

EFUDEX- fluorouracil solution
EFUDEX- fluorouracil cream
Bausch Health US, LLC

EFUDEX[®]
(fluorouracil)
TOPICAL SOLUTIONS AND CREAM
FOR TOPICAL USE ONLY
NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE

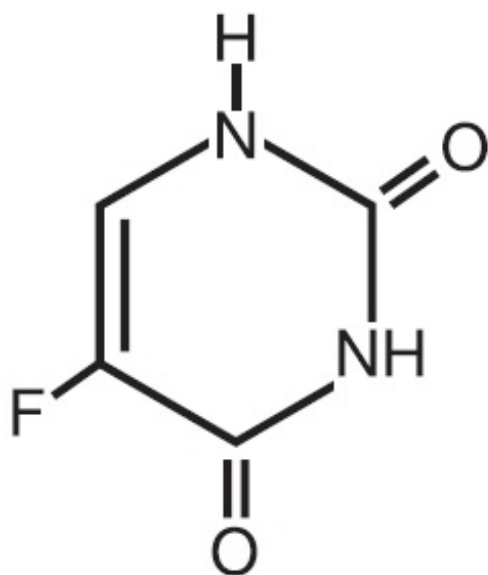
DESCRIPTION:

EFUDEX Topical Solutions and Cream are topical preparations containing the fluorinated pyrimidine 5-fluorouracil, an antineoplastic antimetabolite.

EFUDEX Topical Solution consists of 2% or 5% fluorouracil on a weight/weight basis, compounded with disodium edetate, hydroxypropyl cellulose, methylparaben, propylene glycol, propylparaben, and tris (hydroxymethyl) aminomethane.

EFUDEX Cream contains 5% fluorouracil in a vanishing cream base consisting of methylparaben, polysorbate 60, propylene glycol, propylparaben, purified water, stearyl alcohol, and white petrolatum.

Chemically, fluorouracil is a 5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione. 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 (e.g., CO₂, 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 ¹⁴C-labeled fluorouracil added to a 5% preparation. All patients had been receiving nonlabeled 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 CO₂ after 3 days of treatment with topically applied ¹⁴C-labeled fluorouracil.

INDICATIONS AND USAGE:

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.

CONTRAINDICATIONS:

EFUDEX 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 EFUDEX as recommended. One birth defect (ventricular septal defect) and cases of miscarriage have been reported when EFUDEX 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 EFUDEX. 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 (i.e., resulted in increased resorptions or embryoletality). 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.

EFUDEX 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.

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.

EFUDEX 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 EFUDEX 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 EFUDEX because the intensity of the reaction may be increased.

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

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 EFUDEX 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.

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 EFUDEX because the intensity of the reaction may be increased. If EFUDEX is applied with the fingers, the hands should be washed immediately afterward. EFUDEX should not be applied on the eyelids or directly into the eyes, nose, or mouth because irritation may occur.

Fluorouracil, including EFUDEX may be fatal if ingested by pets. Avoid allowing pets to contact the EFUDEX container or the skin where EFUDEX has been applied. Store EFUDEX out of reach of pets. Safely discard or clean any cloth or applicator that may retain EFUDEX and avoid leaving any residues of EFUDEX on your hands, clothing, carpeting or furniture.

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 EFUDEX, 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/10T $\frac{1}{2}$ 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 (three studies), fluorouracil has been shown to be mutagenic in the survival count rec-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 (i.e., chromatid gaps, breaks, and exchanges) in Chinese hamster fibroblasts at concentrations of 1.0 and 2.0 mcg/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: See **CONTRAINDICATIONS**.

Nursing Mothers: It is not known whether EFUDEX 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 EFUDEX occur locally and are often related to an extension of the pharmacological activity of the drug. These include burning, crusting, allergic contact dermatitis, pruritus, scarring, rash, soreness, and ulceration. Ulcerations, other local reactions, cases of miscarriage, and a birth defect (ventricular septal defect) have been reported when EFUDEX 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.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch Health US, LLC at 1-800-321-4576 and/or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE:

There have been no reports of overdosage with EFUDEX.

The oral LD₅₀ 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 LD₅₀ 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 LD₅₀ of greater than 500 mg/kg.

DOSAGE AND ADMINISTRATION:

When EFUDEX is applied to a lesion, a response occurs with the following sequence: erythema, usually followed by vesiculation, desquamation, erosion, and re-epithelialization.

EFUDEX should be applied preferably with a nonmetal applicator or suitable glove. If EFUDEX 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 EFUDEX 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:

EFUDEX Topical Solution is available in 10 mL drop dispensers containing either 2% (NDC 0187-3202-10) or 5% (NDC 0187-3203-10) fluorouracil and 25 mL drop dispensers containing either 2% (NDC 0187-3202-02) or 5% (NDC 0187-3203-02) fluorouracil on a weight/weight basis compounded with disodium edetate, hydroxypropyl cellulose, methylparaben, propylene glycol, propylparaben, and tris (hydroxymethyl) aminomethane.

EFUDEX Cream is available in 40 g tubes containing 5% fluorouracil (NDC 0187-3204-47) in a vanishing cream base consisting of methylparaben, polysorbate 60, propylene glycol, propylparaben, purified water, stearyl alcohol, and white petrolatum.

