

# EFUDEX® (fluorouracil)

## TOPICAL SOLUTIONS AND CREAM

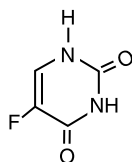
For Topical Dermatological Use Only  
Not for Ophthalmic Use or Application to Mucous  
Membranes, including Intravaginal Application

**DESCRIPTION:** Efdex Solutions and Cream are topical preparations containing the fluorinated pyrimidine 5-fluorouracil, an antineoplastic antimetabolite.

Efdex Solution consists of 2% or 5% fluorouracil on a weight/weight basis, compounded with propylene glycol, tris (hydroxymethyl) aminomethane, hydroxypropyl cellulose, parabens (methyl and propyl) and disodium edetate.

Efdex Cream contains 5% fluorouracil in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl).

Chemically, fluorouracil is 5-fluoro-2,4-(1*H*,3*H*)-pyrimidinone. It is a white to practically white, crystalline powder which is sparingly soluble in water and slightly soluble in alcohol. One gram of fluorouracil is soluble in 100 mL of propylene glycol. The molecular weight of 5-fluorouracil is 130.08 and the structural formula is:



**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 which provokes unbalanced growth and death of the cell. The effects of DNA and RNA deprivation are most marked on those cells which grow more rapidly and take up fluorouracil at a more rapid rate. The catabolic metabolism of fluorouracil results in degradation products (eg, CO<sub>2</sub>, urea, α-fluoro-β-alanine) which are inactive.

Systemic absorption studies of topically applied fluorouracil have been performed on patients with actinic keratoses using tracer amounts of <sup>14</sup>C-labeled fluorouracil added to a 5% preparation. All patients had been receiving unlabeled fluorouracil until the peak of the inflammatory reaction occurred (2 to 3 weeks), ensuring that the time of maximum absorption was used for measurement. One gram of labeled preparation was applied to the entire face and neck and left in place for 12 hours. Urine samples were collected. At the end of 3 days, the total recovery ranged between 0.48% and 0.94% with an average of 0.76%, indicating that approximately 5.98% of the topical dose was absorbed systemically. If applied twice daily, this would indicate systemic absorption of topical fluorouracil to be in the range of 5 to 6 mg per daily dose of 100 mg. In an additional study, negligible amounts of labeled material were found in plasma, urine and expired CO<sub>2</sub> after 3 days of treatment with topically applied <sup>14</sup>C-labeled fluorouracil.

**INDICATIONS AND USAGE:** Efdex 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 Efdex 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.

**CONTRAINDICATIONS:** Efdex may cause fetal harm when administered to a pregnant woman.

There are no adequate and well-controlled studies in pregnant women with either the topical or the parenteral forms of fluorouracil. One birth defect (cleft lip and palate) has been reported in the newborn of a patient using Efdex as recommended. One birth defect (ventricular septal defect) and cases of miscarriage have been reported when Efdex was applied to mucous membrane areas. Multiple birth defects have been reported in a fetus of a patient treated with intravenous fluorouracil.

Animal reproduction studies have not been conducted with Efdex. Fluorouracil administered parenterally has been shown to be teratogenic in mice, rats, and hamsters when given at doses equivalent to the usual human intravenous dose; however, the amount of fluorouracil absorbed systemically after topical administration to actinic keratoses is minimal (see CLINICAL PHARMACOLOGY). Fluorouracil exhibited maximum teratogenicity when given to mice as single intraperitoneal injections of 10 to 40 mg/kg on Day 10 or 12 of gestation. Similarly, intraperitoneal doses of 12 to 37 mg/kg given to rats between Days 9 and 12 of gestation and intramuscular doses of 3 to 9 mg/kg given to hamsters between Days 8 and 11 of gestation were teratogenic and/or embryotoxic (ie, resulted in increased resorptions or embryolethality). In monkeys, divided doses of 40 mg/kg given between Days 20 and 24 of gestation were not teratogenic. Doses higher than 40 mg/kg resulted in abortion.

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

Efdex 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.

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

**WARNINGS:** 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 Efdex was applied to mucous membrane areas during pregnancy.

