Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Efudix Cream 5%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Efudix Cream 5% contains 5% w/w fluorouracil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, opaque cream.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antineoplastic agent to treat actinic keratosis multiple and superfacial basal cell carcinoma.

4.2 Posology and method of administration

Efudix Cream 5% 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 Cream 5% is indicated are common in the elderly. No special precautions are necessary.

Children

In view of the lack of clinical data available, Efudix Cream 5% is not recommended for use in children.

4.3 Contraindications

Efudix Cream 5% is contraindicated in patients with known hypersensitivity to fluorouracil or any of the excipients listed in section 6.1.

Coadministration of Efudix Cream 5% 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 Cream 5% 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 Cream 5%. 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 Cream 5% 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.

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 Cream 5% 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.

Instruct patients not to smoke or go near naked flames - risk of severe burns. Fabric (clothing, bedding, dressings etc) that has been in contact with this product burns more easily and is a serious fire hazard. Washing clothing and bedding may reduce product build-up but not totally remove it.

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

Pre-existing subclinical lesions may become apparent following Efudix Cream 5% use.

Any severe skin discomfort during treatment with Efudix Cream 5% may be alleviated by the use of an appropriate topical steroid cream.

When used according to the approved prescribing information Efudix Cream 5% 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). 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 Cream 5%% 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 Cream 5%.

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 Cream 5% 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 Cream 5% Cream 5% is contraindicated (see section 4.3)

4.6 Fertility, pregnancy and lactation

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 Cream 5% Cream 5% should not be used during pregnancy (see section 4.3)

Women of childbearing potential should not become pregnant during topical fluorouracil therapy and should use effective method of contraception during treatment with 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 the fluorouracil is teratogenic (see section 5.3). A risk to the suckling child cannot be excluded, so Efudix Cream 5% 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 humans are available on the effects of topical fluorouracil on fertility.
Experiments in various species revealed an impairment of the fertility and 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.

Immune system disorders

Very rare: Allergic conditions (e.g. hypersensitivity and allergic reactions).

Nervous system disorders

Frequency not known: Dysgeusia, headache, dizziness.

Eye disorders

Frequency not known: Conjunctival irritation, keratitis, increased lacrimation.

Gastrointestinal disorders

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

Frequency not known: Nausea.

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, and alopecia.

Exposure to sunlight may increase the intensity of the reaction.

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 authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

If Efudix Cream 5% 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: Pyrimidine analogues, ATC code: L01BC02

Efudix Cream 5% 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 the 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.

Fluorouracilmay 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

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

6.2 Incompatibilities

None known.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Shelf life after first opening the immediate packaging: 90 days for the 20g tube.

6.4 Special precautions for storage

Storage
The recommended maximum storage temperature for Efudix Cream 5% is 30 °C.

Dilution
Efudix Cream 5% should not be diluted.

6.5 Nature and contents of container

Efudix Cream 5% is supplied in a 20 g aluminium tube with a plastic screw cap.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

ICN Polfa Rzeszow, Poland

2 Przemyslowa ST., 35-959 Rzeszow, Poland

8. MARKETING AUTHORISATION NUMBER

062 40 21478

9. LICENSE HOLDER

MegaPharm Ltd. P.O. Box 519, Hod HaSharon 4510501, Israel

10. REVIEWED ON

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