DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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® (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® (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}

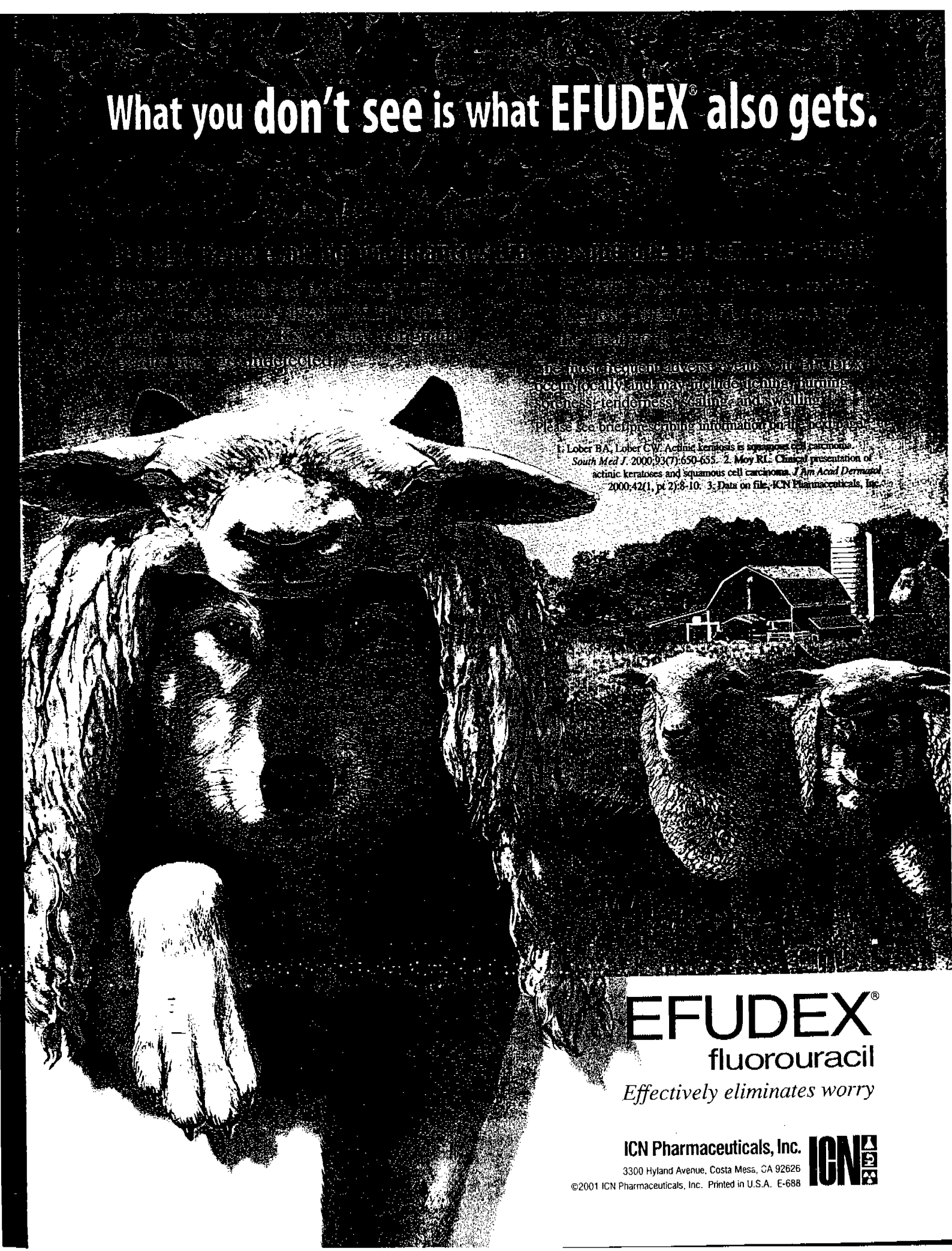
Rebecca Williams, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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® also gets.



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 keratoses and squamous cell carcinoma. *J Am Acad Dermatol*. 2000;42(1, pt 2):8-10. 3. Data on file, ICN Pharmaceuticals, Inc.

EFUDEX®
fluorouracil

Effectively eliminates worry

ICN Pharmaceuticals, Inc.
3300 Hyland Avenue, Costa Mesa, CA 92626