Occlusion of the skin with resultant hydration has been shown to increase percutaneous penetration of several topical preparations. If any occlusive dressing is used in treatment of basal cell carcinoma, there may be an increase in the severity of inflammatory reactions in the adjacent normal skin. A porous gauze dressing may be applied for cosmetic reasons without increase in reaction.

Exposure to ultraviolet rays should be minimized during and immediately following treatment with Efdex because the intensity of the reaction may be increased.

Patients should discontinue therapy with Efdex if symptoms of DPD enzyme deficiency develop (see CONTRAINDICATIONS section).

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

### EFUDEX® (fluorouracil)

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

**Information for Patients:** Patients should be forewarned that the reaction in the treated areas may be unsightly during therapy and, usually, for several weeks following cessation of therapy. Patients should be instructed to avoid exposure to ultraviolet rays during and immediately following treatment with Efdex because the intensity of the reaction may be increased. If Efdex is applied with the fingers, the hands should be washed immediately afterward. Efdex should not be applied on the eyelids or directly into the eyes, nose or mouth because irritation may occur.

**Laboratory Tests:** Solar keratoses which do not respond should be biopsied to confirm the diagnosis. Follow-up biopsies should be performed as indicated in the management of superficial basal cell carcinoma.

**Carcinogenesis, Mutagenesis, 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 Efdex, 5-fluorouracil, have shown positive effects in *in vitro* tests for mutagenicity and on impairment of fertility.

5-Fluorouracil was positive in three *in vitro* cell neoplastic transformation assays. In the C3H/10T½ clone 8 mouse embryo cell system, the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed syngeneic mice.

While no evidence for mutagenic activity was observed in the Ames test (3 studies), fluorouracil has been shown to be mutagenic in the survival count re-assay with *Bacillus subtilis* and in the *Drosophila* wing-hair spot test. Fluorouracil produced petite mutations in *Saccharomyces cerevisiae* and was positive in the micronucleus test (bone marrow cells of male mice).

Fluorouracil was clastogenic *in vitro* (ie, chromatid gaps, breaks and exchanges) in Chinese hamster fibroblasts at concentrations of 1.0 and 2.0 µg/mL and has been shown to increase sister chromatid exchange *in vitro* in human lymphocytes. In addition, 5-fluorouracil has been reported to produce an increase in numerical and structural chromosome aberrations in peripheral lymphocytes of patients treated with this product.

Doses of 125 to 250 mg/kg, administered intraperitoneally, have been shown to induce chromosomal aberrations and changes in chromosome organization of spermatogonia in rats. Spermatogonial differentiation was also inhibited by fluorouracil, resulting in transient infertility. However, in studies with a strain of mouse which is sensitive to the induction of sperm head abnormalities after exposure to a range of chemical mutagens and carcinogens, fluorouracil was inactive at oral doses of 5 to 80 mg/kg/day. In female rats, fluorouracil administered intraperitoneally at doses of 25 and 50 mg/kg during the preovulatory phase of oogenesis significantly reduced the incidence of fertile matings, delayed the development of preimplantation and postimplantation embryos, increased the incidence of preimplantation lethality and induced chromosomal anomalies in these embryos. Single dose intravenous and intraperitoneal injections of 5-fluorouracil have been reported to kill differentiated spermatogonia and spermatocytes (at 500 mg/kg) and to produce abnormalities in spermatids (at 50 mg/kg) in mice.

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

**Nursing Mothers:** It is not known whether Efdex is excreted in human milk. Because there is some systemic absorption of fluorouracil after topical administration (see CLINICAL PHARMACOLOGY), because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue use of the drug, taking into account the importance of the drug to the mother.

**Pediatric Use:** Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS:** The most frequent adverse reactions to Efdex occur locally and are often related to an extension of the pharmacological activity of the drug. These include burning, crusting, allergic contact dermatitis, erosions, erythema, hyperpigmentation, irritation, pain, photosensitivity, pruritus, scarring, rash, soreness and ulceration. Ulcerations, other local reactions, cases of miscarriage and a birth defect (ventricular septal defect) have been reported when Efdex was applied to mucous membrane areas. Leukocytosis is the most frequent hematological side effect.

