HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

6 March 2013

EFFALA 8 mg, medicated plaster

B/4 sachets (CIP code: 34009 397 996 4 3)
B/8 sachets (CIP code: 34009 387 997 0 4)

Applicant: SPIRIG PHARMA

INN	5-Aminolevulinic acid
ATC Code (2011)	L01XD (sensitizers used in photodynamic / radiation therapy)
Reason for the request	**Inclusion**
List(s) concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication(s) concerned	**"Single-use device for the treatment of mild actinic keratoses (AK) of the face and scalp (bald/hairless areas) not exceeding 1.8 cm in diameter."**

Actual Benefit	**Substantial**
Improvement in Actual Benefit	**EFFALA 8 mg, medicated plaster, offers a minor improvement in actual benefit (IAB IV) in terms of efficacy in comparison with cryotherapy.**
Therapeutic use	**This proprietary medicinal product may be a first-line treatment for multiple fine and non-pigmented keratosis lesions of the face and scalp not exceeding 1.8 cm in diameter, as an alternative to cryotherapy.**
Recommendations	**The Committee is requesting that a study be carried out whose objectives will be to describe:** **- the population treated with EFFALA (indication, clinical picture, size and severity of the lesions, single or multiple lesions, recurrence, etc.),** **- its conditions of use (compliance with the indication, dosages, treatment frequency and duration, repeat sessions, combined treatments, etc.) and the treatment's place in the management strategy,** **- patients' long-term clinical course (disappearance of lesions, recurrence after 18 months), in particular in the event of withdrawal** **- safety.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation date (procedure)	15/02/2010 (decentralised procedure)
Prescribing and dispensing conditions / special status	List I

ATC Classification	2011	
	L	Antineoplastic and immunomodulating agents
	L01	Antineoplastic agents
	L01X	Other antineoplastic agents
	L01XD	Sensitizers used in photodynamic / radiation therapy

02 BACKGROUND

This opinion concerns a request for inclusion on the National Health Insurance list and on the list for hospital use of a new proprietary medicinal product based on 5-aminolevulinic acid, a photosensitizing agent indicated in the treatment by photodynamic therapy of mild actinic keratoses of the face and scalp.

There is another proprietary medicinal product that can be used for treatment by photodynamic therapy, METVIXIA 168 mg/g containing methyl aminolevulinate hydrochloride (closely related to 5-aminolevulinic acid). EFFALA is a plaster which differs, therefore, from METVIXIA, whose pharmaceutical form is a cream.
In its opinion of 28 March 2007, the Committee considered that the actual benefit of METVIXIA was substantial, but that this proprietary medicinal product did not offer any improvement in actual benefit (level V) compared to cryotherapy in the treatment of fine or non-hyperkeratotic and non-pigmented facial and scalp actinic keratoses and constituted an additional therapeutic resource.

The Committee had requested that a study be carried out whose objectives were to describe:
- the population treated with METVIXIA (indication, clinical picture, size of the lesions, single or multiple lesions, histology, recurrence, etc.),
- its conditions of use (dosages, treatment frequency and duration, combined treatments, place in the management strategy, etc.),
- the availability of any histological control (at the time of diagnosis or follow-up),
- the patients' clinical course,
- the impact of safety on continuation with the treatment.

03 THERAPEUTIC INDICATION(S)

“Single-use device for the treatment of mild actinic keratoses (AK) of the face and scalp (bald/hairless areas) with a maximum diameter of 1.8 cm.”

04 DOSAGE

“Adults (including elderly subjects):
For the treatment of AK with single-session photodynamic therapy (PDT), up to a maximum of six EFFALA plasters may be used per patient (on six different lesions) during the course of a single treatment session. If the EFFALA plaster does not stick properly to the lesions, it can be fixed with an adhesive strip.

After four hours, remove the EFFALA plaster(s) and expose the lesion(s) to red light with a narrow-band red light source with a spectrum of 630 ± 3 nm and a total light dose of 37 J/cm^2 at the lesion surface. Only lamps stamped EC are authorised for use. Moreover, these should be equipped with the necessary filters and/or reflecting mirrors to minimize exposure to heat, blue light and UV radiation. It is important to check that the patient is receiving the correct light dose. The light dose is determined by factors such as the size of the light field, the distance between lamp and skin surface, and the illumination time. These factors vary with the type of lamp used. It is vitally important therefore that the lamp be used in accordance with the appropriate user manual. Both patient and operator should adhere to safety instructions provided with the light source. Throughout illumination the patient and operator should wear protective goggles that correspond to the lamp spectrum.

