NEW ZEALAND DATA SHEET

EFUDIX®

1 PRODUCT NAME

EFUDIX cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

EFUDIX cream contains 5% w/w fluorouracil.

Excipients with known effects:

Methyl hydroxybenzoate (E 218)
Propyl hydroxybenzoate (E 216)
Stearyl alcohol
Propylene glycol

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Homogenous, opaque, white cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

EFUDIX is used for the topical treatment of superficial pre-malignant and malignant skin lesions; keratoses including senile, actinic and arsenical forms; keratoa canthoma; Bowen's disease; superficial basal-cell carcinoma.

Deep, penetrating or nodular basal cell and squamous cell carcinomas do not usually respond to EFUDIX therapy. It should be used only as a palliative therapy in such cases where no other form of treatment is possible.

4.2 Dose and method of administration

EFUDIX cream is for topical application and should not be diluted.

Pre-malignant Conditions

The cream should be applied thinly to the affected area once or twice daily; an occlusive dressing is not essential.

Malignant Conditions

The cream should be applied once or twice daily under an occlusive dressing where this is practicable.

The cream should not harm healthy skin. Treatment should be continued until there is marked inflammatory response from the treated area, preferably with some erosion in the case of pre-malignant conditions. Severe discomfort may be alleviated by the use of topical steroid cream. The usual duration of treatment for an initial course of therapy is three to four weeks, but this may be prolonged. Lesions on the face usually respond more quickly than those on the trunk or lower limbs whilst lesions on the hands and forearms respond more slowly.

Healing may not be complete until one or two months after therapy is stopped.

Limitation of Treatment Area
The total area of skin being treated with EFUDIX cream at any time should not exceed 500 square centimetres. Larger areas should be treated a section at a time.

Elderly
Many of the conditions for which EFUDIX is indicated are common in the elderly. No special precautions are necessary.

Children
EFUDIX is not recommended for use on children.

4.3 Contraindications

EFUDIX is contraindicated in patients with known hypersensitivity to EFUDIX or parabens or any of the other excipients.

EFUDIX is contraindicated in women who are or may become pregnant during therapy and in mothers who are breast-feeding (see section 4.6). Efudix has been shown to be teratogenic.

EFUDIX should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency.

4.4 Special warnings and precautions for use

Unsightly appearance
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. The patient should be advised of the temporary unsightly appearance and local discomfort to be expected during treatment and, in some cases, for several weeks after cessation of therapy.

Prolonged exposure to sunlight
Exposure to UV-radiation (e.g. natural sunlight, tanning salon) should be avoided. EFUDIX therapy is not advisable in persons who work outdoors for prolonged periods in the sun. Excessive exposure to sunlight or other forms of UV irradiation during treatment 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.

Irritant nature
EFUDIX is highly irritant and so should not be allowed to come in contact with mucous membranes (eyes, nose or mouth) or normal skin due to the possibility of irritation, local inflammation and ulceration. The perioral area or nasolabial fold should be avoided or treated carefully. There is a possibility of increased absorption through ulcerated or inflamed skin.

Excessive reaction in these areas may occur due to irritation from accumulation of medicine. EFUDIX should preferably be applied with a non-metal spatula, cotton bud or suitable glove. Should a glove not be worn, and hands come into contact with EFUDIX during application they should be washed

thoroughly after applying EFUDIX.

Use of occlusive dressing
Occlusion of the skin with resultant hydration has been shown to increase percutaneous penetration of several topical preparations. If an occlusive dressing is used there may be an increase in the incidence of inflammatory reactions in the adjacent normal skin. A porous gauze dressing may be applied for cosmetic reasons without increase in reaction.

Sensitivity to ingredients
Hypersensitivity reactions may occur in susceptible individuals.

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).

Dihydropyridamine dehydrogenase deficiency
A large percentage of fluorouracil is catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD). 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.

Presence of frank neoplasm
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.

Patients with chloasma, rosacea and other inflammatory dermatoses
These patients may encounter accentuation of their condition and should first be treated with appropriate therapy before using the medication.

4.5 Interaction with other medicines and other forms of interaction
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
Pregnancy
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).