Although a causal relationship is remote, other adverse reactions which have been reported infrequently are:

**Central Nervous System:** Emotional upset, insomnia, irritability.

**Gastrointestinal:** Medicinal taste, stomatitis.

**Hematological:** Eosinophilia, thrombocytopenia, toxic granulation.

**Integumentary:** Alopecia, blistering, bullous pemphigoid, discomfort, ichthyosis, scaling, suppuration, swelling, telangiectasia, tenderness, urticaria, skin rash.

**Special Senses:** Conjunctival reaction, corneal reaction, lacrimation, nasal irritation.

**Miscellaneous:** Herpes simplex.

**OVERDOSAGE:** There have been no reports of overdosage with Efdex.

The oral LD<sub>50</sub> for the 5% topical cream was 234 mg/kg in rats and 39 mg/kg in dogs. These doses represented 11.7 and 1.95 mg/kg of fluorouracil, respectively. Studies with a 5% topical solution yielded an oral LD<sub>50</sub> of 214 mg/kg in rats and 28.5 mg/kg in dogs, corresponding to 10.7 and 1.43 mg/kg of fluorouracil, respectively. The topical application of the 5% cream to rats yielded an LD<sub>50</sub> of greater than 500 mg/kg.

**DOSE AND ADMINISTRATION:** When Efdex is applied to a lesion, a response occurs with the following sequence: erythema, usually followed by vesiculation, desquamation, erosion and reepithelialization.

Efdex should be applied preferably with a nonmetal applicator or suitable glove. If Efdex is applied with the fingers, the hands should be washed immediately afterward.

**Actinic or Solar Keratosis:** Apply cream or solution twice daily in an amount sufficient to cover the lesions. Medication should be continued until the inflammatory response reaches the erosion stage, at which time use of the drug should be terminated. The usual duration of therapy is from 2 to 4 weeks. Complete healing of the lesions may not be evident for 1 to 2 months following cessation of Efdex therapy.

**Superficial Basal Cell Carcinomas: Only the 5% strength is recommended.** Apply cream or solution twice daily in an amount sufficient to cover the lesions. Treatment should be continued for at least 3 to 6 weeks. Therapy may be required for as long as 10 to 12 weeks before the lesions are obliterated. As in any neoplastic condition, the patient should be followed for a reasonable period of time to determine if a cure has been obtained.

**HOW SUPPLIED:** Efdex Solution is available in 10-mL drop dispensers containing either 2% (NDC 0187-3202-10) or 5% (NDC 0187-3203-10) fluorouracil on a weight/weight basis compounded with propylene glycol, tris (hydroxymethyl) aminomethane, hydroxypropyl cellulose, parabens (methyl and propyl) and disodium edetate.

Efdex Cream is available in 40-gm tubes containing 5% fluorouracil (NDC 0187-3204-47) in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl).

Store at 25°C (77°F); excursions permitted to 15°C–30°C (59°F–86°F).

Valiant Pharmaceuticals International  
Costa Mesa, CA 92626

EFUDEX®  
(fluorouracil)



3360002EX02

VALEANT™ 3360002EX02  
Rev. March 2005

## POLICY & PRACTICE

### Spotlighting Epidermolysis Bullosa

Members of Congress are trying to raise the public awareness of epidermolysis bullosa by the creation of a national awareness week. Rep. Tim Bishop (D-N.Y.) and Rep. Peter King (R-N.Y.) introduced a resolution (H. Res. 335) this summer that would create a national awareness week for epidermolysis bullosa in October. The resolution, which encourages groups to promote understanding of the impact of the disease on patients and their families, was introduced in the Senate by Sen. Hillary Clinton (D-N.Y.) and Sen. Chuck Schumer (D-N.Y.). Epidermolysis bullosa affects about 12,500 people in the United States. The resolution also notes that more funding is needed in order to conduct research and to develop treatments for the disease.