Untreated healthy skin around the lesion does not need any special protection during illumination.
Lesion response will be assessed three months after the illumination session; if the treated area is not lesion-free at 3 months, the use of alternative treatments could be considered.

Children and adolescents:
There is no experience of treating children below the age of 18 years.”

05 THERAPEUTIC NEED [1, 2, 3, 4, 5, 6, 7]

Actinic keratosis is a skin condition associated principally with exposure to ultraviolet rays. The appearance of these skin lesions can therefore be prevented by avoiding exposure to ultraviolet rays (whether natural or artificial) or other physical or chemical triggers (ionising radiation).
The aim of the treatment is to destroy the lesions, followed by regular post-treatment monitoring to screen for any recurrences. The available therapies are: surgery, cryotherapy (removal with nitrogen), radiotherapy, electrocoagulation and curettage, and dermabrasion, CO_2 laser, topical cytostatics (5-FU and imiquimod), topical diclofenac (not reimbursable in actinic keratosis), and photodynamic therapy using methyl aminolevulinate hydrochloride-containing METVIXIA cream as the sensitizing agent.

When the lesions are few in number, the reference treatment is cryotherapy. This treatment is simple, quick and requires no special equipment.
In case of doubt with squamous cell carcinoma, a biopsy should be carried out prior to cryotherapy.
Photodynamic therapy using methyl aminolevulinate hydrochloride (METVIXIA cream) is an alternative to cryotherapy, especially in cases of multiple lesions of the face and/or scalp (in particular if the patient has alopecia) because it enables all the lesions to be treated at once in a single session with good healing outcome. It only proved of benefit in superficial and non-pigmented lesions.

When lesions are large, surgery is sometimes used; occasionally followed by a graft if the area to be treated is extensive.
With multiple lesions, topical 5-FU, imiquimod, and mechanical dermabrasion are used. CO_2 laser and electrocoagulation and curettage may also offer treatment options.

[1] Dubertret et al. Thérapeutique dermatologique. Médecine Sciences Flamarion (2001) www.therapeutique-dermatologique.org
[2] Skin Cancer (PDQ®): Treatment Health Professional Version. National Cancer Institute (2006). www.cancer.gov
[3] Saurat J.-H. et al. Dermatologie et infections sexuellement transmissibles (MASSON publication, 4th edition)
[4] de Berker D. et al. on behalf of the British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Guidelines for the management of actinic keratoses. *British Journal of Dermatology* 2007;156:222-30
[5] Cox N.H. et al. on behalf of the British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Guidelines for management of Bowen's disease: 2006 update. *British Journal of Dermatology* 2007;156:11-21
[6] Morton C.A. et al. Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group (British Association of Dermatologists). *British Journal of Dermatology* 2002;146:552-67
[7] National Institute for Health and Clinical Excellence. Photodynamic therapy for non-melanoma skin tumours (including premalignant and primary non-metastatic skin lesions). Understanding NICE guidance – information for people considering the procedure, and for the public. February 2006. www.nice.org.uk/page.aspx?o=IP_272&c=cancer

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

NAME (INN) *Company*	Same TC* yes / no	Indications	Date of last opinion	Actual benefit	Improvement in Actual Benefit (wording)	Reimbursement Yes / no
METVIXIA Methyl aminolevulinate hydrochloride *Galderma International*	yes	**Treatment of fine or non-hyperkeratotic and non-pigmented actinic keratoses (AK) of the face and scalp.** Treatment of basal-cell carcinomas […] and non-pigmented intraepidermal carcinomas (Bowen's disease) in immunocompetent subjects, when surgery is not an option. Lesions should previously be confirmed by biopsy and their healing should be monitored for progress […].	27/03/2007	Substantial	IAB V compared to cryotherapy in the treatment of fine or non-hyperkeratotic and non-pigmented facial and scalp actinic keratosis but does constitute an additional treatment resource.	Yes
EFUFIX 5-fluoro-uracil *Meda Pharma*	No	**Pre-epitheliomatous keratosis.** Bowen's disease […] and genital warts.	22/09/2010	Substantial	-	Yes
ALDARA Imiquimod *Meda Pharma*	No	**Clinically typical, non-hypertrophic, non-hyperkeratotic actinic keratoses of the face or scalp in immunocompetent adults, when the size or number of lesions limits the efficacy and/or safety of cryotherapy and if other topical treatments are either contraindicated or less appropriate.** External genital and peri-anal warts (condyloma acuminata) in adults, and small superficial basal cell carcinomas (BCCs) in adults.	10/03/2010	Substantial	IAB V in the treatment of superficial facial or scalp actinic keratoses in adults, but does constitute an additional treatment resource. (26/11/2008)	Yes

