SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Efudix Cream

2. Qualitative and Quantitative Composition

Efudix cream contains 5% w/w fluorouracil.

3. Pharmaceutical Form

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 arsenical 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

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.

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

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

4.3 Contraindications
Efudix is contraindicated in patients with known hypersensitivity to fluorouracil or any of the excipients in Efudix Cream. Coadministration of Efudix with antiviral nucleoside drugs (e.g. brivudine, sorivudine and their analogues) may lead to a substantial increase in plasma levels of fluorouracil and associated toxicity and is contraindicated (see section 4.4). 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 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.

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 Pregnancy and lactation
There are no adequate data from the use of 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 and in nursing mothers (see section 4.3).

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) 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.

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, increased lacrimation.

Skin and subcutaneous tissue disorders
Very rare: Pruritus, urticaria, rash (usually local but also generalised if associated with systemic drug toxicity); erythemas including erythema multiforme; dermal and epidermal conditions (such as skin burning sensation, skin exfoliation, skin swelling); skin and subcutaneous skin ulcerations; dermatitis and eczema conditions (such as contact dermatitis, skin irritation); blisters, alopecia and skin pain.

Exposure to sunlight may increase the intensity of the reaction.

See also normal pattern of response in section 4.4.

**Blood and lymphatic system disorders**

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

**Gastrointestinal disorders**

Very rare: Diarrhoea haemorrhagic, diarrhoea, vomiting, abdominal pain, stomatitis, associated with systemic drug toxicity.

Frequency not known: Nausea.

**General disorders and administration site conditions**

Very rare: Pyrexia, chills and mucosal inflammation, associated with systemic drug toxicity.

**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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

### 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.
5.1 **Pharmacodynamic properties**
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**
Animal studies have shown that after topical application of fluorouracil, less than 10% is systemically absorbed. This 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: 90 days for the 20g and 40g tubes.

6.4. **Special Precautions for Storage**

*Storage*
The recommended maximum storage temperature for Efudix cream is 30°C.

_Dilution_
Efudix cream should not be diluted.

6.5 **Nature and contents of container**
Efudix cream is supplied in a 20g and a 40g aluminium tube with a plastic screw cap.
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
Any unused product or waste material should be disposed of in accordance with local requirements.

7. **Marketing Authorisation Holder**
Meda Pharmaceuticals Ltd
Skyway House
Parsonage Road
Takeley
Bishop’s Stortford
CM22 6PU

8. **MARKETING AUTHORISATION NUMBER(S)**
PL 15142/0003

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
22/07/2008

10 **DATE OF REVISION OF THE TEXT**