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

Distributed by:

Bausch Health US, LLC

Bridgewater, NJ 08807 USA

Manufactured by:

Kavis Pharma LLC

Sugar Land, TX 77478 USA

9734603

NDC0187-3204-47

Rx only

Efudex®

(fluorouracil)

Topical Cream

5%

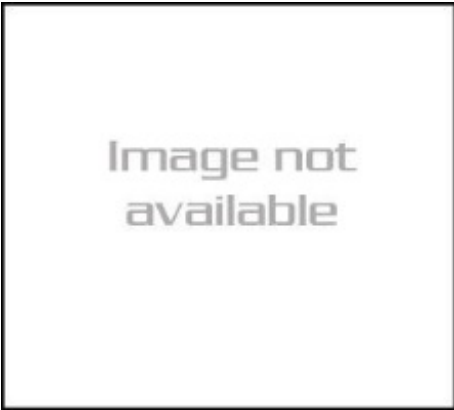
Net Wt. 40 g

FOR TOPICAL USE ONLY

**NOT FOR OPHTHALMIC,
ORAL, OR INTRAVAGINAL USE**

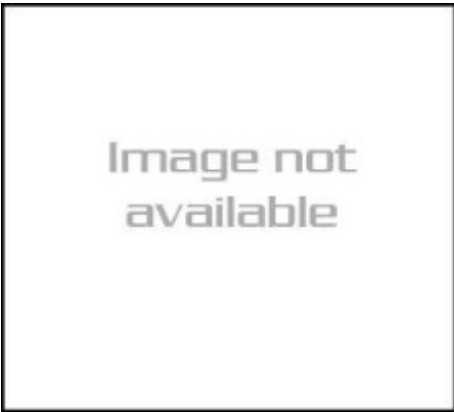
OrthoDermatologics

Package/Label Display Panel-Solution Carton



PRODUCT DELISTED -
IMAGE NOT AVAILABLE

Package/Label Display Panel-Solution Carton



PRODUCT DELISTED -
IMAGE NOT AVAILABLE

<div>EFUDEX</div> <div>fluorouracil solution</div>			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0187-3202
Route of Administration	TOPICAL		
Active Ingredient/Active Moiety			
Ingredient Name		Basis of Strength	Strength
FLUOROURACIL (UNII: U3P01618RT) (FLUOROURACIL - UNII:U3P01618RT)		FLUOROURACIL	0.5 g in 10 mL

Inactive Ingredients				
Ingredient Name				Strength
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)				
TROMETHAMINE (UNII: 023C2WHX2V)				
METHYLPARABEN (UNII: A2I8C7HI9T)				
PROPYLPARABEN (UNII: Z8IX2SC1OH)				
EDETATE DISODIUM (UNII: 7FLD91C86K)				
HYDROXYPROPYL CELLULOSE (110000 WAMW) (UNII: 5Y0974F5PW)				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0187-3202-10	1 in 1 CARTON	07/29/1970	02/28/2008
1		10 mL in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:0187-3202-02	1 in 1 CARTON	07/29/1970	02/28/2008
2		25 mL in 1 BOTTLE; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category	Application Number or Monograph Citation		Marketing Start Date	Marketing End Date
NDA	NDA016831		07/29/1970	02/28/2008

EFUDEX			
fluorouracil solution			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0187-3203
Route of Administration	TOPICAL		
Active Ingredient/Active Moiety			
Ingredient Name		Basis of Strength	Strength
FLUOROURACIL (UNII: U3P01618RT) (FLUOROURACIL - UNII:U3P01618RT)		FLUOROURACIL	1.25 g in 10 mL
Inactive Ingredients			
Ingredient Name			Strength
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)			
TROMETHAMINE (UNII: 023C2WHX2V)			
METHYLPARABEN (UNII: A2I8C7HI9T)			
PROPYLPARABEN (UNII: Z8IX2SC1OH)			

EDETATE DISODIUM (UNII: 7FLD91C86K)				
HYDROXYPROPYL CELLULOSE (110000 WAMW) (UNII: 5Y0974F5PW)				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0187-3203-10	1 in 1 CARTON	07/29/1970	02/28/2008
1		10 mL in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:0187-3203-02	1 in 1 CARTON	07/29/1970	02/28/2008
2		25 mL in 1 BOTTLE; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA		NDA016831	07/29/1970	01/31/2010

EFUDEX			
fluorouracil cream			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0187-3204
Route of Administration	TOPICAL		
Active Ingredient/Active Moiety			
Ingredient Name		Basis of Strength	Strength
FLUOROURACIL (UNII: U3P01618RT) (FLUOROURACIL - UNII:U3P01618RT)		FLUOROURACIL	2 g in 40 g
Inactive Ingredients			
Ingredient Name			Strength
METHYLPARABEN (UNII: A2I8C7HI9T)			
POLYSORBATE 60 (UNII: CAL22UVI4M)			
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)			
PROPYLPARABEN (UNII: Z8IX2SC1OH)			
WATER (UNII: 059QF0KO0R)			
STEARYL ALCOHOL (UNII: 2KR89I4H1Y)			
PETROLATUM (UNII: 4T6H12BN9U)			
Packaging			

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0187-3204-47	1 in 1 CARTON	07/29/1970	09/30/2026
1		40 g in 1 TUBE; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA		NDA016831	07/29/1970	

Labeler -
Bausch Health US, LLC (831922468)

Establishment			
Name	Address	ID/FEI	Business Operations
Bausch Health Companies Inc.		245141858	manufacture(0187-3202, 0187-3203, 0187-3204)

Establishment			
Name	Address	ID/FEI	Business Operations
Kavis Pharma LLC		119014974	manufacture(0187-3202, 0187-3203, 0187-3204)