*therapeutic category

06.2 Other health technologies

Other non-medicinal treatments are: Cryotherapy (reference treatment for actinic keratosis), surgery, radiotherapy, CO_2 laser, and electrocoagulation and curettage.

◗ Conclusion

The most relevant comparators are cryotherapy, which remains the reference treatment for superficial actinic keratoses, and METVIXIA.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSED	
	YES/NO If not, why not	Population(s) That of the Marketing Authorisation or restricted
Europe (decentralised procedure: Austria, Denmark, Finland, Germany, Ireland, Italy, Norway, Poland, Spain, Sweden)	No, except in Sweden, where EFFALA is reimbursable but not yet marketed	Treatment of mild actinic keratoses (AK) of the face and scalp (bald/hairless areas) with a maximum diameter of 1.8 cm.

08 ANALYSIS OF AVAILABLE DATA

The Applicant's request is based primarily on:
- a randomised, double-blind, phase III study versus placebo. (AK03)
- a randomised, double-blind, phase III study versus cryotherapy and placebo (PDT) (AK04).

The preliminary studies (listed below), which allowed the rules for using PDT to be adjusted by 5-aminolevulinic acid in the phase III studies, will not be presented:
- open study designed to measure the effect and duration of application of the EFFALA plaster on the fluorescence emitted by protoporphyrine in AK (AK01),
- randomised observer-blinded study with the aim of determining the optimal duration of application of EFFALA (AK02),
- open pharmacokinetics study in 12 patients.

There are no clinical studies comparing EFFALA with METVIXIA, its closest comparator. In the absence of any direct comparison between these two medicinal products, the results of the indirect comparison study were supplied by the Applicant. In this study, the following treatments were compared:
- METVIXIA in one PDT session
- METVIXIA in two PDT sessions 1 week apart
- EFFALA in one PDT session
- Cryotherapy

However, in the absence of any reports or publications specifying the conditions under which this study was carried out, it is not possible to arrive at any firm conclusion regarding the results of this indirect comparison.

08.1 Efficacy

Study versus placebo: Study AK03

This randomised, double-blind phase III study compared EFFALA with placebo for the treatment of mild to moderate actinic keratoses of the head and face.[8]

Inclusion criteria:
- age ≥ 18 years
- mild (superficial, non-hyperkeratotic, not rough, pinkish spots) to moderate (rough, hyperkeratotic, pinkish to red papules or plaques of variable induration) actinic keratosis lesions of the head and/or face, with at least three well-separated lesions (≥ 1 cm between the various lesions).
- lesions not exceeding 1.8 cm in diameter and with clearly-defined margins.
- phototype I to IV, according to Fitzpatrick's classification.[9]

[8] Only mild actinic keratosis lesions with a max. diameter of 1.8 cm were included in the wording of the indication in the Marketing Authorisation.

[9] The Fitzpatrick classification recognizes 7 phototypes:

Phototype	Colour of non-photoexposed skin	Minimum erythema-inducing dose in MJ/cm^2	UV sensitivity	Sunburn / Tanning
I	Pale white	15-30	Very sensitive	Always burns, never tans
II	White	25-40	Very sensitive	Usually burns, tans with difficulty
III	White to olive	30-50	Sensitive	Sometimes mild burn, tans lightly and uniformly (light brown)
IV	Light brown	40-60	Moderately sensitive	Rarely burns, tans with ease (moderate brown)
V	Dark brown	60-90	Very slightly sensitive	Very rarely burns (dark brown)
VI	Very dark brown/Black	90-150	Not sensitive or hardly sensitive at all	Never burns (black)

Treatment groups:
Patients were treated with one photodynamic therapy session with EFFALA or one placebo plaster. The plaster was applied to each lesion for 4 hours. After its removal, the area was illuminated with red light at a dose of 37 J/cm^2 and a wavelength of 630 ± 32 nm.

