CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-985

FINAL PRINTED LABELING

NDA 20-985

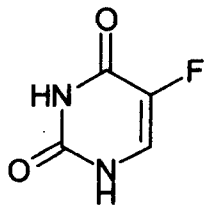
Rx Only

TRADENAME
(fluorouracil cream) **Cream, 0.5%**

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

DESCRIPTION

TRADENAME (fluorouracil cream) **Cream, 0.5%,** contains fluorouracil for topical dermatologic use. Chemically, fluorouracil is 5-fluoro-2,4(1H, 3H)-pyrimidinedione. The molecular formula is $C_4H_3FN_2O_2$. Fluorouracil has a molecular weight of 130.08.



TRADENAME Cream contains 0.5% fluorouracil, with 0.35% being incorporated into a patented porous microsphere (Microsponge®) composed of methyl methacrylate / glycol dimethacrylate crosspolymer and dimethicone. The cream formulation contains the following other inactive ingredients: carbomer 940, dimethicone, glycerin, methyl gluceth-20, methyl methacrylate / glycol dimethacrylate crosspolymer, methylparaben, octyl hydroxy stearate, polyethylene glycol 400, polysorbate 80, propylene glycol, propylparaben, purified water, sorbitan monooleate, stearic acid, and trolamine.

CLINICAL PHARMACOLOGY

There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid. In this manner, fluorouracil interferes with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibits the formation of ribonucleic acid (RNA). Since DNA and RNA are essential for cell division and growth, the effect of fluorouracil may be to create a thymine deficiency that provokes unbalanced growth and death of the cell. The effects of DNA and RNA deprivation are most marked on those cells that grow more rapidly and take up fluorouracil at a more rapid rate. The contribution to efficacy or safety of individual components of the vehicle has not been established.

Pharmacokinetics: A multiple-dose, randomized, open-label, parallel study was performed in 21 patients with actinic keratoses. Twenty patients had pharmacokinetic samples collected: 10 patients treated with **TRADENAME** and 10 treated with Efudex®‡‡ 5% Cream. Patients were treated for a maximum of 28 days with **TRADENAME**, 1 g once daily in the morning; or Efudex® 5% Cream, 1 g twice daily, in the morning and evening. Steady-state plasma

concentrations and the amounts of fluorouracil in urine resulting from the topical application of either product were measured.
Three patients who received **TRADENAME** and nine patients who received Efudex® 5% Cream had measurable plasma fluorouracil levels; however, only one patient receiving **TRADENAME** and six patients receiving Efudex® 5% Cream had a sufficient number of data points to calculate mean pharmacokinetic parameters.

Plasma Pharmacokinetic Summary

PK Parameter	TRADENAME n=1	Efudex (Mean ± SD) n=6
C_{max}	0.77 ng/mL	11.49 ± 8.24 ng/mL
T_{max}	1.00 hr	1.03 ± 0.028 hr
AUC (0-24)	2.80 ng hr/mL	22.39 ± 7.89 ng hr/mL

Five of 10 patients receiving **TRADENAME** and nine of 10 patients receiving Efudex® 5% Cream had measurable urine fluorouracil levels.

Urine Pharmacokinetic Summary

PK Parameter	TRADENAME (Mean ± SD) (Range) n=10	Efudex (Mean ± SD) (Range) n=10
Cum Ae†	2.74± 5.22 mcg	119.83± 94.80 mcg
(min-max)	(0-15.02)	(0-329.87)
Max excretion rate	0.19 ± 0.52 mcg/hr	40.27 ±47.14 mcg/hr
(min-max)	(0-1.67)	(0-164.5)

