is hereditary.

Saying a disease is genetic gives the pa-

tient more than just a point of information. Heredity is one of the “Big Seven,” the ways people explain illness to themselves and make its appearance feel more plausible and less like a bolt from the blue: heredity, diet, environment (“the air,” “the water”), allergy, infection, cancer, and aging (which explains almost anything—“When you get old, everything happens”). Calling something hereditary helps it make sense, which is useful.

What people mean by hereditary (they call it “taking after”) is not the same as what we mean by genetics, although the two concepts overlap somewhat. Patients think of genetics in a global sense: If you look like someone, have the same skin type, or otherwise resemble a forebear somehow, then you’re considered likely to get what they had and unlikely to get what they didn’t. People are always saying things like, “I inherited my Dad’s fair skin, but my sister is

dark like my mother.” Genetics is a bit more complex than that, of course. Besides, the alleged resemblance is supposed to explain not just being prone to skin cancer—which sounds semireasonable—but being vulnerable to lots of other diseases that have nothing to do with UV tolerance.

People also tend to think that if someone they take after had a problem to a certain extent, then they too will suffer the same way. Psoriasis does indeed have a genetic component, but onset, duration, and severity hardly follow set familial patterns.

To further complicate matters, family mythology about what so-and-so had and how bad it was may be imprecise, to say the least. Think of statements like, “My aunt had a dozen melanomas.”

In addition, people assign genetics to specific things in a way we physicians never would. Many insist that their mother/sister/aunt had “the same mole” as the one we’re examining or planning to biopsy. What does the same mole mean? That it occupied the same exact anatomical place? How would they know? And what difference would it make? Yet, to the patient this designation makes good sense, implying a commonality of medical fate, for good or ill, with their similarly moled relative.

So when a 40-year-old shows up with atopic dermatitis, she’s going to consider it mighty unlikely that it “just came” for no reason. (She “didn’t change anything,” “did not eat anything different,” and so forth.) Explaining that eczema is hereditary makes its arrival more reasonable to her, without the need to blame something she did or ate.

That is, if you can convince her when she claims “nobody in the family has it!” There are several reasons patients may not know any relatives with the condition:

► **Actually, nobody does have it.** Not every hereditary condition affects every family member.

► **They would have had it if they’d lived long enough.** Seborrheic keratoses, for instance.

► **They do have it but never told you.** Imagine a Thanksgiving dinner: “So how’s it going, Uncle Ebenezer?” “Pretty tolerable, Clem. But those pesky skin tags in my groin’ve been acting up again. Got ’em from Ma.”

► **They do have it, but nobody told them.** How many patients with atopic dermatitis go through life thinking or being told that they have “dry skin” or “allergies”?

Specifying genetics can have negative effects, too. Even modern folks may not be free of the guilt associated with “passing something on.” Rationally, no one should feel guilty for having a gene someone gave him or her. But guilt is not rational.

Perhaps some day the Human Genome Project will provide us with a more precise and detailed understanding of what gets passed on and how. Even then, however, it will still be true that you can pick your friends ...

You know the rest. ■

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### Rx Only

#### Brief summary.

Please see full prescribing information for complete product information.

#### Carac Cream 0.5%

(fluorouracil cream)

FOR TOPICAL DERMATOLOGICAL USE ONLY (NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE)

#### INDICATIONS AND USAGE

Carac is indicated for the topical treatment of multiple actinic or solar keratoses of the face and anterior scalp.

#### CONTRAINDICATIONS

Fluorouracil may cause fetal harm when administered to a pregnant woman. Fluorouracil is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

No adequate and well-controlled studies have been conducted in pregnant women with either topical or parenteral forms of fluorouracil. One birth defect (ventricular septal defect) and cases of miscarriage have been reported when fluorouracil was applied to mucous membrane areas. Multiple birth defects have been reported in the fetus of a patient treated with intravenous fluorouracil.

Animal reproduction studies have not been conducted with Carac. Fluorouracil, the active ingredient, has been shown to be teratogenic in mice, rats, and hamsters when administered parenterally at doses greater than or equal to 10, 15, and 33 mg/kg/day, respectively, [4X, 11X, and 20X, respectively, the Maximum Recommended Human Dose (MRHD) based on body surface area (BSA)]. Fluorouracil was administered during the period of organogenesis for each species. Embryolethal effects occurred in monkeys at parenteral doses greater than 40 mg/kg/day (65X the MRHD based on BSA) administered during the period of organogenesis.

Carac should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large percentage of fluorouracil is catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD). DPD enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to cytotoxic activity and potential toxicities.

Carac is contraindicated in patients with known hypersensitivity to any of its components.

#### WARNINGS

The potential for a delayed hypersensitivity reaction to fluorouracil exists. Patch testing to prove hypersensitivity may be inconclusive.

Patients should discontinue therapy with Carac if symptoms of DPD enzyme deficiency develop.