Primary efficacy endpoint: percentage of lesions clinically eliminated after 3 months.

Among the secondary endpoints:
- percentage of lesions that have clinically completely disappeared after 12 months;
- percentage of patients in whom all lesions have clinically completely disappeared after 3 months;
- percentage of patients in whom all lesions have clinically completely disappeared after 12 months.

Results:
A total of 103 patients were included, of whom 69 in the EFFALA group and 34 in the placebo group. The results were analysed in the intention-to-treat population.

The patients, with a mean age of 70.7 years, were mostly men (82%). They were light-skinned, of phototype I or II, in 92% of cases.
The total number of lesions was 384 in the EFFALA group and 179 in the placebo group. They were confined for the most part to the forehead (52%), scalp (26%), and cheeks (12%).
They were benign in 44% of cases and moderate in 56% of cases.
Their maximum diameter, on average, was 9.68 mm.

Primary efficacy endpoint:
After 3 months, the percentage of lesions that had clinically disappeared was greater in the EFFALA group than in the placebo group: 82% of the lesions versus 19% ($p < 0.0001$).

Secondary endpoints:
After 3 months, the percentage of patients in whom all the lesions had clinically disappeared was greater in the EFFALA group than in the placebo group: 62% of patients versus 6% ($p < 0.001$).

After 12 months, the percentages of lesions that had clinically completely disappeared and of patients in whom all the lesions had clinically completely disappeared fell in both groups, though EFFALA was superior to placebo:
- 63% of lesions clinically disappeared versus 9% ($p < 0.0001$)
- 32% of patients with lesions that had all clinically disappeared versus 0% ($p < 0.001$).

Study versus cryotherapy and placebo: study AK04
This randomised, double-blind, phase III study compared EFFALA with cryotherapy and placebo for the treatment of mild to moderate actinic keratoses of the head and face.

Inclusion criteria:
- age ≥ 18 years
- mild to moderate actinic keratosis of the head and/or face with at least three well-separated lesions (≥ 1 cm between the various lesions)
- lesions not exceeding 1.8 cm in diameter and with clearly-defined margins
- phototype I to IV according to Fitzpatrick's classification.

Treatment groups:
- PDT with EFFALA
- Cryotherapy
- PDT with placebo (plaster)

The EFFALA or placebo plaster was applied to every lesion for 4 hours. After removal of the plaster, the area was illuminated with red light at a dose of 37 J/cm^2 and a wavelength of 630 ± 32 nm.

Cryotherapy was administered using a vaporization procedure with freeze-thaw times of 5 to 10 seconds following the formation of an iceball.

Primary efficacy endpoint: percentage of lesions that had clinically disappeared after 3 months.

Among the secondary endpoints:
- percentage of lesions that had clinically completely disappeared after 12 months
- percentage of patients in whom all lesions had clinically disappeared after 3 months
- percentage of patients in whom all lesions had clinically completely disappeared after 12 months
- aesthetic appearance of the eliminated lesions.

Results:
A total of 346 patients were included, of whom 148 were in the EFFALA group, 149 in the cryotherapy group, and 49 in the placebo group.
The results were analysed in the intention-to-treat population.

The principal characteristics of the patients, similar to those of patients in study AK03, are shown in Table 1.

Table 1: Patient characteristics (study AK04)

Characteristic	**EFFALA (n = 148)**	**Cryotherapy (n = 149)**	**Placebo (n = 49)**
Mean age (years)	70.0	70.6	71.6
Men (%)	70	70	82
Phototype I and II (%)	83	87	79
Number of lesions	750	692	259
Confined to (%):			
Forehead	40	47	56
Scalp	31	29	23
Cheek	19	12	13
Nose	6	6	5
Ear	1	1	2
Other	3	4	2
Severity (%):			
Benign	42	45	46
Moderate	58	55	54
Maximum lesion diameter in cm (mean)	1.011	0.967	1.039

PDT with EFFALA was superior to cryotherapy and PDT with placebo in terms of the percentage of lesions showing clinical complete disappearance after 3 months (primary efficacy endpoint) and 12 months, as well as the percentage of patients whose lesions had clinically completely disappeared after 3 and 12 months. However, these percentages are lower at 12 months than at 3 months for all groups and endpoints (see Table 2).