†Cumulative urinary excretion

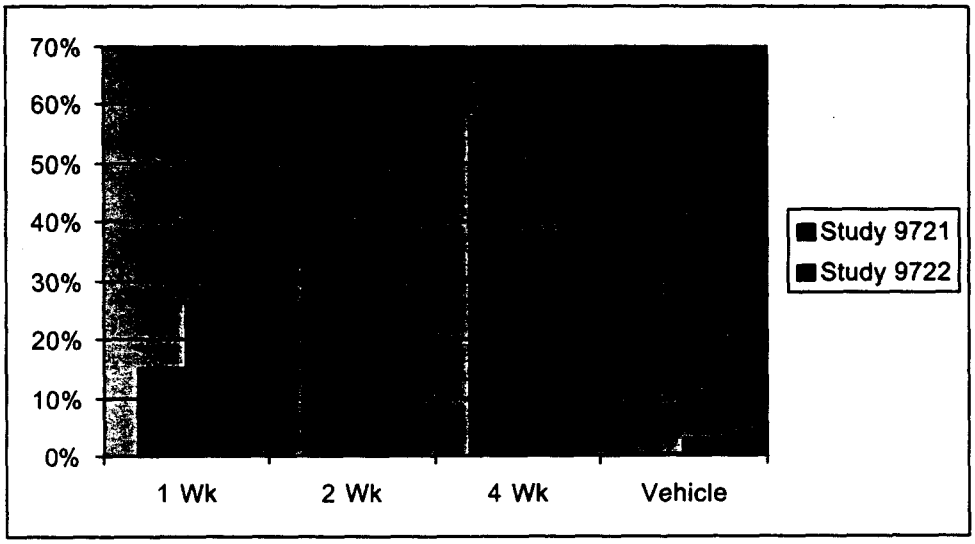
Both **TRADENAME** and Efudex® 5% Cream demonstrated low measurable plasma concentrations for fluorouracil when administered under steady-state conditions. Cumulative urinary excretion of fluorouracil was low for **TRADENAME** and for Efudex®, corresponding to 0.055% and 0.24% of the applied doses, respectively.

Clinical Trials:
Under the experimental conditions of the topical safety studies, **TRADENAME** was not observed to cause contact sensitization. However, approximately 95% of subjects in the active arms of the Phase 3 clinical studies experienced facial irritation. Irritation is likely and sensitization is unlikely based on the results of the topical safety and Phase 3 studies.

Two Phase 3 identically designed, multi-center, vehicle-controlled, double-blind studies were conducted to evaluate the clinical safety and efficacy of **TRADENAME**. Patients with 5 or more actinic keratoses (AKs) on the face or anterior bald scalp were randomly allocated to active or vehicle treatment in a 2:1 ratio. Patients were randomly allocated to treatment durations of 1, 2, or 4 weeks in a 1:1:1 ratio. They applied the study cream once daily to the entire face/anterior bald scalp. Each patient's clinical response was evaluated 4 weeks after the patient's last scheduled application of study cream. No additional post-treatment follow-up efficacy or safety

assessments were performed beyond 4 weeks after the last scheduled application. The following graphs show the percentage of patients in whom 100% of treated lesions cleared, and the percentage of patients in whom 75% or more of treated lesions cleared. Treatment with **TRADENAME** cream for 1, 2, or 4 weeks is compared to treatment with vehicle cream. Outcomes from 1, 2, and 4 weeks of treatment with vehicle cream are pooled because duration of treatment with vehicle had no substantive effect on clearance. Results from the two Phase 3 studies are shown separately. Although all treatment regimens of TRADENAME studied demonstrated efficacy over vehicle for treatment of actinic keratosis, continuing treatment up to 4 weeks as tolerated results in further lesion reduction and clearing.

Percentage of Subjects with 100% Clearance



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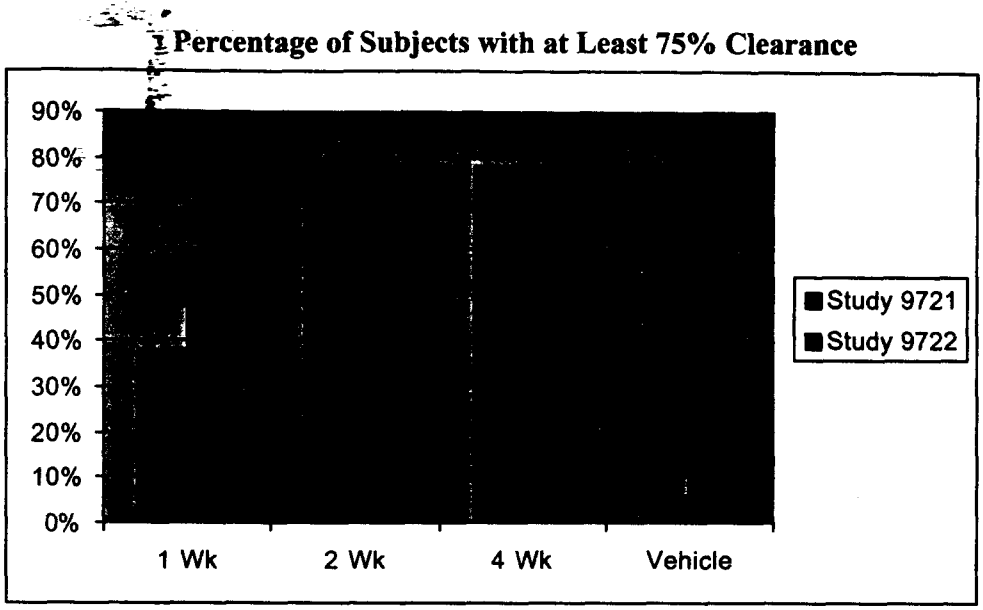

