PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrEFUDEX®

Fluorouracil
Cream 5 % w/w

Topical Antineoplastic Agent

Bausch Health, Canada Inc.
2150 St-Elzear Blvd. West
Laval, Quebec
H7L 4A8

Date of Initial Authorization:
September 19, 1997

Date of Revision:
June 9, 2021

Control #: 246337

RECENT MAJOR LABEL CHANGES

CONTRAINDICATIONS	03/2020
WARNINGS AND PRECAUTIONS	03/2020

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

1.1 Pediatrics (≥ 18 years of age)

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of EFUDEX in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use

2 CONTRAINDICATIONS

- EFUDEX is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- EFUDEX is contraindicated during pregnancy and during the lactation period (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Woman; 7.1.2 Breast-feeding).

- EFUDEX is contraindicated in patients with known dihydropyridine dehydrogenase (DPD) enzyme deficiency (see 7 WARNINGS AND PRECAUTIONS).

- EFUDEX must not be used in conjunction with brivudine*, sorivudine* and analogues. Brivudine, sorivudine and analogues are potent inhibitors of the fluorouracil-degrading enzyme dihydropyrimidine dehydrogenase (DPD) (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS, 9.2 Drug-Drug Interactions).

*Not authorized for sale in Canada

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Life-threatening systemic toxicity has been reported with the topical use of fluorouracil a patient with DPD deficiency (see 7 WARNINGS AND PRECAUTIONS).

- Since fluorouracil is known to have teratogenic properties, the potential value of its use in women of childbearing potential should be weighed against the risks involved (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

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.

Health Canada has not authorized an indication for pediatric use.

4.4 Administration

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.

4.5 Missed Dose

If you miss a dose of EFUDEX, 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.

4.7 Instructions for Preparation and Use

a. Wash the affected area with soap and water.
b. Carefully dry the affected area and wait until it is completely dry.
c. Apply a thin layer of EFUDEX enough to cover the entire area. It is recommended that a cotton-tipped swab or a suitable glove is used to apply EFUDEX. However, if you have to use your fingertips, wash your hands immediately after use.

   Note: Be careful if you are applying EFUDEX to your face and avoid getting any into your eyes, nostrils, or mouth.
d. Wash your hands thoroughly immediately after using EFUDEX.

5 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Topical	5 % w/w Cream	Propylene Glycol, Polysorbate 60 and Parabens (Methyl and Propyl), Purified Water, Stearyl Alcohol and White Petrolatum

EFUDEX (fluorouracil) is cytotoxic.

Packaging

EFUDEX cream contains 5 % w/w of fluorouracil. Available in a tube of 40 g.

7 WARNINGS AND PRECAUTIONS

Endocrine and Metabolism

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.

Skin

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.

Appropriate therapy for pre-existing concomitant inflammatory dermatoses should be instituted before using the drug (see 2 CONTRAINDICATIONS).

7.1 Special Populations

7.1.1 Pregnant Women

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

7.1.2 Breast-feeding

EFUDEX should not be used when breastfeeding or plan to breastfeed. It is unknown if the drug is excreted in human milk. Because many drugs are excreted in human milk and there is some systemic absorption of fluorouracil after topical administration, and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue drug use, taking into account the importance of the drug to the mother.

7.1.3 Pediatrics (≥ 18 years of age)

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of EFUDEX in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings

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

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Concomitantly administration of nucleoside analogues such as capecitabine, brivudine* and sorivudine* with EFUDEX is contraindicated (see 2 CONTRAINDICATIONS), as concomitantly administered nucleoside analogues may result in an inhibition of dihydropyrimidine dehydrogenase (DPD).

*Not authorized for sale in Canada

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of 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 C14 labelled EFUDEX demonstrate insignificant absorption as measured by C14 content of plasma, urine and respiratory CO_2.

10.2 Pharmacokinetics

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 C14 labelled fluorouracil indicated that the levels of C14 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.

11 STORAGE, STABILITY AND DISPOSAL

- Store between 15ºC and 30ºC.
- Medicines should not be disposed of down the drain or in household garbage.
- Any unused product or waste material should be disposed of in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

- Do not use EFUDEX after the expiration date printed on the tube.
- Keep EFUDEX and all medicines out of the reach of children.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

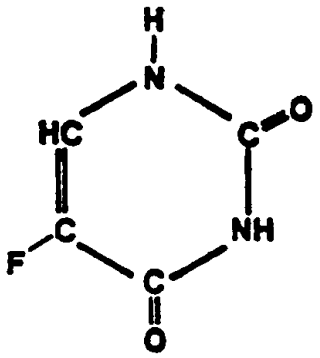
Proper name: Fluorouracil

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

Molecular formula: $C_4H_3FN_2O_2$

Molecular mass: 130.08 g/mol

Structural formula:



Physicochemical properties

Description: White to almost white, almost odourless, crystalline powder.

Solubility: Sparingly soluble in water, slightly soluble in alcohol, almost insoluble in chloroform and ether.

14 CLINICAL TRIALS

The clinical trial data based on which the original indication was initially authorized are not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL 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 C14 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.

PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrEFUDEX®
Fluorouracil Cream

Read this carefully before you start taking **EFUDEX** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **EFUDEX**.

Serious Warnings and Precautions

- Topical treatment with fluorouracil can be fatal in patients with low levels of dihydropyridine dehydrogenase (DPD; an enzyme made by the liver). If you have low levels of DPD enzyme, your healthcare professional will not prescribe EFUDEX.
- Fluorouracil has teratogenic properties that can cause potential birth defects. Your healthcare professional will not prescribe EDUFEX to you if you are pregnant or planning to become pregnant.

