AUSTRALIAN PRODUCT INFORMATION – EFUDIX (FLUOROURACIL) CREAM

1 NAME OF THE MEDICINE

Fluorouracil

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Efudix is a homogenous, opaque, white cream containing fluorouracil 5% w/w.

Contains:

- methyl hydroxybenzoate
- propyl hydroxybenzoate
- propylene glycol
- stearyl alcohol

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Cream

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Solar and senile keratoses, Bowen's disease.

4.2 DOSE AND METHOD OF ADMINISTRATION

Efudix should only be used under medical supervision.

Efudix is well tolerated. The healthy skin surrounding the area being treated may occasionally become reddened, but soon resumes its normal colour on cessation of treatment.

In cases of senile and solar keratoses a thin layer of the cream is applied to the affected areas once or twice daily, generally without a dressing. In the treatment of other conditions (including keratosis palmaris) a fresh occlusive dressing should be applied daily. Treatment should be continued up to the erosion stage. Duration of therapy is usually 3-4 weeks, but it may prove necessary to exceed this on occasion. When Efudix is applied to the skin, the following usually happens: a redness of the affected area (generally within 3 to 5 days) followed by blistering, peeling, and cracking (within 11 to 14 days) with occasional open sores and some discomfort. Although the skin seems to be worse, it is a sign that the medication is working. The treated skin will flake away. Some redness of the skin will continue for some time after the drug is stopped.

Limitation of Treatment Area
The total area of skin being treated with Efudix at any time should not exceed 500 sq cm (approx. 23 x 23 cm). Larger areas should be treated a section at a time.

4.3 CONTRAINDICATIONS

Efudix is contraindicated in women who are or may become pregnant during therapy (see Section 4.6 Fertility, Pregnancy and Lactation).

Known hypersensitivity to fluorouracil or any of its excipients.

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

Rarely, life-threatening toxicities such as stomatitis, diarrhoea, neutropenia, and neurotoxicity have been reported with intravenous administration of fluorouracil in patients with DPD enzyme deficiency.

A case of life-threatening systemic toxicity has been reported with the topical use of fluorouracil 5% in a patient with DPD enzyme deficiency. Symptoms included severe abdominal pain, bloody diarrhoea, vomiting, fever, and chills. Physical examination revealed stomatitis, erythematous skin rash, neutropenia, thrombocytopenia, inflammation of the oesophagus, 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The normal pattern of response includes: early and severe inflammatory phases (typically characterised by erythema, which may become intense and blotchy), a necrotic phase (characterised by skin erosion) and finally healing (when epithelialisation occurs). The clinical manifestation of response usually occurs in the second week of Efudix treatment. However, these treatment effects sometimes are more severe and include pain, blistering and ulceration.

Efudix is highly irritant, and so should not be allowed to come in contact with mucous membranes (eyes, nose or mouth) due to the possibility of irritation, local inflammation and ulceration. There is a possibility of increased absorption through ulcerated or inflamed skin.

Treatment of perioral area or nasolabial fold should be avoided, or treated carefully. Because of its irritant nature, care should be taken to ensure that Efudix does not come into contact with normal skin. Efudix should be applied with a non-metal applicator or rubber glove. Should a glove not be worn and the hands come in contact with Efudix during application they should be washed thoroughly after applying Efudix.

Exposure to UV-radiation, (e.g., natural sunlight or tanning salon) should be avoided. Efudix therapy is not advisable in persons who work outdoors for prolonged periods in the sun. Excessive sun exposure may produce a diffuse phototoxic response in the areas of application;

therefore exposure should be minimised during and immediately following treatment with Efudix because the intensity of the reaction may be increased.

While treatment is in progress, avoid cosmetics on treated areas and other topical medication applied to the same area, unless otherwise directed.

Occlusion of the skin with resultant hydration has been shown to increase percutaneous penetration of several topical preparations. If any occlusive dressing is to be used, 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.

The excipients stearyl alcohol and propylene glycol may cause local skin irritations (e.g. contact dermatitis); the excipients methyl hydroxybenzoate and propyl hydroxybenzoate may cause allergic reactions (possibly delayed).

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

Use in the elderly

No data available.

Paediatric use

Safety and effectiveness in children have not been established.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Although no significant medicine interactions with Efudix have been reported, potential medicine interactions are possible, caution should be taken with medicines that may have an effect on the DPD enzyme.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy – Pregnancy Category D

Category D. Drugs which have caused, are suspected to have caused, or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Studies in animals have shown that fluorouracil is teratogenic. The potential risk for humans is unknown, hence Efudix is contraindicated in pregnancy or where pregnancy cannot be excluded (see Section 4.3 Contraindications).

Use in lactation

It is not known whether Efudix is excreted in human milk. Because there is some systemic absorption of fluorouracil after topical administration, because many medicines are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, Efudix use should be avoided in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most frequently encountered reactions are often related to an extension of the pharmacological activity of the medicine. These include pain, pruritus, hyperpigmentation, burning, crusting, allergic contact dermatitis, erosions, erythema, hyperpigmentation, irritation, photosensitivity, scarring, rash, soreness and ulceration at the site of application. Leukocytosis is the most frequent haematological adverse effect.

Application site haemorrhage has also been reported (frequency unknown).

The patient should be advised of the temporary unsightly appearance and local discomfort to be expected during treatment with this drug (see Section 4.4 Special Warnings and Precautions for Use). Patients with chloasma and rosacea and other inflammatory dermatoses may encounter accentuation of their condition and should first be treated with appropriate therapy before using the medication. While absorption of Efudix through healthy skin is negligible, absorption is considerably increased when it is applied to diseased skin.

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

Nervous System Disorders: Dizziness, emotional upset, insomnia, irritability, headache.

Gastrointestinal Disorders: Nausea.

Skin and Subcutaneous Tissue Disorders: Alopecia, blistering, bullous pemphigoid, discomfort, ichthyosis, scaling, suppuration, swelling, telangiectasia, tenderness, urticarial, skin rash.

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

Miscellaneous: Herpes simplex.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

If Efudix is accidentally ingested, signs of fluorouracil overdosage may include nausea, vomiting and diarrhoea. Stomatitis and blood dyscrasias may occur in severe cases. Appropriate measures should be taken for the prevention of systemic infection and daily white cell counts should be performed.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

When the preparation is applied to keratotic and preneoplastic lesions it produces the following pattern of response: first erythema, then, usually, vesiculation, erosion, ulceration, necrosis and epithelialisation.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

No data available.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Methyl hydroxybenzoate
Polysorbate 60
Propylene glycol
Propyl hydroxybenzoate
Purified water
Stearyl alcohol
White soft paraffin.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from heat.

6.5 NATURE AND CONTENTS OF CONTAINER

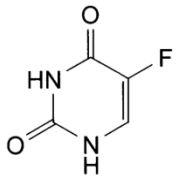
Tube, aluminium: 20 g.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

51-21-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine

8 SPONSOR

iNova Pharmaceuticals (Australia) Pty Ltd
Level 10, 12 Help Street,
Chatswood, NSW 2067

Toll free 1800 630 056

9 DATE OF FIRST APPROVAL

23 August 1991

10 DATE OF REVISION

12 October 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Add: Information for Patients: Ingestion of cream by pets.