Clinical efficacy and safety in the treatment of AKs on the ears and other sun-exposed areas were not evaluated in the studies.

INDICATIONS AND USAGE

TRADENAME 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 **TRADENAME**. 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.

TRADENAME 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. Rarely, life-threatening toxicities such as stomatitis, diarrhea, neutropenia, and neurotoxicity have been reported with intravenous administration of fluorouracil in patients with DPD enzyme deficiency.

A case of life-threatening systemic toxicity has been reported with the topical use of fluorouracil 5% in a patient with DPD enzyme deficiency. 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% flourouracil cream, it is unknown whether patients with profound DPD enzyme deficiency would develop systemic toxicity with lower concentrations of topically applied fluorouracil.

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

WARNINGS

Patients should discontinue therapy with **TRADENAME** if symptoms of DPD enzyme deficiency develop. See **CONTRAINDICATIONS**.

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

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 **TRADENAME** should receive the following information and instructions:

1. This medication is to be used as directed.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. It is for external use only.
4. Avoid contact with the eyes, eyelids, nostrils, and mouth.
5. Cleanse affected area and wait 10 minutes before applying **TRADENAME**.
6. Wash hands immediately after applying **TRADENAME.**
7. Avoid prolonged exposure to sunlight or other forms of ultraviolet irradiation during treatment, as the intensity of the reaction may be increased.
8. Most patients using **TRADENAME** 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.

9. If you develop abdominal pain, bloody diarrhea, vomiting, fever, or chills while on **TRADENAME** therapy, stop the medication and contact your physician and/or pharmacist.
10. 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 **TRADENAME**, 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. **TRADENAME** should not be used in children. The safety and effectiveness of **TRADENAME** 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.**

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 ≥1% with **TRADENAME**: 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 N=85	Active Two Week N=87	Active Four Week N=85	ALL Active Treatments N=257	Vehicle Treatments N=127
	n (%)	n (%)	n (%)	n (%)	n (%)
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 **TRADENAME** 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 ≥ 1% of Patients in the Combined Active Treatment and Vehicle Groups – Pooled Phase 3 Studies

9721 and 9722 Combined										
Adverse Event	**Active One Week** N= 85		**Active Two Week** N= 87		**Active Four Week** N= 85		**ALL Active Treatments** N=257		**Vehicle Treatments** N=127	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
BODY AS A WHOLE	7	(8.2)	6	(6.9)	12	(14.1)	25	(9.7)	15	(11.8)
Headache	3	(3.5)	2	(2.3)	3	(3.5)	8	(3.1)	3	(2.4)
Common Cold	4	(4.7)	0		2	(2.4)	6	(2.3)	3	(2.4)
Allergy	0		2	(2.3)	1	(1.2)	3	(1.2)	2	(1.6)
Infection Upper Respiratory	0		0		0		0		2	(1.6)
MUSCULOSKELETAL	1	(1.2)	1	(1.1)	1	(1.2)	3	(1.2)	5	(3.9)
Muscle Soreness	0		0		0		0		2	(1.6)
RESPIRATORY	5	(5.9)	0		1	(1.2)	6	(2.3)	6	(4.7)
Sinusitis	4	(4.7)	0		0		4	(1.6)	2	(1.6)
SKIN & APPENDAGES	78	(91.8)	83	(95.4)	82	(96.5)	243	(94.6)	85	(66.9)
Application Site Reaction	78	(91.8)	83	(95.4)	82	(96.5)	243	(94.6)	83	(65.4)
Irritation Skin	1	(1.2)	0		2	(2.4)	3	(1.2)	0	
SPECIAL SENSES	6	(7.1)	4	(4.6)	6	(7.1)	16	(6.2)	6	(4.7)
Eye Irritation	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
TRADENAME 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. **TRADENAME** cream should not be applied near the eyes, nostrils or mouth. **TRADENAME** cream should be applied ten minutes after thoroughly washing, rinsing, and drying the entire area. TRADENAME cream may be applied using the fingertips. Immediately after application, the hands should be thoroughly

