



**TRANSMITTED BY FACSIMILE**

Anil K. Hiteshi, R.A.C.  
Senior Manager, Corporate Regulatory Affairs  
ICN Pharmaceuticals, Inc.  
3300 Hyland Avenue  
Costa Mesa, CA 92626

**RE: NDA 16-831**  
Efudex<sup>®</sup> (fluorouracil) topical solutions and cream  
MACMIS # 10467

Dear Mr. Hiteshi:

This letter objects to ICN Pharmaceuticals, Inc. (ICN) dissemination of violative promotional materials for Efudex<sup>®</sup> (fluorouracil) topical solutions and cream. As part of its routine monitoring program, the Division of Drug Marketing, Advertising and Communications (DDMAC) has become aware of a promotional journal advertisement for Efudex that is false or misleading, in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. The journal advertisement (E-688), submitted under cover of FDA Form 2253, appeared in the October 2001 issue of the Journal of the American Academy of Dermatology and is violative for the reasons described below.

**Lack of Fair Balance**

The journal advertisement lacks fair balance because it fails to disclose serious risk information included in the approved product labeling (PI) for Efudex. For example, the PI for Efudex contains a bolded contraindication that states, "**Efudex is contraindicated in women who are or may become pregnant during therapy. If this drug is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.**" Similarly, the PI for Efudex contains a bolded warning that states, "**Application to mucous membranes should be avoided due to the possibility of local inflammation and ulceration. Additionally, cases of miscarriage and a birth defect (ventricular septal defect) have been reported when Efudex was applied to mucous membrane areas during pregnancy.**" The journal advertisement lacks fair balance because it fails to disclose these serious risks associated with Efudex treatment.

All advertisements for any prescription drug shall present a true statement of information in brief summary relating to side effects, contraindications, and effectiveness. The information relating to side effects and contraindications shall disclose each specific side effect and contraindication (this includes side effects, warnings, and contraindications and includes any such information under such headings as cautions, special considerations, important notes, etc.). However, the brief summary referenced in the journal ad and appearing on the previous page fails to disclose information relating to each specific side effect and contraindication in the labeling associated with the use of Efudex. For example, the

brief summary fails to include the bolded warning, “**Application to mucous membranes should be avoided due to the possibility of local inflammation and ulceration. Additionally, cases of miscarriage and a birth defect (ventricular septal defect) have been reported when Efudex was applied to mucous membrane areas during pregnancy.**” In addition, the journal ad is misleading because the brief summary minimizes the fact that Efudex is contraindicated during pregnancy because treatment with Efudex has been associated with birth defects and miscarriages. Specifically, the brief summary states, “Safe use in pregnancy is not established” under a “Warning” header.

### **Promotion of Unapproved Use**

The journal advertisement is misleading because it contains claims such as, “EFUDEX treats evolving malignancies that masquerade as actinic keratoses” and “What you don’t see is what EFUDEX also gets.” These claims are misleading because they imply that Efudex is indicated to prevent and treat undetected malignant lesions, when such is not the case. Specifically, the “Indications and Usage” section of the Efudex PI states the following:

“Efudex is recommended for the topical treatment of multiple actinic or solar keratoses. In the 5% strength it is also useful in the treatment of superficial basal cell carcinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites. Safety and efficacy in other indications have not been established.

The diagnosis should be established prior to treatment, since this method has not been proven effective in other types of basal cell carcinomas. With isolated, easily accessible basal cell carcinomas, surgery is preferred since success with such lesions is almost 100%. The success rate with Efudex Cream and Solution is approximately 93%, based on 113 lesions in 54 patients. Twenty-five lesions treated with the solution produced 1 failure and 88 lesions treated with the cream produced 7 failures.”

Although Efudex is indicated to treat superficial basal cell carcinoma when specific conditions are met (as described above), the general term “malignancies” is insufficient to convey the specific limitations of the indication.

### **Unsubstantiated Claims**

The claim, “EFUDEX provides an extra margin of safety when treating areas with multiple actinic keratoses...” is misleading because it implies that Efudex is safer than other available treatment options for AK, when such has not been demonstrated by substantial evidence. In addition, the claim “Effectively eliminates worry” is misleading because it implies an outcome of Efudex treatment that has not been demonstrated by substantial evidence.

### **Requested Action**

ICN should immediately discontinue this and all other promotional materials and activities for Efudex that contain the same or similar claims or presentations. We request that ICN respond, in writing, with its intent to comply with the above. This response should list similarly violative materials with a description of the method for discontinuation and the discontinuation date. DDMAC should receive your written response no later than January 3, 2001.

