PRODUCT MONOGRAPH

^{Pr}EFUDEX®

Fluorouracil
Topical Cream 5 %

Topical Antineoplastic Agent

Valeant Canada LP
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Canada

Date of Revision:
March 12, 2020

Control # 235663

NAME OF DRUG

PrEFUDEX®
Fluorouracil
Topical Cream

THERAPEUTIC CLASSIFICATION

Topical Antineoplastic Agent

ACTION

There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid. In this fashion 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 which take up fluorouracil at a more rapid pace. The catabolic metabolism of fluorouracil results in degradative products (e.g., CO_2, urea, alpha-fluoro-beta-alanine) which are inactive.

Studies in man with topical application of C^{14}-labelled EFUDEX demonstrate insignificant absorption as measured by C^{14} content of plasma, urine and respiratory CO_2.

INDICATIONS

EFUDEX is recommended for the topical treatment of premalignant keratoses and superficial basal cell carcinoma.

CONTRAINDICATIONS

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

EFUDEX is contraindicated in patients with known dihydropyridine dehydrogenase (DPD) enzyme deficiency (see WARNINGS).

WARNINGS

The enzyme dihydropyrimidine dehydrogenase (DPD) plays an important role in the breakdown of fluorouracil. Inhibition, deficiency or decreased activity of this enzyme can result in accumulation of fluorouracil. EFUDEX must not be used on patients with known dihydropyrimidine dehydrogenase

(DPD) deficiency. Life-threatening systemic toxicity has been reported with the topical use of fluorouracil a patient with DPD deficiency. Signs of fluorouracil toxicity may include nausea, vomiting, diarrhea, stomatitis, esophagopharyngitis, gastrointestinal ulceration and bleeding, hemorrhage from any site and bone marrow depression (thrombocytopenia and agranulocytosis). If toxicity is observed or suspected, immediately stop treatment, wash treated area with warm water and seek medical attention immediately.

If an occlusive dressing is used, there may be an increase in the incidence of inflammatory reactions in the adjacent normal skin.

Prolonged exposure to ultraviolet lights should be avoided while under treatment with EFUDEX because the intensity of the reaction may be increased.

Since fluorouracil is known to have teratogenic properties, the potential value of its use in women of child-bearing potential should be weighed against the risks involved.

Appropriate therapy for pre-existing concomitant inflammatory dermatoses should be instituted before using the drug.

PRECAUTIONS

EFUDEX is preferably applied with a non-metal applicator or suitable glove; if it is applied with the fingertips, the hands should be washed immediately afterward. EFUDEX should be applied with care near the eyes, nostrils and mouth. To rule out the presence of a frank neoplasm, a biopsy should be made of those lesions failing to respond to treatment or recurring after treatment.

ADVERSE REACTIONS

The most frequently encountered local reactions are pain, pruritus, hyperpigmentation and burning at the site of application. Other local reactions include dermatitis, scarring, soreness and tenderness. Insomnia, stomatitis, suppuration, scaling, swelling, irritability, medicinal taste, photosensitivity and lacrimation have also been reported.

Laboratory abnormalities reported include leucocytosis, thrombocytopenia, toxic granulation and eosinophilia.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Since EFUDEX is applied topically it is highly unlikely that an overdosage would occur. In the event that this preparation is accidentally ingested, signs of toxicity may include diarrhea, stomatitis, thrombocytopenia (platelets under 100,000) and leukopenia (WBC under 3,500). These symptoms may be ameliorated by Leucovorin.

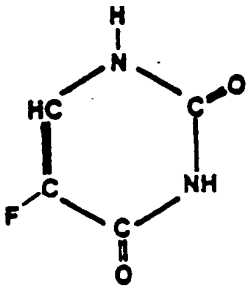
DOSAGE AND ADMINISTRATION

EFUDEX should be applied twice daily with a non-metal applicator or suitable glove in an amount of the cream sufficient to cover the lesion. When EFUDEX is applied to a lesion, a response occurs with the following sequence: erythema, usually followed by vesiculation, erosion, ulceration, necrosis and epithelization. The lower frequency and intensity of activity in adjacent normal skin indicate a selective cytotoxic property. Medication should be continued until the inflammatory reaction reaches the erosion, ulceration, and necrosis stage, at which time use of the drug should be terminated. The usual duration of therapy is from two to four weeks. Complete healing of the lesion may not be evident for one to two months following cessation of EFUDEX therapy.

While the patient is undergoing EFUDEX therapy, consideration can be given to curettage, wound excision and removal of pathological tissue.