### Psoriasis Awareness Increases

Psoriasis advocates are also celebrating increased awareness on Capitol Hill. As the National Psoriasis Foundation was ramping up awareness activities last month, the U.S. Senate passed a resolution officially designating August 2005 as "Psoriasis Awareness Month" and acknowledging the large physical and financial toll created by the disease. "Awareness is a powerful force against the painful misconceptions that surround many medical problems," Sen. Gordon Smith (R-Ore.), one of the sponsors of the Senate resolution, said in a statement. "To the extent that we can increase the common understanding of this chronic disease, we can improve patients' lives." The National Psoriasis Foundation last month also launched its first-ever Local Lobby Week, in which volunteers from across the country visited their members of Congress in order to talk about psoriasis and how the disease affects their daily lives. The foundation continues to push for increased federal funding for psoriasis research and for the enactment of the Arthritis Prevention, Control, and Cure Act of 2005 (S. 424/H.R. 583).

### Bill Would Repeal SGR

Physician groups are hailing the fact that a forthcoming bill from Rep. Nancy Johnson (R-Conn.), chair of the House Ways and Means Subcommittee on Health, would repeal Medicare's current sustainable growth rate and base future updates for physician payments on the Medicare Economic Index. At a recent hearing, Mark McClellan, M.D., administrator for the federal Centers for Medicare and Medicaid Services, informed Rep. Johnson that such a measure could come at a high cost: specifically, that the Medicare Economic Index-based increases would be \$183 billion over 10 years. Rep. Johnson's bill seeks to establish a performance measurement and reporting system. C. Anderson Hedberg, M.D., president of the American College of Physicians, testified that Rep. Johnson's bill should provide funding to support quality improvement, so that all physicians would receive a positive update linked to inflation with the opportunity to receive additional reimburse-

ment for their participating in performance measurement.

### Wisconsin Loses Cap on Damages

The Wisconsin Supreme Court's decision to remove a 30-year-old cap on noneconomic damages in malpractice cases opens the door for a medical liability crisis, the American Medical Association said. The court held that the cap, currently set at \$445,775, was "unconstitutional beyond a reasonable doubt." The decision will endanger Wisconsin's stable health care environment, AMA Trustee Cyril M. Hetsko, M.D., said in a statement. Wisconsin medical groups are concerned that the decision "will force a wave of doctors to retire early or stop performing high-risk procedures," such as delivering babies in rural areas, said Susan Turney, M.D., chief executive officer of the Wisconsin Medical Society.

### IT Deficit Noted Among Physicians

Most Medicare fee-for-service outpatient visits in 2001 were made to physicians with limited information technology support for patient care, the Center for Studying Health System Change (HSC) reported. Linking Medicare claims data to HSC's national physician survey, researchers found that a total of 57% of Medicare outpatient visits were made to physicians in practices that used IT for no more than one of the following five clinical functions: obtaining treatment guidelines, exchanging clinical data with other physicians, accessing patient notes, generating preventive treatment reminders for the physician's use, and for writing prescriptions. While half of those patient visits were to physicians using information technology in order to obtain treatment guidelines, the proportion of visits to physicians in practices with IT support for other patient care functions was much lower. Rates for electronic prescribing fell to 9%. While access to "wired" practices was found to be low for all beneficiaries, HSC determined that there were few differences in access between sicker and healthier beneficiaries.

### Disability Call to Action Debuts

The U.S. Surgeon General has issued his first-ever Call to Action on disability. The new report outlines a series of goals that are aimed at helping individuals who have disabilities to receive better health care. The overall goals include providing health care professionals with the tools needed to screen, diagnose, and treat the whole person with a disability with dignity; helping those persons with disabilities to maintain healthy lifestyles; and also increasing accessible health care and various support services for people with disabilities. "The reality is that for too long we provided lesser care to people with disabilities," Surgeon General Richard H. Carmona, M.D., said in a statement. "Today, we must redouble our efforts so that people with disabilities achieve full access to disease prevention and health promotion services." The full text of the "Surgeon General's Call to Action to Improve the Health and Wellness of Persons with Disabilities" is available at [www.surgeongeneral.gov](http://www.surgeongeneral.gov).

—Mary Ellen Schneider