If you have any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Room 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID# 10467 in addition to the NDA number.

Sincerely,

*{See appended electronic signature page}*

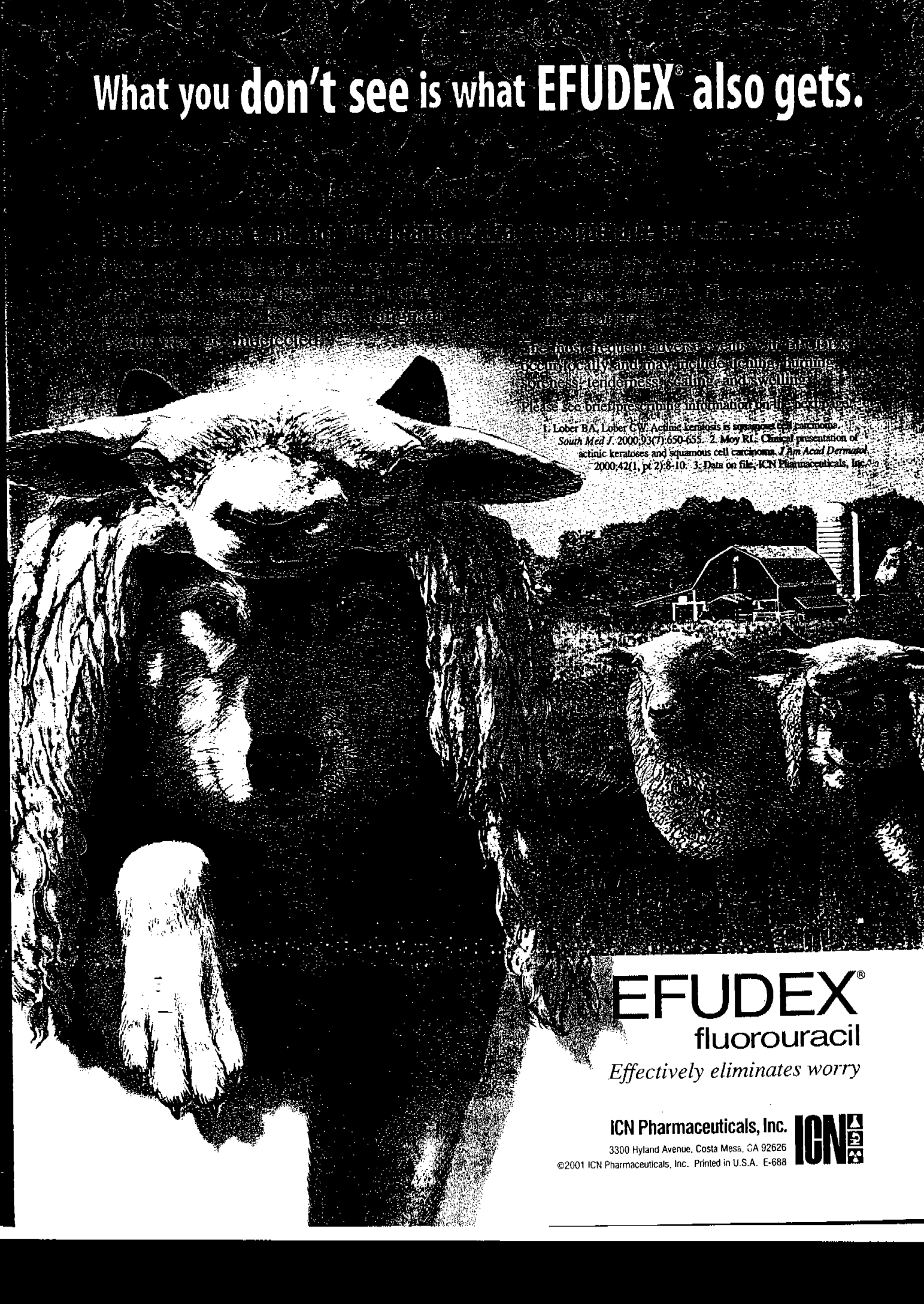
Rebecca Williams, Pharm.D.  
Regulatory Review Officer  
Division of Drug Marketing,  
Advertising, and Communications

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Rebecca Williams  
12/18/01 01:00:52 PM

What you don't see is what EFUDEX<sup>®</sup> also gets.



...the most frequent adverse events with EFUDEX<sup>®</sup> are erythema, pruritus, and may include itching, burning, stinging, tenderness, scaling, and swelling. Please see brief prescribing information on the next page.

