**Pediatric Use:**

- **Human**: 5-fluorouracil is not a weight-based dosing, compared with standard edetate, hydroxypropylsorbitol, methylparaben, propylparaben, and white petrolatun.

- **Nursing Mothers**: There are no adequate and well-controlled studies in pregnant women with either the topical or the parenteral forms of Efudex. There is no adequate evidence for the safety of 5-fluorouracil to the human fetus.

- **Pregnancy**: There are no adequate and well-controlled studies in pregnant women with either the topical or the parenteral forms of Efudex. There is no adequate evidence for the safety of 5-fluorouracil to the human fetus.

-** Pharmacology:**

  - **Absorption**: Efudex is absorbed systemically following topical application. The systemic absorption appears to be dose-dependent. The extent of systemic absorption of fluorouracil from topical dermatological preparations is not known. It is not known if 5-fluorouracil is absorbed through intact skin. Therefore, its absorption will vary depending on the skin condition and site of application.

  - **Distribution**: The distribution of fluorouracil in plasma is not significantly affected by the route of administration. The volume of distribution is approximately 100 mL of plasma per kg of body weight.

  - **Metabolism**: The metabolism of fluorouracil results in degradation products (e.g., CO₂, H₂O, and a series of uracil-derived substances).

  - **Excretion**: The urinary excretion of fluorouracil following topical application was not studied in humans. The urinary excretion of fluorouracil following intravenous administration in humans has not been reported.

- **Clinical Pharmacology**

  - **Mechanism of Action**: Fluorouracil is a nucleoside antimetabolite that inhibits DNA synthesis by causing misincorporation of uracil into DNA, leading to cell death.

  - **Pharmacodynamics**: The biological effects of fluorouracil are related to its ability to inhibit DNA synthesis and DNA repair in dividing cells.

  - **Pharmacokinetics**: The pharmacokinetics of fluorouracil have not been extensively studied in humans. Following topical application, the extent and rate of systemic absorption are not known. Following intravenous administration, the time to peak plasma concentration is approximately 1 hour, and the elimination half-life is about 2 hours.

- **CONTRAINDICATIONS**: Efudex is contraindicated in patients with known hypersensitivity to any of its components.

- **Warnings**: Use of Efudex should be avoided in patients with known hypersensitivity to any of its components. Additionally, Efudex should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large number of cases of leukopenia and neutropenia have been reported in patients treated with Efudex who had not been warned of this risk. Efudex should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large number of cases of leukopenia and neutropenia have been reported in patients treated with Efudex who had not been warned of this risk.

- **Precautions**: Efudex is not recommended for use in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large number of cases of leukopenia and neutropenia have been reported in patients treated with Efudex who had not been warned of this risk.

- **Drug Interactions**: The use of Efudex in patients receiving other antineoplastic agents or other immunosuppressive agents has not been studied. Therefore, caution should be exercised when Efudex is used concomitantly with other antineoplastic agents.

- **Adverse Reactions**: The most common adverse reactions reported in patients treated with Efudex include skin reactions, such as erythema, pruritus, and irritation. Other adverse reactions reported include neutropenia, thrombocytopenia, and stomatitis.

- **Dosage and Administration**: Efudex is applied to the skin as a cream or solution. The dosage should be determined by the severity of the condition and the site of application.

- **Patient Information**: Patients should be instructed to wash the skin with soap and water before applying Efudex. Efudex should be applied to the skin once or twice daily, depending on the severity of the condition. Efudex should be applied to the skin in a thin layer 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.

- **Occlusion**: Occlusion of the skin with resultant hydration has been shown to increase percutaneous penetration of several compounds. If an occlusive dressing is used in treatment of basal cell carcinomas, there may be an increase in systemic effects. When occlusive dressings are used, the skin should be cleansed with soap and water before application of Efudex.

- **Monitoring**: Monitoring for hematologic toxicity is recommended. Patients should be monitored for changes in hematologic parameters, including white blood cell count, hemoglobin, and platelet count.

- **Special Populations**: Efudex is not recommended for use in pregnant women or in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency.

- **Geriatric Use**: Efudex is not recommended for use in elderly patients. The safety and efficacy of Efudex have not been established in this population.

- **Pediatric Use**: Efudex is not recommended for use in children. The safety and efficacy of Efudex have not been established in this population.

- **Information for Patients**: Patients should be informed of the potential for hematologic toxicity and should be monitored for changes in hematologic parameters, including white blood cell count, hemoglobin, and platelet count.

- **Accidental Overdosage**: There are no reports of accidental overdosage with Efudex. However, in case of overdose, supportive and symptomatic therapy should be administered.

- **Antineoplastic Drugs**: Efudex is an antineoplastic antimetabolite.

- **Description**: Efudex Cream contains 5% fluorouracil in a vanishing cream base consisting of methylparaben, polysorbate 60, propylparaben, purified water, stearyl alcohol, and white petrolatum. Efudex Solution consists of 2% or 5% fluorouracil on a weight/weight basis, compounded with disodium edetate, disodium edetate, and water. Efudex is a white or practically white, sterile, isotonic solution.

- **Nociceptors**: The diagnosis should be established prior to treatment, since this method has not been proven effective in other conditions. If the diagnosis is not established prior to treatment, since this method has not been proven effective in other conditions.

- **Efficacy**: Efudex has been shown to be effective 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.

- **Patient Education**: Patients should be instructed to wash the skin with soap and water before applying Efudex. Efudex should be applied to the skin in a thin layer 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.

- **Revised**: 2018-01-01

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, disciform, cynthia, scaling, suppurative, swelling, telangiectasia, tenderness, urticaria, skin rash.

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

Miscellaneous:
- Herpes simplex.

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America 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 in 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 Solution is available in (10 ml) dropper dispensers containing either 2% (NDC 0187-3202-10) or 5% (NDC 0187-3203-10) fluorouracil and 25 mL dropper 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 (10 g) tubes containing 5% fluorouracil (NDC 0187-3204-47) in a vanishing cream base consisting of methylparaben, polysorbate 60, propylene glycol, propylparaben, purified water, sorbitan stearate, and white petrolatum.

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

MANUFACTURER:

Valeant Pharmaceuticals North America LLC
Brookville, PA 16404 USA
By: Valeant Pharmaceuticals International, Inc.
Laval, Quebec H7L 4A8, Canada
Efudex is a registered trademark of Valeant Pharmaceuticals International, Inc. or its affiliates.

©Valeant Pharmaceuticals North America LLC
Rev. 05/17 9491201 56598777C