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 (see section 4.3).

4.7 Effects on ability to drive and use machines
EFUDIX cream is unlikely to produce an effect on the ability to drive or use machinery when used according to the dosage instructions.

4.8 Undesirable effects
The most frequently encountered reactions are often related to an extension of the pharmacological activity of the medicine. These include pain, pruritus, rash, burning, crusting, allergic contact dermatitis, erosions, erythema, hyperpigmentation, irritation, inflammation, photosensitivity, scarring, 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),

These side effects on healthy skin surrounding the area being treated are usually transient. Pre-existing subclinical lesions may become apparent. Exposure to sunlight may increase the intensity of the reaction.

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). 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
Frequency not known: Dizziness, emotional upset, headache, insomnia, irritability.

Gastrointestinal disorders
Frequency not known: Nausea

Skin and subcutaneous tissue disorders
Frequency not known: Alopecia, blistering, bullous pemphigoid, discomfort, ichthyosis, scaling, suppuration, swelling, telangiectasia, tenderness, urticaria.

Special senses
Frequency not known: Conjunctival reaction, corneal reaction, lacrimation, nasal irritation.

Miscellaneous
Frequency not known: Herpes simplex.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic Group: Antimetabolites, pyrimidine analogues. ATC Code: L01BC02

5.1 Pharmacodynamic properties
EFUDIX is a competitive antagonist for uracil in the formation of RNA and inhibits the incorporation of uracil into RNA. DNA may be inhibited indirectly because of its dependence for synthesis on RNA.

When applied topically to keratoses and preneoplastic skin lesions, EFUDIX produced the following pattern of response: erythema usually followed by scaling, tenderness, erosion, ulceration, necrosis and re-epithelialisation. Responses may sometimes occur in areas which appear clinically normal. These may be sites of subclinical actinic (solar) keratoses which the medication is affecting.

5.2 Pharmacokinetic properties
Little is absorbed when EFUDIX is applied to healthy skin but up to 20% of a dose applied to diseased skin may be excreted in the urine over 24 hours. It is also absorbed to a small extent through serous membranes. EFUDIX is converted to active nucleotide metabolites within the target cells. EFUDIX is excreted unchanged in the urine or inactivated in the liver or excreted as respiratory carbon dioxide (with the production of urea).

5.3 Preclinical safety data
Studies in animals have shown that fluorouracil is teratogenic (see section 4.6).

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Stearyl alcohol
Soft white paraffin
Polysorbate 60
Propylene glycol
Methyl hydroxybenzoate

Propyl hydroxybenzoate
Water - purified.

6.2 Incompatibilities
None known

6.3 Shelf life
5 years.

6.4 Special precautions for storage
EFUDIX cream should be stored at or below 30°C.

6.5 Nature and contents of container
EFUDIX Cream is supplied in a 20 g aluminium tube.

7 MEDICINE SCHEDULE
Prescription

8 SPONSOR
iNova Pharmaceuticals (New Zealand) Limited
c/- Simpson Grierson
88 Shortland Street,
Auckland 1141

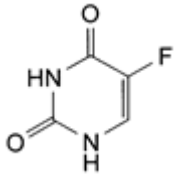
Toll-free number: 0508 375 394

9 DATE OF FIRST APPROVAL
29 October 1973

10 DATE OF REVISION OF THE TEXT
16 June 2020

Trademark: EFUDIX is a trademark.

SUMMARY TABLE OF CHANGES

Date	Changes
29 January 2018	DS reformatted. Delete structural formula – not required in new format :  Section 4.3 and 4.4: DPD contraindication retained in Section 4.3. The following descriptive text moved to section 4.4, i.e.: “A large percentage of fluorouracil is catabolized by the enzyme

	dihydropyrimidine dehydrogenase (DPD). 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." Section 5: added pharmacotherapeutic group and ATC Code Section 6: changed methyl parahydroxybenzoate to methyl hydroxybenzoate and propyl parahydroxybenzoate (consistent with TPDR)
16 June 2020	Section 4.8 added Application site haemorrhage has also been reported (frequency unknown).