HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
21 OCTOBER 2020
The legally binding text is the original French opinion version

5-fluorouracil
TOLAK 40 mg/g cream

First assessment

Key points

Favourable opinion for reimbursement in the topical treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade I and II) of the face, ears and/or scalp in adults.

What therapeutic improvement ?

No therapeutic improvement compared to EFUDIX 5 % (5-fluorouracil) cream.

Role in the care pathway ?

The objective of treatment is to destroy the lesions. Regular monitoring is initiated to detect recurrences. The choice of treatment depends on the seriousness of the lesions, the location, contraindications and the prescriber's habits.

If cutaneous squamous cell carcinoma is suspected, pathology testing of the lesions is necessary before they are treated.

Cryotherapy is the reference treatment in the event of a small number of lesions (≤ 5 lesions). This aggressive, painful method cannot be used in the event of multiple lesions.

Dynamic phototherapy using a sensitising agent is an alternative to cryotherapy, particularly in the event of multiple lesions, of mild to moderate severity (non-hyperkeratotic), and located on the face and/or alopecic scalp, since this enables treatment of all the lesions in a single session, with a good

healing result. The sensitising agents with an MA in this indication are methyl aminolevulinate hydrochloride (METVIXIA cream) and 5-aminolevulinic acid (EFFALA medicated plaster and AMELUZ gel, not marketed).
In this clinical situation, METVIXIA is an alternative to first-line cryotherapy.

The other alternatives to cryotherapy in the event of multiple lesions are 5-fluorouracil (5-FU) as a topical treatment (EFUDIX 5 %), imiquimod (ALDARA) and mechanical dermabrasion. Diclofenac (SOLARAZE) is not recommended in the absence of valid demonstration of its efficacy compared to 5-FU and cryotherapy (Opinion of 16/12/2009). CO_2 laser treatment and electrocoagulation and curettage can also be treatment options.

When the lesions are large, surgery is sometimes used, possibly followed by a skin graft if the area to be treated is extensive.

Role of the medicinal product in the care pathway

TOLAK 40 mg/g cream (5-FU, 4 %, 1 application/day) has demonstrated its superiority compared to placebo in terms of the complete disappearance of lesions, with a substantial effect size. However, its non-inferiority compared to the other medicinal product containing the same active substance currently used (EFUDIX 5 % cream, 5-FU 5 %, 2 applications/day) has not been demonstrated. Furthermore, a better tolerability of TOLAK compared to that of EFUDIX has not been demonstrated.

No data are available having compared TOLAK 40 mg/g (5-FU) cream to the other available alternatives.

The Transparency Committee considers that TOLAK 40 mg/g (5-FU) cream is liable to be an alternative to cryotherapy in the event of multiple lesions of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade I and II) of the face, ears and/or scalp in adults. However, its role in the care pathway cannot be specified compared to the other alternatives available, including 5-FU 5 % (in the absence of demonstration of its non-inferiority compared to this treatment).

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers :

Clinical benefit

◗ Actinic keratosis lesions are skin lesions that occur on sun-exposed areas, usually in the elderly. They are often multiple lesions that, in the absence of effective treatment, can progress to become skin cancers.

◗ TOLAK 40 mg/g (5-FU) cream (1 application/day) is a curative treatment.

◗ The efficacy of 5-FU 4 % (1 application/day) has been demonstrated versus placebo, its non-inferiority to 5-FU 5 % (2 applications/d) has not been demonstrated (see "Summary of discussions" paragraph of the opinion). In all the studies, the adverse effects were mainly transient reactions at the application site.
Consequently, the efficacy/adverse effects ratio is low.

◗ There are medicinal therapeutic alternatives (including EFUDIX 5 % cream containing 5-FU at a concentration of 5 %) and non-medicinal ones.

◗ The Transparency Committee considers that TOLAK 40 mg/g (5-FU) cream is liable to be an alternative to cryotherapy in the event of multiple lesions of non-hyperkeratotic, non-hypertrophic actinic keratosis (Olsen grade I and II) of the face, ears and/or scalp in adults. However, its role in the care pathway cannot be specified compared to the other alternatives available, including 5-FU 5 % (in the absence of demonstration of its non-inferiority compared to this treatment).

Public health impact :
Considering :
- the seriousness of the disease insofar as it can progress to become a skin cancer in the absence of effective treatment,
- its prevalence, which increases with age,
- the medical need currently met by various medicinal treatments, including EFUDIX 5 % (5-FU) cream and non-medicinal treatments,
- the absence of data on the quality of life of patients treated with TOLAK 40 mg/g cream
- the lack of any demonstrated impact on the organisation of care,
- the very partial response to the identified need,

TOLAK 40 mg/g cream is unlikely to have an additional impact on public health.

Given all these elements, the Committee deems that the clinical benefit of TOLAK 40 mg/g (5-fluorouracil) cream is low in the MA indication.
The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the marketing authorisation indication and dosages.

- **Recommended reimbursement rate : 15 %**

Clinical Added Value

Considering :
- **its demonstrated superiority versus placebo in terms of the complete disappearance of lesions (primary endpoint) with a substantial effect size,**
- **the absence of demonstration of its non-inferiority compared to the other medicinal product containing the same active substance, 5-fluorouracil (5-FU) (EFUDIX 5 % cream), in terms of the complete disappearance of lesions (primary endpoint) in the study implementation conditions,**
- **the absence of robust demonstration of a better safety compared to that of 5-FU 5 % whereas it was expected given the reduction in the number of daily applications (1 with TOLAK versus 2 with EFUDIX) and the reduction in 5-FU concentration (4% versus 5 %),**

the Transparency Committee considers that TOLAK 40 mg/g (5-fluorouracil) cream provides no clinical added value (CAV V) compared to EFUDIX 5 % (5-FU) cream.