The aesthetic appearance of the eliminated lesions was better with EFFALA than with cryotherapy, with a percentage of EFFALA-treated lesions showing, after clinically complete disappearance, a

greater amount of normal skin (88% versus 66%) and less hypopigmentation (3% versus 33%) ($p < 0.001$).

Table 2: Results for the primary and secondary endpoints (study AK04)

	EFFALA (n = 148)	**Cryotherapy (n = 149)**	**Placebo (n = 49)**
% of clinically completely eliminated lesions			
At 3 months (primary efficacy endpoint) **p vs cryotherapy** **p vs placebo**	**89** **0.00007** **< 0.00001**	**77**	**29**
At 12 months p vs cryotherapy p vs placebo	79 < 0.001 < 0.001	63	25
% of patients with all lesions clinically completely eliminated			
At 3 months p vs cryotherapy p vs placebo	67 0.02 < 0.0001	52	12
At 12 months p vs cryotherapy p vs placebo	50 < 0.001 < 0.001	37	9

08.2 Safety/Adverse effects

Data from clinical studies

Study AK03:
During application of the plaster, local reactions occurred more frequently in the EFFALA group (42%) than in the placebo group (18%).

During illumination, virtually every patient in the EFFALA group had had local reactions versus 24% of patients in the placebo group.

At the end of illumination, 9% of patients in each group had had local reactions.
These local reactions were transient and mild to moderate. One case of a burn necessitating termination of illumination was observed in a patient treated with EFFALA.
On the day after PDT, adverse events were reported in the case of 94% of the lesions treated with EFFALA versus 10% for those in the placebo group.
In the EFFALA group, the adverse events were:
- erythema (92% of lesions, severe in 21% of cases),
- burns (31% of lesions, severe in 10% of cases),
- pain (16% of lesions),
- pruritus (18% of lesions),
- peeling (15% of lesions),
- crusts (14% of lesions).

In the placebo group, local reactions were of mild intensity and limited to erythema (2% of lesions) and pruritus (9% of lesions).

Study AK04
During application of the plaster, local reactions were observed in 34% of patients in the EFFALA group and 10% of those in the placebo group, principally pruritus, burns (with EFFALA) and erythema.

During illumination, virtually every patient in the EFFALA group had local reactions (principally erythema, burns and pain) versus 29% of patients in the placebo group.
In three patients treated by cryotherapy, oedema of the face and eyelids and swelling of the face were observed. The three simultaneous reactions, which were of severe intensity, were observed in one patient and lasted ten days or so.

On the days following illumination or cryotherapy, local reactions were observed affecting virtually all lesions regardless of whether the treatment consisted of EFFALA (99.7%) or cryotherapy (99.1%). With EFFALA, these were mainly burns, and with cryotherapy there was formation of bubbles or blisters.
Severe reactions were more common in the EFFALA group (31% versus 15% with cryotherapy).

SPC-related issues
Virtually all patients (99%) exhibited adverse effects confined to the treated area (local reactions), which are attributable to the toxic effects of photodynamic therapy (phototoxicity). During application of EFFALA and before exposure of the treated area to light, 33% of patients exhibited local reactions, the most common ones being pruritus, burns and erythema. During exposure to light, erythema, burns and pain are the most commonly reported local reactions. These symptoms are generally of mild to moderate intensity and necessitated early termination of illumination in 1% of patients. After treatment, pruritus, erythema, appearance of crusts and peeling are the most common local reactions, also of mild to moderate intensity, capable of persisting for 1 or 2 weeks, sometimes longer.
Headache is another common adverse effect (< 10%).

