Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Efudix 5 % w/w Cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Efudix cream contains:
Active substance:
5 %w/w Fluorouracil

Excipients:
15 %w/w Stearyl alcohol
11.5 %w/w Propylene glycol (E1520)
0.025 %w/w Methyl parahydroxybenzoate (E218)
0.015 %w/w Propyl parahydroxybenzoate (E216)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream
Smooth, white, opaque 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 arsenic forms; keratoacanthoma, 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 Posology and method of administration

Posology

Adults, including elderly:
Efudix cream is for topical application.

Pre-malignant conditions
The cream should be applied thinly once or twice daily to the lesion; an occlusive dressing is not essential.

Malignant conditions
The cream should be applied once or twice daily under an occlusive dressing where this is applicable. Treatment should be continued until there is marked inflammatory response from the treated area, preferably some erosion in the case of pre-malignant conditions. Severe discomfort may be alleviated by the use of topical steroid cream. The usual treatment for an initial course is 3 to 4 weeks, but this may be prolonged if required. 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.

Children:
In view of the lack of clinical data available, Efudix is not recommended for use in children.

Special population

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

Method of application
The hands should be washed carefully after applying Efudix. Also care should be taken to avoid contact with mucous membranes or the eyes when applying the cream.
The total area of skin being treated with Efudix at any one time should not exceed 500 cm2 (approximately 23 x 23 cm). Larger areas should be treated a section at a time.

4.3 Contraindications

- Known hypersensitivity to fluorouracil or any of the excipients listed in section 6.1
- Co-administration with antiviral nucleoside drugs (e.g. brivudine and analogues)
- Pregnancy or in breast-feeding

4.4 Special warnings and precautions for use

The pattern of normal therapeutic 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 be more severe and include pain, blistering and ulceration (see section 4.8). Occlusive dressing may increase inflammatory reactions of the skin. There is a possibility of increased absorption through ulcerated or inflamed skin (see section 5.2).

Exposure to UV-radiation (e.g. natural sunlight, tanning salon) should be avoided.

Pre-existing subclinical lesions may become apparent following Efudix use.

Any severe skin discomfort during treatment with Efudix may be alleviated by the use of an appropriate topical steroid cream.

When used according to the approved prescribing information Efudix should have minimal effect on healthy skin.

Significant systemic drug toxicity is unlikely via percutaneous absorption of fluorouracil when Efudix is administered as per the approved prescribing information. However, the likelihood of this is increased if the product is used on skin areas in which the barrier function is impaired (e.g. cuts), if the product is applied under an occlusive dressing, and/or in individuals with deficiency in dihydropyrimidine dehydrogenase (DPD), see section 4.8. DPD is a key enzyme involved in metabolising and eliminating fluorouracil. Determination of DPD activity may be considered where systemic drug toxicity is confirmed or suspected. There have been reports of increased toxicity in patients who have reduced activity of the enzyme dihydropyrimidine dehydrogenase. In the event of suspected systemic drug toxicity, Efudix treatment should be stopped.

An interval of at least four weeks should elapse between treatment with brivudine, sorivudine or analogues and subsequent administration of Efudix.

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

4.5 Interaction with other medicinal products and other forms of interaction

Although no significant drug interactions with Efudix have been reported, potential drug interactions are possible as indicated below.

Brivudine, sorivudine and analogues are potent inhibitors of DPD, a fluorouracil metabolising enzyme (see section 4.4). For this reason, concomitant administration of these drugs with Efudix is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Contraception in males and females
Due to the genotoxic potential of fluorouracil (see section 5.3), women of childbearing potential should use effective contraceptive measures while being treated with fluorouracil and for 6 months following completion of treatment.

Men are recommended to use effective contraceptive measures and to not father a child while receiving fluorouracil and for 3 months following completion of treatment.

Pregnancy
There are no adequate data from the use of topical fluorouracil in pregnant women.
Studies in animals have shown that fluorouracil is teratogenic (see section 5.3). The potential risk for humans is unknown, hence Efudix should not be used during pregnancy (see section 4.3).

Women of childbearing potential should not become pregnant during topical fluorouracil therapy. If a pregnancy occurs during treatment the patient should be advised about the risk for the child of adverse effects associated with the treatment and genetic counselling is recommended.

Breast-feeding
No information is available on the excretion of fluorouracil into breast milk.
Studies in animals have shown that fluorouracil is teratogenic (see section 5.3). A risk to the suckling child cannot be excluded, so Efudix should not be used in nursing mothers (see section 4.3). If use during breastfeeding is absolutely necessary, breastfeeding must be discontinued.