washed. **TRADENAME** 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 **TRADENAME** 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].

Keep out of the reach of children.

Manufactured for:
Dermik Laboratories, Inc.
Berwyn, PA 19312 USA
Manufactured by:
Pharmaceutical Manufacturing Research Services
Horsham, PA 19044 USA

PATIENT INFORMATION

TRADENAME Cream, 0.5%
(fluorouracil cream)

Read this leaflet carefully before you start to use your medicine. Read the information you get every time you get more medicine. There may be new information about the drug. This leaflet does not take the place of talks with your doctor. If you have any questions or are not sure about something, ask your doctor or pharmacist.

What is TRADENAME?
TRADENAME (TRAYD naym) is a cream used by adults to treat skin conditions on the face and front part of the scalp called solar keratosis or actinic keratosis.

Who should not use TRADENAME?
Do not use **TRADENAME**

- if you are pregnant or might become pregnant. **TRADENAME** may harm your unborn child.
- if you are nursing a baby. We do not know if **TRADENAME** can pass to the baby through the milk.

- if you have dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. If you have DPD enzyme deficiency and use **TRADENAME**, you may develop serious side effects such as stomach pain, bloody diarrhea, vomiting, fever, or chills.
- if you are allergic to the ingredients in **TRADENAME**. The active ingredient is fluorouracil. Ask your doctor or pharmacist about the inactive ingredients.
- if under 18 years of age. **TRADENAME** should not be used in children.

Tell your doctor if you are able to become pregnant. Your doctor may advise you about birth control to avoid pregnancy.

How should I use TRADENAME?
Use **TRADENAME** once a day as instructed by your doctor. Use it only on your skin. You should use **TRADENAME** for up to 4 weeks.

1. Clean the area where you will apply **TRADENAME**. Rinse well and dry the area with a towel and wait 10 minutes before applying **TRADENAME**.
2. Put **TRADENAME** on your face as directed by your physician, using your fingertips. Use enough to cover the affected skin.
3. Avoid contact with your eyes, nostrils, and mouth.
4. Wash your hands as soon as you finish putting the **TRADENAME** on your skin.
5. A moisturizer/sunscreen may be applied 2 hours after **TRADENAME** has been applied. Do not use any other skin products including creams, lotions, medications or cosmetics –unless instructed by your doctor.

What should I avoid while using TRADENAME?
Avoid sunlight or other ultraviolet light (such as tanning booths) as much as possible while using **TRADENAME**. Sunlight may increase your side effects. When exposed to sunlight, wear a hat and use sunscreen.

Do not cover the treated skin with a dressing.

Do not breast feed or become pregnant while using **TRADENAME**. If you do become pregnant, stop using **TRADENAME** and tell your doctor right away.

What are the possible side effects of TRADENAME?
Most patients using **TRADENAME** 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 may continue for two or more weeks after treatment is over. The treated area may become unsightly during therapy.

Some patients get eye irritation. Eye irritation might consist of burning, sensitivity, itching, stinging, and watering. If you are concerned about side effects, talk to your doctor.

Storage information
Keep this medicine at room temperature (68-77° F/ 20-25° C). Throw away unused medicine. Keep this medicine out of the reach of children.

General advice about prescription medicines

Medicines are sometimes prescribed for conditions that are not described in patient information leaflets. Do not use it for a condition for which it was not prescribed. This medicine is for your use only. Never give it to other people. It may harm them even if their skin problem appears to be the same as yours. Do not use **TRADENAME** after the expiration date on the tube.

Microsponge® is a registered trademark of Enhanced Derm Technology.
‡‡ Efudex® is a registered trademark of ICN Pharmaceuticals, Inc.

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