1. Lober BA, Lober CW. Actinic keratosis is squamous cell carcinoma. *South Med J.* 2000;93(7):650-655. 2. Moy RL. Clinical presentation of actinic keratosis and squamous cell carcinoma. *J Am Acad Dermatol.* 2000;42(1, pt 2):8-10. 3. Data on file; ICN Pharmaceuticals, Inc.

**EFUDEX<sup>®</sup>**  
fluorouracil  
*Effectively eliminates worry*

**ICN Pharmaceuticals, Inc.**

3300 Hyland Avenue, Costa Mesa, CA 92626

©2001 ICN Pharmaceuticals, Inc. Printed in U.S.A. E-688



# ADVANTAGE

American Academy of Dermatology

~~\$\$\$~~  
**Save**  
Time and Money

with AAD Advantage, the new  
Member Buying Program developed  
specifically for dermatologists.

Dermatology Services, Inc., the Academy's  
for profit subsidiary, has partnered with Henry Schein  
Inc. to create the *AAD Advantage Program*, a  
medical, surgical and pharmaceutical member buying  
program.

The *AAD Member Buying Program* will allow you  
to...

- **Save \$\$\$\$**
- **Increase office efficiency**
- **Consolidate buying**

*Sign up today*

and start saving with this new member benefit!

There are no order commitments or membership  
fees. Call for a formulary and compare. You'll soon  
see why this is going to be one of our most popular  
benefits yet!

dermatology services, inc.



**DSI**

a subsidiary of the  
american academy of dermatology

For your copy of the AAD formulary contact  
Henry Schein Inc. at (800) 772-4346 (program code SL)  
or visit our Web site at [www.aad.org](http://www.aad.org).

## EFUDEX<sup>®</sup> fluorouracil

### TOPICAL SOLUTIONS AND CREAM

For Topical Dermatological Use Only—  
Not for Ophthalmic Use

Before prescribing, please consult complete product  
information, a summary of which follows:

#### INDICATIONS

Multiple actinic or solar keratoses. In 5% strength, superficial  
basal cell carcinoma when conventional methods are  
impractical, such as with multiple lesions or difficult treatment  
sites. Establish diagnosis before treating, as this method has  
not been proven effective in other types of basal cell  
carcinomas. Conventional techniques preferred for isolated,  
easily accessible lesions, as success rate is nearly 100%.  
Success rate with Efudex is about 93%.

#### CONTRAINDICATIONS

Patients with known hypersensitivity to any of its components.

#### WARNINGS

If occlusive dressing is used, may increase inflammatory  
reactions in adjacent normal skin. Avoid prolonged exposure  
to ultraviolet rays. Safe use in pregnancy not established.

#### PRECAUTIONS

If applied with fingers, wash hands immediately. Apply with  
care near eyes, nose and mouth. Solar keratoses failing to  
respond should be biopsied. Warn patients that treated area  
may be unsightly during therapy and sometimes for several  
weeks after. Perform follow-up biopsies in superficial basal  
cell carcinoma.

#### ADVERSE REACTIONS

Local—pain, pruritus, hyperpigmentation and burning at  
application site most frequent; also allergic contact dermati-  
tis, scarring, soreness, tenderness, suppuration, scaling and  
swelling. Also reported—alopecia, insomnia, stomatitis,  
irritability, medicinal taste, photosensitivity, lacrimation,  
telangiectasia, urticaria, leukocytosis, thrombocytopenia, toxic  
granulation and eosinophilia.

#### DOSAGE AND ADMINISTRATION

When Efudex is applied, erythema occurs, then vesiculation,  
erosion, ulceration, necrosis, epithelialization. *Actinic or Solar  
Keratoses*—apply sufficient quantity to cover lesions, twice  
daily. Usual length of therapy is 2 to 4 weeks. *Superficial  
Basal Cell Carcinomas*—apply sufficient quantity (**only 5%  
strength recommended**) to cover lesions, twice daily.  
Continue treatment for at least 3 to 6 weeks, but possibly as  
long as 10 to 12.

#### HOW SUPPLIED

Solutions, 10-mL drop dispensers containing 2% or 5%  
fluorouracil on a weight/weight basis. Cream, 25-gm tubes  
containing 5% fluorouracil in a vanishing cream base.

REVISED: January 1998



ICN Pharmaceuticals, Inc.  
ICN Plaza  
3300 Hyland Avenue  
Costa Mesa, California 92626