Rarely, unexpected, systemic toxicity (e.g. stomatitis, diarrhea, neutropenia, and neurotoxicity) associated with parenteral administration of fluorouracil has been attributed to deficiency of dihydropyrimidine dehydrogenase “DPD” activity. One case of life threatening systemic toxicity has been reported with the topical use of 5% fluorouracil in a patient with a complete absence of DPD enzyme activity. Symptoms included severe abdominal pain, bloody diarrhea, vomiting, fever, and chills. Physical examination revealed stomatitis, erythematous skin rash, neutropenia, thrombocytopenia, inflammation of the esophagus, stomach, and small bowel. Although this case was observed with 5% fluorouracil cream, it is unknown whether patients with profound DPD enzyme deficiency would develop systemic toxicity with lower concentrations of topically applied fluorouracil.

Applications to mucous membranes should be avoided due to the possibility of local inflammation and ulceration.

#### PRECAUTIONS

**General:** There is a possibility of increased absorption through ulcerated or inflamed skin.

**Information for the Patient:** Patients using Carac should receive the following information and instructions:

- This medication is to be used as directed.
- This medication should not be used for any disorder other than that for which it was prescribed.
- It is for external use only.
- Avoid contact with the eyes, eyelids, nostrils, and mouth.
- Cleanse affected area and wait 10 minutes before applying Carac.
- Wash hands immediately after applying Carac.
- Avoid prolonged exposure to sunlight or other forms of ultraviolet irradiation during treatment, as the intensity of the reaction may be increased.
- Most patients using Carac get skin reactions where the medicine is used. These reactions include redness, dryness, burning, pain, erosion (loss of the upper layer of skin), and swelling. Irritation at the application site may persist for two or more weeks after therapy is discontinued. Treated areas may be unsightly during and after therapy.
- If you develop abdominal pain, bloody diarrhea, vomiting, fever, or chills while on Carac therapy, stop the medication and contact your physician and/or pharmacist.
- Report any side effects to the physician and/or pharmacist.

**Laboratory Tests:** To rule out the presence of a frank neoplasm, a biopsy may be considered for those areas failing to respond to treatment or recurring after treatment.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Adequate long-term studies in animals to evaluate carcinogenic potential have not been conducted with fluorouracil. Studies with the active ingredient of Carac, fluorouracil, have shown positive effects in *in vitro* and *in vivo* tests for mutagenicity and on impairment of fertility in *in vivo* animal studies.

Fluorouracil produced morphological transformation of cells in *in vitro* cell transformation assays. Morphological transformation was also produced in an *in vitro* assay by a metabolite of fluorouracil, and the transformed cells produced malignant tumors when injected into immunosuppressed syngeneic mice. Fluorouracil has been shown to exert mutagenic activity in yeast cells, *Bacillus subtilis*, and *Drosophila* assays. In addition, fluorouracil has produced chromosome damage at concentrations of 1.0 and 2.0 mcg/mL in an *in vitro* hamster fibroblast assay, was positive in a microwell mouse lymphoma assay, and was positive in *in vivo* micronucleus assays in rats and mice following intraperitoneal administration. Some patients receiving cumulative doses of 0.24 to 1.0 g of fluorouracil parenterally have shown an increase in numerical and structural chromosome aberrations in peripheral blood lymphocytes.

Fluorouracil has been shown to impair fertility after parenteral administration in rats. Fluorouracil administered at intraperitoneal doses of 125 and 250 mg/kg has been shown to induce chromosomal aberrations and changes in chromosome organization of spermatogonia in rats. In mice, single-dose intravenous and intraperitoneal injections of fluorouracil have been reported to kill differentiated spermatogonia and spermatocytes at a dose of 500 mg/kg and produce abnormalities in spermatids at 50 mg/kg.

**Pediatric Use:** Actinic keratosis is not a condition seen within the pediatric population, except in association with rare genetic diseases. Carac should not be used in children. The safety and effectiveness of Carac have not been established in patients less than 18 years old.

**Geriatric Use:** No significant differences in safety and efficacy measures were demonstrated in patients age 65 and older compared to all other patients.

**Pregnancy: Teratogenic Effects: Pregnancy Category X:** See CONTRAINDICATIONS.

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**Nursing Women:** It is not known whether fluorouracil is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from fluorouracil, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

#### ADVERSE REACTIONS

The following were adverse events considered to be drug-related and occurring with a frequency of  $\geq 1\%$  with Carac: application site reaction (94.6%) and eye irritation (5.4%). The signs and symptoms of facial irritation (application site reaction) are presented below.