08.3 Summary & discussion

The efficacy of EFFALA in one session of photodynamic therapy was evaluated in two randomised comparative studies, one in double-blind mode versus placebo (plaster) and the other open-label versus cryotherapy (single session) and placebo (plaster) in patients with mild (superficial, non-hyperkeratotic) or moderate (hyperkeratotic) actinic keratosis of the face and scalp, whose lesions measured a maximum of 1.8 cm in diameter. The appearance of the lesions was assessed 3 and 12 months after treatment.

In both studies, the patients actually included, with a mean age of 70 years, were men in 75% of cases and were of the fair phototype (I and II according to Fitzpatrick's classification). Patients had on average five lesions, half of which were confined to the forehead. Lesions were more often moderate than mild in intensity.

In the study versus placebo (n = 103), after 3 months EFFALA was superior to placebo as regards:
- the percentage of lesions having completely disappeared (primary efficacy endpoint): 82% versus 19% ($p < 0.0001$)
- the percentage of patients with complete resolution of the lesions: 62% versus 6% ($p < 0.001$).

In the study versus cryotherapy and placebo (n = 346), after 3 months EFFALA was superior to cryotherapy and placebo in terms of:
- the percentage of lesions that had completely disappeared (primary efficacy endpoint): 89% versus 77% with cryotherapy ($p = 0.00007$) and 29% with placebo ($p < 0.00001$).
- the percentage of patients with complete resolution of the lesions: 67% versus 52% with cryotherapy ($p = 0.02$) and 12% with placebo ($p < 0.0001$).

At 12 months, in both studies, the superiority of EFFALA compared with placebo and with cryotherapy was maintained; however, in all three groups the percentages of lesions that had completely disappeared were smaller than at 3 months, suggesting that the lesions had reappeared or that new lesions had appeared, justifying the long-term monitoring of patients after treatment.

The aesthetic appearance of treated lesions was better with EFFALA than with cryotherapy. Indeed, after complete disappearance of the lesions, the skin more often looked normal (88% versus 66%, $p < 0.001$) and hypopigmentation was less frequent (3% versus 33%, $p < 0.001$) after treatment with EFFALA than with cryotherapy.

There are no clinical studies directly comparing EFFALA with METVIXIA, its closest comparator. The methodological quality of the indirect comparison performed by the Applicant cannot be assessed on account of the insufficiency of the information provided. METVIXIA had been compared with cryotherapy in two non-inferiority studies and one superiority study whose results were contradictory; however, only one phase IV superiority study using the dosage scheme adopted in the Marketing Authorisation for METVIXIA (one photodynamic therapy session, repeatable after 3 months) was carried out and it did not show any difference between the treatments in terms of the percentage reduction in the number of lesions 3 months after treatment (see the Transparency Committee opinion of 28 March 2007).

The adverse events that can occur during treatment with EFFALA are related to the application of the plaster and also to the phototoxicity of photodynamic therapy.
During the course of the studies described above, adverse events were more common with EFFALA than with placebo during application of the plaster (42% versus 18% in one study and 34% versus 10% in the other), during (99% versus 24 and 29%) and after illumination (94% versus 10%). These were mainly local reactions such as erythema, pruritus, burns, and pain. These symptoms, generally of mild to moderate intensity, can persist for 2 weeks. In 1% of cases they necessitated premature termination of illumination.
With cryotherapy, oedema of the face and eyelids and swelling of the face were observed in three patients during the session. In the following days, local reactions (bubbles and blisters) were reported in 99% of patients. Severe reactions were more common in the EFFALA group than in the cryotherapy group (31% versus 15%).

09 THERAPEUTIC USE

Like METVIXIA, EFFALA is a photosensitizing agent used in photodynamic therapy for the treatment of mild (superficial) actinic keratosis lesions of the face and scalp. These agents are first-line treatments as an alternative to cryotherapy. They are particularly useful for the treatment of multiple actinic keratosis lesions of the face and/or (alopecic) scalp because they enable all the lesions to be treated together in a single session, with a good healing outcome. With EFFALA, treated lesions should not exceed 1.8 cm in diameter.
With the clinical data available it is not possible to position EFFALA with respect to METVIXIA by direct comparison; however, only EFFALA has shown its superiority with respect to cryotherapy.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

◗ Actinic keratoses are lesions occurring on areas exposed to the sun, most often in elderly persons. Lesions are commonly multiple and in the absence of effective treatment can develop into skin cancers (squamous cell carcinoma).

