# C o m p a n y  C o r e  D a t a  S h e e t

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| Product | **Fluorouracil cream** Date: 22-Jan-2016 |
| CTD-Code: | N/A (to be used for preparation of 1.3.1 / to be attached to 5.3.6) |
| Title: | **Efudix®**<br>**Fluorouracil**<br>**50 mg/g cream** |
| Product Names: | **Efudix®** |
| Version: | 03 |
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| Reviewed by: | Dr. Wendelin Krause, Dr. Ina Feldkämper |
| Released by: | Manfred Singer |
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Document History

| Version | Change/References | Valid from |
|---|---|---|
| 01 | First CCDS Version | 22.12.2011 |
| 02 | • Formatting changes in section 4.2<br>• Outcome of the PSUSA/00010000/201412 procedure: Update of section 4.8 to include the adverse reactions headache, dizziness and nausea with a frequency unknown; update of section 4.4 to include warnings on the need to avoid exposure to UV-radiation and occlusive dressing; update of section 4.7 with regards to the effect on the ability to drive and use machines. Section 5.1 is reworded for clarity.<br>• Update of section 4.6 to include additional clinical data<br>• Update of section 5.2 to include additional clinical data | 18.12.2015 |
| 03 | • Correction in section 4.6. | 22.01.2016 |

## 1. NAME OF THE MEDICINAL PRODUCT

Name: Efudix 50 mg/g cream

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Fluorouracil (INN)

### 2.1 General description

See local labelling

### 2.2 Qualitative and quantitative composition

Efudix cream contains 50 mg/g fluorouracil.

*The way of writing may differ in some countries.*

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

White, opaque cream
Information might differ in some countries.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

The following are representative indications. Locally approved indications may differ.

Efudix is used for the topical treatment of superficial pre-malignant and malignant skin lesions; keratoses including senile, actinic and arsenical forms; keratoacanthoma; Bowen's disease; erythroplasia of Queyrat; superficial basal-cell carcinoma; acuminated condyloma. 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

The text in this section represents representative dosage recommendations; locally approved dosage recommendations may differ.

<u>Posology</u>

*Adults*

Efudix cream is for topical application.

*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.

*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 $cm^2$ (approximately 23 x 23 cm). Larger areas should be treated a section at a time.

## 4.3 Contraindications

Efudix is contraindicated for patients with known hypersensitivity to fluorouracil or any of the excipients listed in section 6.1. Coadministration of Efudix with antiviral nucleoside drugs (e.g. brivudine and analogues) may lead to a substantial increase in plasma levels of fluorouracil and associated toxicity and is contraindicated. Brivudine and analogues are potent inhibitors of DPD, a fluorouracil metabolising enzyme (see section 4.4 and 4.5)
Use of Efudix during pregnancy and in breast-feeding mothers is contraindicated.

## 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 be more severe and include pain, blistering and ulceration (see section 4.8). Occlusive dressing may increase inflammatory reactions of the skin.
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 excessively, especially on skin areas in which the barrier function is impaired (e.g. cuts) 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/deficiency of the enzyme dihydropyrimidine dehydrogenase. In the event of suspected systemic drug toxicity, consideration should be given to stopping Efudix treatment.
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

<u>Pregnancy</u>

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)

Nerveous system disorder

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

### 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.

### 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

There is evidence from animal work that fluorouracil is teratogenic.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

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

### 6.2 Incompatibilities

None known.

### 6.3 Shelf life

The recommended shelf life of Efudix cream is 60 months.
Shelf life after first opening the immediate packaging:
28 days for 5g tube, 90 days for the 20g and 40g tubes.

### 6.4 Special precautions for storage

See local labelling

### 6.5 Nature and contents of container

See local labelling

### 6.6 Special precautions for disposal

See local labelling

## 7. MARKETING AUTHORISATION HOLDER

See local labelling

## 8. MARKETING AUTHORISATION NUMBER(S)

See local labelling

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

See local labelling