#### Summary of Facial Irritation Signs and Symptoms - Pooled Phase 3 Studies

Clinical Sign or Symptom	Active One Week	Active Two Week	Active Four Week	ALL Active Treatments	Vehicle Treatments
	n (%) N=85	n (%) N=87	n (%) N=85	n (%) N=257	n (%) N=127
Erythema	76 (89.4)	82 (94.3)	82 (96.5)	240 (93.4)	76 (59.8)
Dryness	59 (69.4)	76 (87.4)	79 (92.9)	214 (83.3)	60 (47.2)
Burning	51 (60.0)	70 (80.5)	71 (83.5)	192 (74.7)	28 (22.0)
Erosion	21 (24.7)	38 (43.7)	54 (63.5)	113 (44.0)	17 (13.4)
Pain	26 (30.6)	34 (39.1)	52 (61.2)	112 (43.6)	7 (5.5)
Edema	12 (14.1)	28 (32.2)	51 (60.0)	91 (35.4)	6 (4.7)

During clinical trials, irritation generally began on day 4 and persisted for the remainder of treatment. Severity of facial irritation at the last treatment visit was slightly below baseline for the vehicle group, mild to moderate for the 1 week active treatment group, and moderate for the 2 and 4 week active treatment groups. Mean severity declined rapidly for each active group after completion of treatment and was below baseline for each group at the week 2 post-treatment follow-up visit.

Thirty-one patients (12% of those treated with Carac in the Phase 3 clinical studies) discontinued study treatment early due to facial irritation. Except for three patients, discontinuation of treatment occurred on or after day 11 of treatment.

Eye irritation adverse events, described as mild to moderate in intensity, were characterized as burning, watering, sensitivity, stinging and itching. These adverse events occurred across all treatment arms in one of the two Phase 3 studies.

#### Summary of All Adverse Events Reported in $\geq 1\%$ of Patients in the Combined Active Treatment and Vehicle Groups - Pooled Phase 3 Studies

Adverse Event	9721 and 9722 Combined				
	Active One Week	Active Two Week	Active Four Week	ALL Active Treatments	Vehicle Treatments
	n (%) N=85	n (%) N=87	n (%) N=85	n (%) N=257	n (%) N=127
<b>Body as a whole</b>					
Headache	7 (8.2)	6 (6.9)	12 (14.1)	25 (9.7)	15 (11.8)
Common Cold	3 (3.5)	2 (2.3)	3 (3.5)	8 (3.1)	3 (2.4)
Allergy	4 (4.7)	0	2 (2.4)	6 (2.3)	3 (2.4)
Infection Upper Respiratory	0	2 (2.3)	1 (1.2)	3 (1.2)	2 (1.6)
Musculoskeletal					
Muscle Soreness	1 (1.2)	1 (1.1)	1 (1.2)	3 (1.2)	5 (3.9)
Respiratory Sinusitis	0	0	0	0	2 (1.6)
Skin & Appendages					
Application Site Reaction	5 (5.9)	0	1 (1.2)	6 (2.3)	6 (4.7)
Irritation Skin	4 (4.7)	0	0	4 (1.6)	2 (1.6)
Special Senses					
Eye Irritation	6 (7.1)	4 (4.6)	6 (7.1)	16 (6.2)	6 (4.7)
	5 (5.9)	3 (3.4)	6 (7.1)	14 (5.4)	3 (2.4)

#### Adverse Experiences Reported by Body System:

In the Phase 3 studies, no serious adverse event was considered related to study drug. A total of five patients, three in the active treatment groups and two in the vehicle group, experienced at least one serious adverse event. Three patients died as a result of adverse event(s) considered unrelated to study drug (stomach cancer, myocardial infarction, and cardiac failure).

Post-treatment clinical laboratory tests other than pregnancy tests were not performed during the Phase 3 clinical studies. Clinical laboratory tests were performed during conduct of a Phase 2 study of 104 patients and 21 patients in a Phase 1 study. No abnormal serum chemistry, hematology, or urinalysis results in these studies were considered clinically significant.

#### DOSAGE AND ADMINISTRATION

Carac cream should be applied once a day to the skin where actinic keratosis lesions appear, using enough to cover the entire area with a thin film. Carac cream should not be applied near the eyes, nostrils, or mouth. Carac cream should be applied ten minutes after thoroughly washing, rinsing, and drying the entire area. Carac cream may be applied using the fingertips. Immediately after application, the hands should be thoroughly washed. Carac should be applied up to 4 weeks as tolerated. Continued treatment up to 4 weeks results in greater lesion reduction. Local irritation is not markedly increased by extending treatment from 2 to 4 weeks, and is generally resolved within 2 weeks of cessation of treatment.

#### OVERDOSE

Ordinarily, topical overdosage will not cause acute problems. If Carac is accidentally ingested, induce emesis and gastric lavage. Administer symptomatic and supportive care as needed. If contact is made with the eye, flush with copious amounts of water.

#### HOW SUPPLIED

Cream - 30 gram tube NDC 0066-7150-30  
Store at Controlled Room Temperature 20 to 25°C (68 to 77°F) [see USP].

Prescribing Information as of December 2003(a).

#### Keep out of the reach of children.

#### Rx Only

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Dermik Laboratories, Inc.  
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Manufactured by:  
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