1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Efudix (50 mg/g, ointment)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Efudix Ointment contains fluorouracil 50 mg/g

Preservative: Contains 0,025 % methylhydroxybenzoate and 0,015 % propylhydroxybenzoate.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White to almost white, homogenous, smooth, opaque ointment.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Solar and senile keratoses, Bowen's disease, single or multiple superficial basal-cell carcinomas; premalignant conditions and superficial basal-cell carcinomas in radiation damaged skin.
- Nodular basal-cell and squamous-cell carcinoma do not respond to Efudix treatment.

4.2 Posology and method of administration

Posology

Efudix should only be used under strict medical supervision.

In cases of senile and solar keratoses a thin layer of the ointment is applied to the affected areas once or twice daily, generally without a dressing.

In the treatment of other conditions (including keratosis palmaris) a fresh occlusive dressing should be applied daily.

Treatment should be continued up to the ulceration stage in the case of basal-cell carcinoma and up to the erosion stage in the case of other types of lesions.

Duration of therapy is usually 3 – 4 weeks, but it may prove necessary to exceed this on occasion.

Special populations

Elderly population:

No dosage adjustment is required for this population.

Paediatric population

No data are available

Method of administration

- Topical 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 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.
- Efudix should not be used during pregnancy and breastfeeding, nor where pregnancy cannot be excluded *(see section 4.6 Fertility, pregnancy and lactation).*
- Coadministration of Efudix with antiviral nucleoside medicines (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 Special warnings and precautions for use and 4.5 Interaction with other medicinal products and other forms of interaction).*

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 Undesirable effects*).
- 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 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 medicine 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 medicine 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 medicines and other forms of Interaction

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

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

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.

Pregnancy

Efudix should not be used during pregnancy *(see section 4.3 Contraindications).*

Breastfeeding

Efudix should not be used during breastfeeding *(see section 4.3 Contraindications).*

Fertility

No data available. 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

Efudix is unlikely to affect mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects

a. Summary of the safety profile

Efudix is well tolerated.

Adverse reactions associated with exacerbations of normal pattern of response *(see section 4.4 Special warnings and precautiuons for use)* 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.

The healthy skin surrounding the area being treated may occasionally become reddened, but soon resumes its normal colour on cessation of treatment.

Tabulated list of adverse reactions

Body System	**Undesirable effect**		
	Rare	Very rare	Frequency not known
Blood and the lymphatic system disorders:		Haematological disorders, associated with systemic drug toxicity, e.g. pancytopenia, neutropenia, thrombocytopenia.	
Immune system disorders:		Allergic conditions (e.g. hypersensitivity and allergic reactions)	
Nervous system disorders:			Dysgeusia, headache, dizziness.
Eye disorders:			Conjunctival irritation, keratitis, increased lacrimation
Gastrointestinal disorders:		Diarrhoea haemorrhagic, diarrhoea, vomiting, abdominal pain, stomatitis, associated with systemic drug toxicity	Nausea
Skin and subcutaneo		Pruritus, urticaria, rash (usually local but also	

us tissue disorders:		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 administrative site conditions:		Pyrexia, chills and mucosal inflammation, associated with systemic drug toxicity	Application site haemorrhage

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 to SAHPRA via the “Report Drug Reaction Process”, found online under SAHPRA’s safety publications: https://www.sahpra.org.za/

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity *(see section 4.8 Undesirable effects).*

- Systemic symptoms of overdosage have to date not been reported or observed because of the negligible cutaneous absorption. Local signs may range from mild to severe skin irritation (erythema to ulceration).
- Treatment consists of withdrawal of drug and supportive measures to promote healing which may include the application of an antihistaminic or steroid ointment and possibly a systemic antibacterial agent to prevent local infection in ulcerated areas.
- 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

A: 13.8 Keratolytics.

Pharmacotherapeutic group: Pyrimidine analogues, ATC code: L01BC02

Efudix, a cytostatically active preparation exerts a beneficial therapeutic effect on neoplastic and pre-neoplastic skin lesions. When the preparation is applied to such lesions, the action of fluorouracil produces the following pattern of response: first erythema, then usually vesiculation, erosion, ulceration, necrosis and epithelialization

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

Not applicable.

6.3 Shelf life

60 months.

After opening:

90 days

6.4 Special precautions for storage

Store at or below 30 °C.

Store in the original package/container.

6.5 Nature and contents of container

Efudix is packed in 20 g aluminium membrane-sealed tube coated inside with Valspar J3092 lacquer. The tube is closed with a polypropylene (PP) membrane-piercing caps.

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

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

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street,

Isando,

Gauteng,

1601

8 REGISTRATION NUMBER(S)

D/13.8/122

NAMIBIA NS2
04/13.8/105

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 November 1994

10 DATE OF REVISION OF TEXT

1 September 2021