PHARMACEUTICAL INFORMATION

Fluorouracil



Structural Formula: $C_4H_3FN_2O_2$

Molecular Weight: 130.08 g/mol

Chemical Name: 5-Fluoropyrimidine-2, 4-dione

Description: White to almost white, almost odourless, crystalline powder, sparingly soluble in water, slightly soluble in alcohol, almost insoluble in chloroform and ether.

DOSAGE FORM

EFUDEX cream, 40 g tube, containing 5% fluorouracil in a vanishing cream base consisting of white Petrolatum, Stearyl Alcohol, Propylene Glycol, Polysorbate 60 and Parabens (Methyl and Propyl).

INFORMATION FOR THE CONSUMER

Description

EFUDEX (fluorouracil) belongs to the group of medications known as antimetabolites. When applied to the skin, it is used to treat certain skin problems, including cancer or conditions that could become cancerous if not treated. EFUDEX interferes with the growth of abnormal cells, which are eventually destroyed. EFUDEX is available only with a physician' s prescription as 5 % cream.

Before Using EFUDEX

For EFUDEX (fluorouracil), the following should be considered and discussed with your physician before using this medication:

Allergies – Tell your physician if you have ever had any unusual or allergic reaction to fluorouracil or any of EFUDEX components.

Immune – Tell your physician if you have dihydropyridine dehydrogenase (DPD) enzyme deficiency.

Pregnancy – Tell your physician if you are pregnant or if you intend to become pregnant. Although EFUDEX applied to the skin has not been shown to cause problems in humans, some of it is absorbed through the skin and there is a chance that it could cause birth defects. Be sure that you have discussed this with your doctor before using this medication.

Breast-feeding – Although EFUDEX applied to the skin has not been shown to cause problems in nursing babies, some of it is absorbed through the skin.

Children – There is no specific information comparing the use of EFUDEX on the skin in children with the use in other age groups.

Older adults – Many medications have not been studied specifically in older people. Therefore, it may not be known whether they work exactly the same way they do in younger adults or if they cause different side effects or problems in older people. Although there is no specific information comparing the use of EFUDEX on the skin in the elderly with the use in other age groups, this medication is not expected to cause different side effects or problems in older people than it does in younger adults.

Other medical problems – The presence of other medical problems may affect the use of EFUDEX on the skin. Make sure you tell your physician if you have any other medical problems, especially since **other skin problems may be aggravated.**

Proper Use of EFUDEX

Keep using EFUDEX (fluorouracil) for the full length of treatment. However, **do not use EFUDEX more often or for a longer time than your doctor ordered.** Apply enough medication each time to cover the entire affected area with a thin layer.

After washing the area with soap and water and drying carefully, use a cotton-tipped applicator or wear suitable gloves to apply the medication in a thin layer to your skin.

EFUDEX should be applied with care near the eyes, nostrils and mouth.

EFUDEX may cause redness, soreness, scaling, and peeling of affected skin after 1 or 2 weeks of use. This effect may last for several weeks after you stop using EFUDEX and is to be expected. Sometimes a pink, smooth area is left when the skin treated with EFUDEX heals. This area will usually fade after 1 to 2 months. Do not stop using EFUDEX without first checking with your doctor. If the reaction is very uncomfortable, check with your doctor.

Dosing

The dose of EFUDEX (fluorouracil) will vary for different patients. **Follow your doctor's recommendations or the directions on the label.** The following information includes only the average doses of fluorouracil. **If your dose is different, do not change it** unless your doctor tells you to do so.

EFUDEX (fluorouracil) 5 %

EFUDEX is recommended for the topical treatment of premalignant keratoses and superficial basal cell carcinoma.

- Adults – Apply 5 % cream on the affected areas of skin two times daily.
- Children – use and dose must be determined by your doctor.

Missed Dose

If you miss a dose of EFUDEX (fluorouracil), apply it as soon as you remember. However, if more than a few hours have passed, skip the missed dose and go back to your regular dosing schedule. If you miss more than one dose, check with your doctor.

Storage of EFUDEX

- Keep out of the reach of children
- Store away from heat and direct light
- Do not store in the bathroom, near the kitchen sink, or in other damp places. Heat or moisture may cause the medication to break down.
- Do not keep outdated medication or medication no longer needed. Be sure that any discarded medication is out of the reach of children.

Precautions While Using EFUDEX

It is very important that your doctor checks your progress at regular visits to make sure that EFUDEX is working properly and to check for unwanted effects.

Apply EFUDEX very carefully when using it on your face. Avoid getting any into your eyes, nostrils, or mouth.