What is EFUDEX used for?
EFUDEX is used in adults to treat:
- pre-cancerous keratosis (keratin growth on the skin), and
- superficial basal cell carcinoma (a type of skin cancer).

How does EFUDEX work?
EFUDEX (fluorouracil) is an antimetabolite medication. It works by interfering with the growth of abnormal cells to kill these cells.

What are the ingredients in EFUDEX?
Medicinal ingredient: Fluorouracil
Non-medicinal ingredients: Propylene Glycol, Polysorbate 60 and Parabens (Methyl and Propyl), Purified Water, Stearyl Alcohol and White Petrolatum

EFUDEX comes in the following dosage forms:
Cream: 40 g in a tube

Do not use EFUDEX if:
- you are allergic to fluorouracil, or any of the other ingredients in EFUDEX .
- you have low levels of DPD (an enzyme made by the liver).
- you are pregnant or planning to become pregnant.
- are breastfeeding or planning to breastfeed.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take EFUDEX. Talk about any health conditions or problems you may have, including if you:
- have or have had severe skin problems. Your doctor may decide to treat these before starting your treatment with EFUDEX.

Other warnings you should know about:

Fluorouracil toxicity
Treatment with EFUDEX can cause fluorouracil toxicity in some patients. Some of the signs of fluorouracil toxicity may include nausea, vomiting, diarrhea, bleeding, mouth sores, stomach ulcers, decreased blood platelets, and decreased white blood cells. If you notice any signs of fluorouracil toxicity:

- stop taking EFUDEX right away,
- wash the treated area with warm water, and
- seek immediate medical attention.

Skin problems
EFUDEX may cause redness, soreness, scaling, and peeling of the affected skin for several weeks after EFUDEX is stopped. In some instances, a pink, smooth area is left when the skin treated with EFUDEX heals. This area will usually fade after 1 to 2 months. If the reaction is very uncomfortable, check with your healthcare professional.

Occlusive dressings
While using EFUDEX, the use of an occlusive dressing (a barrier that covers skin from being exposed) can increase the risk of inflammatory effects to the surrounding normal skin. Do not cover the treated area unless your healthcare professional tells you to.

Ultraviolet (UV) light
UV light exposure can increase the effects of EFUDEX and increase your sensitivity to sunlight. During your treatment with EFUDEX and 1-2 months after your treatment, it is recommended that you:

- Stay out of direct sunlight, especially between 10:00 a.m. and 3:00 p.m., if possible.
- Wear protective clothing, including a hat and sunglasses.
- Apply a sun block product with a skin protection factor (SPF) of 15 or more. If you have a light skin tone, you may need a product with a higher SPF. If you have any questions about this, talk to your healthcare professional.
- Do not use a sunlamp or tanning bed or booth.

Check-ups and testing
Your healthcare professional will monitor and assess your health, which may include conducting tests. These tests may be performed during or after your treatment with EFUDEX. This is important to check if EFUDEX is working properly and to avoid any unwanted effects.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take EFUDEX:

- Use EFUDEX exactly as prescribed by your healthcare professional. If you are not sure, check with your healthcare professional.
- Do not change your dose or stop using EFUDEX without first checking with your healthcare professional.
- Your healthcare professional will monitor your health during your treatment and may interrupt, reduce, or stop your dose.
- You may not see complete healing of the affect area until 1-2 months after stopping your treatment with EFUDEX.

Instructions for Use:

1. Wash the affected area with soap and water.
2. Carefully dry the affected area and wait until it is completely dry.
3. Apply a thin layer of EFUDEX enough to cover the entire area. It is recommended that a cotton-tipped swab or a suitable glove is used to apply EFUDEX. However, if you have to use your fingertips, wash your hands immediately after use.

   Note: Be careful if you are applying EFUDEX to your face and avoid getting any into your eyes, nostrils, or mouth.
4. Wash your hands thoroughly immediately after using EFUDEX.

Usual dose:

- Apply cream on the affected areas of skin two times daily.

Overdose:

If you think you, or a person you are caring for, have taken too much EFUDEX, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of EFUDEX, 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 healthcare professional.

What are possible side effects from using EFUDEX?

These are not all the possible side effects you may have when taking EFUDEX. If you experience any side effects not listed here, tell your healthcare professional.

Some side effects include:

- pain;
- itchiness;
- darkening of skin;
- burning sensation;
- skin irritation;
- skin rash;
- scarring;
- soreness or tenderness of skin;
- insomnia (a sleep disorder that can make it hard to fall asleep);
- stomatitis (inflammation of the mouth and lips);
- oozing and production of pus;
- scaling of skin;
- swelling;
- change in sense of taste;
- watery eyes;
- leukocytosis (high levels of white blood cells);

- toxic granulation (increased number of dark granules in neutrophils, a type of white blood cells);
- photosensitivity (sensitivity to sunlight): itchiness, or red skin when exposed to sunlight;
- eosinophilia (high levels of certain type of white blood cells): abdominal pain, rash, weight loss, or wheezing.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Thrombocytopenia (low levels of blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue, or weakness		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store EFUDEX between 15ºC and 30ºC
- 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 that is no longer needed. Be sure that any discarded medication is out of the reach of children.
- Keep out of the reach and sight of children.

If you want more information about EFUDEX:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.bauschhealth.ca, or by calling 1-800-361-4261.

This leaflet was prepared by:

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