◗ This proprietary medicinal product is intended as a curative therapy.

◗ The efficacy/adverse effects ratio is high.

◗ There are treatment alternatives.

◗ This proprietary medicinal product may be a first-line treatment for multiple fine and non-pigmented keratosis lesions confined to the face and scalp not exceeding 1.8 cm in diameter, as an alternative to cryotherapy.

◗ Public health benefit:

In public health terms, although this condition is fairly common, actinic keratosis represents only a small burden inasmuch as the condition has a good prognosis.

Improving the management of actinic keratoses does not constitute a public health need (there are effective non-medicinal alternatives for preventing the onset of cancer). In cases of multiple actinic keratoses this alternative could be beneficial.

In light of the clinical trial data and given the existing treatment alternatives, patients with keratosis are not expected to be impacted in terms of morbidity.
Furthermore, it is not certain that these results can be carried over into clinical practice in so far as, among other things, the profile of patients treated may differ from that of patients in studies.

Consequently, in view of the available data and the existence of non-medicinal alternatives, the proprietary medicinal product EFFALA is not expected to offer any public health benefit in this indication.

Taking account of these points, the Committee considers that the actual benefit of EFFALA, medicated plaster, is <u>substantial</u> in the Marketing Authorisation indication.

The Committee recommends inclusion of EFFALA, medicated plaster, on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication "treatment of mild actinic keratosis (AK) of the face and scalp (bald/hairless areas) with a maximum diameter of 1.8 cm" at the dosages in the Marketing Authorisation.

◗ **Proposed reimbursement rate: 65%**

010.2 Improvement in actual benefit (IAB)

EFFALA 8 mg, medicated plaster, offers a minor improvement in actual benefit (IAB IV) in terms of efficacy in comparison with cryotherapy.

010.3 Target population

The target population for EFFALA is defined as patients with mild actinic keratoses of the face and scalp not exceeding 1.8 cm in diameter.

There are few epidemiological data on actinic keratosis. Data from the United Kingdom[10,11] and Ireland[12] have shown a prevalence of actinic keratosis of the order of 19% to 24% in the over-60s. In the Irish study, the prevalence was estimated in those over 21 years of age at 13.6% in men and 7.6% in women. Extrapolating these values to the French population (INED 2012 data), the population of those affected by actinic keratosis may be estimated at between 3 and 5 million.
According to the study by Frost[13] (1994), lesions are confined to the face in 20 to 60% of cases, which would reduce the population to between 0.6 and 3 million.
There are no epidemiological data that would allow an estimate of the proportion of superficial actinic keratosis lesions. In study PC-T301/99, which included patients with grade 1, 2 and 3 lesions, about 90% of the lesions were non-hyperkeratotic (grade 1 and 2).
Consequently, the target population for METVIXIA in this indication may be estimated to be between 0.5 and 2.7 million.

However, not all of this population is likely to be treated with EFFALA to the extent that cryotherapy remains the reference treatment and that there are alternatives. Moreover, current guidelines (see §05) tend to reserve this treatment for large or multiple actinic keratoses, and the diameter of lesions treated with EFFALA should not exceed 1.8 cm.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

Appropriate for the prescription conditions.

◗ Request for data

The Committee is requesting that a study be carried out whose objectives will be to describe:
- the population treated with EFFALA (indication, clinical picture, size and severity of the lesions, single or multiple lesions, recurrence, etc.),
- its methods of use (compliance with the indication, dosages, treatment frequency and duration, repeat sessions, combined treatments, etc.) and the treatment's place in the management strategy,
- patients' long-term clinical course (disappearance of the lesions, recurrence after 18 months), in particular in the event of withdrawal,
- safety.

[10] Harvey I, Frankel S, Marks R et al. Non-melanoma skin cancer and solar keratoses. 1. Method and descriptive results of the South Wales skin cancer study. Br J Cancer 1996; 74:1302-7

[11] Memon AA, Tomenson JA, Bothwell J, Friedman PS. Prevalence of solar damage and actinic keratosis in a Merseyside population. Br J Dermatol 2000; 142:1154-9

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[13] Frost CA, Green AC. Epidemiology of solar keratoses. Br J Dermatol 1994; 24:79-82