Fertility
No clinical data in human are available on the effects of Efudix on fertility.
Experiments in various species revealed an impairment of the fertility and the reproductive performance of systemic 5-Fluorouracil. The reduced systemic exposure to 5-FU following its topical administration will reduce the potential toxicity. The use of topical 5-Fluorouracil may impair female and male fertility. Topical Fluorouracil is not recommended in men attempting to father a child.

4.7 Effects on ability to drive and use machines

It is unlikely that treatment will have any effect on the ability to drive and use machines when used according to the dosage instructions.

4.8 Undesirable effects

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Frequency not known (cannot be estimated from the available data)

Adverse reactions associated with exacerbations of normal pattern of response (see section 4.4) which are related to pharmacological activity of fluorouracil on the skin are the most frequently reported reactions. Allergic type skin reactions and reactions related to systemic drug toxicity are very rarely reported.

Blood and lymphatic system disorders
Very rare: Haematological disorders, associated with systemic drug toxicity, e.g. pancytopenia, neutropenia, thrombocytopenia, leukocytosis

Immune system disorders
Very rare: Allergic conditions (e.g. hypersensitivity and Type IV hypersensitivity)

Nervous system disorders
Frequency not known: Dysgeusia, headache, dizziness

Eye disorders
Frequency not known: Conjunctival irritation, keratitis, lacrimation increased

Gastrointestinal disorders
Very rare: Hemorrhagic diarrhoea, diarrhoea, vomiting, abdominal pain, stomatitis, associated with systemic drug toxicity
Frequency not known: Nausea

Skin and subcutaneous tissue disorders
Very rare: Erythema multiforme, pain of skin, skin reactions (e.g. urticaria, pruritus, rash (usually local but also generalised if associated with systemic drug toxicity)), dermatitis, contact dermatitis, eczema, application site vesicles, skin irritation, erythema, skin burning sensation, skin exfoliation, skin swelling, skin ulcer, photosensitivity reaction, alopecia
See also normal pattern of response in section 4.4.

General disorders and administration site conditions
Very rare: Pyrexia, chills and mucosal inflammation, associated with systemic drug toxicity
Frequency not known: Application site haemorrhage

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance, Website: www.hpra.ie.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, antimetabolites
ATC Code: L01BC02

Efudix is a topical cytostatic preparation which exerts a beneficial therapeutic effect on neoplastic and pre-neoplastic skin lesions while having less effect on normal cells. The pattern of response follows this sequence, erythema, vesiculation, erosion, ulceration, necrosis and epithelisation. The active ingredient fluorouracil is a fluorinated analogue or uracil, a component of RNA.Fluorouracil interferes with DNA and RNA synthesis at the nucleotide level.

5.2 Pharmacokinetic properties

Fluorouracil is minimally systemically absorbed when applied topically to intact skin. When applied to skin, the skin's barrier function is pathologically altered (e.g., as in ulceration), and the absorption rate can increase to 60 %. In patients with AK, 2.4 - 6 % of the topical dose was absorbed systemically. Similarly, under occlusion, significantly more fluorouracil is absorbed.

Fluorouracil may be metabolised by catabolic or anabolic routes which are similar to that of endogenous uracil.

5.3 Preclinical safety data

5-fluorouracil is genotoxic *in vitro* and *in vivo*.
The systemic administration of high doses of 5-fluorouracil indicates the potential for teratogenic or embryotoxic effects in mice, rats and hamsters (including malformations in the nervous system, palate, skeleton, tails, limbs). Embryotoxic effects

(small fetus, resorption) are also observed in monkeys treated with 5-fluorouracil. 5-fluorouracil is classified as possible human teratogen. 5-fluorouracil crosses the placenta in rats.
Fertility studies with systemic 5-FU show a decrease in adult male fertility and a decrease in pregnancy rates in female rodents.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Stearyl alcohol
White soft paraffin
Polysorbate 60
Propylene glycol (E1520)
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

Shelf life after first opening the immediate packaging: 90 days for the 20g and 40g tubes.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Efudix cream is packed in 20g and 40g aluminium membrane-sealed tubes, coated inside with an epoxy phenolic resin derivative lacquer. The tube is closed with a polypropylene PP membrane piercing cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Efudix is for topical use only and care should be taken to avoid contact with mucous membranes or the eyes. The hands should be washed carefully after applying the cream.

7 MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23355/026/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 1979

Date of last renewal: 1st April 2009

10 DATE OF REVISION OF THE TEXT

March 2026