While using EFUDEX , and for 1 or 2 months after you stop using it, your skin becomes more sensitive to sunlight than usual and too much sunlight may increase the effect of EFUDEX . **During this period of time:**

Stay out of direct sunlight, especially between the hours of 10:00 a.m. and 3 :00 p.m., if possible.

- Wear protective clothing, including a hat and sunglasses.
- Apply a sun block product that has a skin protection factor (SPF) of at least 15. Some patients may require a product with a higher SPF number, especially if they have a fair complexion. If you have any questions about this, check with your physician or pharmacist.
- Do not use a sunlamp or tanning bed or booth.

If you have a severe reaction from the sun, consult with your doctor.

Side Effects of EFUDEX

Along with its needed effects, a medication may cause some unwanted side effects. Although not all of

these side effects may occur, if they do occur they may need medical attention.

Check with your doctor immediately if the following side effects occur: **redness and swelling of normal skin.**

Other side effects may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medication. However, check with your doctor if any of the following side effects continue, worsen, or are bothersome: **More common:** burning sensation where medication is applied; increased sensitivity of skin to sunlight; oozing; skin rash; soreness or tenderness of skin. **Less common or rare:** darkening of skin; scaling; watery eyes.
Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

PHARMACOLOGY

Fluorouracil is a fluorinated pyrimidine antimetabolite which is structurally similar to uracil, one of the necessary building blocks in cellular division and growth. Fluorouracil is a competitive antagonist for uracil in the formulation of RNA. DNA may be inhibited indirectly because of dependence of its synthesis on RNA.

Fluorouracil is a potent inhibitor of: Lactobacillus leichmannii, Lactobacillus plantarum, Lactobacillus casei, and Streptococcus faecalis, and the yeast, Saccharomyces carlsbergensis. It has been shown that parenteral fluorouracil inhibits the growth of human neoplasms and that its therapeutic effects are greatest on the cells of the bone marrow, the intestinal mucosa and certain tumours of the breast, rectum and colon.

A tolerance study of topically applied fluorouracil in 80 volunteers revealed no laboratory abnormalities when treated groups were compared to controls. A second study evaluated the sensitizing and irritating capabilities of topically applied fluorouracil in 216 healthy volunteers by means of the Draize Test. The results of this study indicated that 5% fluorouracil in propylene glycol solution was more irritating than 5% fluorouracil in a cream base and that this formulation produced a degree of conditioned irritability.

An absorption-excretion study conducted in six patients with C^{14}-labelled fluorouracil indicated that the levels of C^{14} activity were insignificant in plasma, urine and CO_2 (expired) after topical application. It was therefore concluded that the drug could safely be used to treat skin lesions.

TOXICOLOGY

Acute toxicological studies in five species with parenterally administered fluorouracil showed that rodents and primates were better able to tolerate this antineoplastic substance than were cats and dogs. Species which metabolize fluorouracil to alpha-fluoro-acetic acid demonstrate signs of abnormal CNS disturbances in addition to the accepted cytotoxicity, thereby demonstrating a greater frequency of acute toxic signs.

Metabolic studies in mice and in man with C^{14}-labelled fluorouracil given parenterally showed that tumor tissue demonstrated higher specific activities than did surrounding tissues. Additionally, fluorouracil is apparently metabolized to acid-soluble fluorouridine nucleotides and is incorporated into RNA, but not DNA.

Long-term testing of 5% fluorouracil as the cream, emulsion, or the solution at doses equivalent to 0.1, 0.3 and 1.0 g/kg/day, 5 days/week for 13 weeks produced a variety of local and systemic effects. The above doses were equivalent to 5, 15 and 50 mg/kg/day of fluorouracil to rats.

Signs of toxic reactions occurred within one week of treatment with the vanishing cream preparation and at about four weeks with the solution and the emulsion. Retardation of hair growth, ulceration, necrosis and infection were noted in the treated skin areas. The majority of the animals being treated with the highest dose of fluorouracil in the vanishing cream base died.

This did not occur in those groups treated with the solution or the emulsion, although weight loss was observed. The difference in toxicity was attributed to the increased percutaneous absorption of the preparation with the vanishing cream base. The lower treatment levels demonstrated, for the most part, only signs of local changes of the skin. This finding is not inconsistent with the cytotoxic properties of fluorouracil.

The use of the topical preparations upon rabbit skin revealed a high degree of sensitivity. Doses approximating 0.3 to 0.6 mg/kg/day, applied 5 days/week resulted in death. In all instances severe skin changes and infection were noted. Those treated with 0.01 g/kg/day (0.5 mg/kg) tolerated the treatment over the four-week test period. Again, it was apparent that the signs observed were consistent with the therapeutic mode of action.

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