HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

5 March 2014

METVIXIA 168 mg/g, cream

Tube of 2 g (CIP: 377 198 5 8)

Applicant: GALDERMA

INN	Methyl aminolevulinate
ATC code (2013)	L01XD03 (Sensitizers used in photodynamic/radiation therapy)
Reason for the review	**Renewal of inclusion**
List concerned	**National Health Insurance** (French Social Security Code L.162-17)
Indications concerned	**"Treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses (AK) of the face and scalp.** **Treatment of superficial, non-recurrent basal cell carcinoma (BCC) of the trunk, limbs and neck. Lesions should previously be confirmed by biopsy.** **Treatment of non-pigmented squamous cell carcinoma in situ (Bowen's disease) in immunocompetent subjects when surgery is not possible. Lesions should previously be confirmed by biopsy and healing should be monitored."**

AB	**Multiple, thin or non-hyperkeratotic and non-pigmented actinic keratoses of the scalp: moderate AB** **Superficial, non-recurrent basal cell carcinoma of the trunk, limbs and neck:** - **substantial AB in inoperable patients with extensive or multiple lesions or lesions that are difficult to access surgically** - **moderate AB in other cases** **Non-pigmented squamous cell carcinoma in situ (Bowen's disease) in immunocompetent subjects when surgery is not possible: substantial AB**
Therapeutic use	**In actinic keratosis, METVIXIA is a first-line therapy as an alternative to cryotherapy for multiple, thin or non-hyperkeratotic and non-pigmented lesions of the face and scalp.** **In superficial, non-recurrent basal cell carcinoma of the trunk, limbs and neck, METVIXIA is a second-line therapy when surgery is not possible in cases of extensive or multiple lesions or lesions that are difficult to access surgically. Lesions should previously be confirmed by biopsy.** **In non-pigmented squamous cell carcinoma in situ (Bowen's disease), METVIXIA is a second-line therapy in immunocompetent subjects when surgery is not possible in cases of extensive or multiple lesions or lesions that are difficult to access surgically. Lesions should previously be confirmed by biopsy and healing should be monitored.**
IAB	**The improvement in actual benefit provided by METVIXIA is unchanged (level V, non-existent) in the treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses of the face and scalp.** **In superficial, non-recurrent basal cell carcinoma of the trunk, limbs and neck, METVIXIA:** - **provides a minor improvement in actual benefit (level IV) in inoperable patients with extensive or multiple lesions or lesions that are difficult to access surgically;** - **does not provide any improvement in actual benefit (level V) in other cases.** **METVIXIA provides a minor improvement in actual benefit (level IV) in the treatment of non-pigmented squamous cell carcinoma in situ (Bowen's disease) in immunocompetent subjects when surgery is not possible.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	19/09/2006 (national procedure)
Prescribing and dispensing conditions/special status	List I

ATC Classification	2013	
	L	Antineoplastic and immunomodulating agents
	L01	Antineoplastic agents
	L01X	Other antineoplastic agents
	L01XD	Sensitizers used in photodynamic/radiation therapy
	L01XD03	Methyl aminolevulinate

02 BACKGROUND

Examination of a proprietary medicinal product included on the list of medicines refundable by National Health Insurance for a 5-year period starting on 30/04/2008 (Official Gazette of 30/04/2008).

03 CHARACTERISTICS OF THE MEDICINAL PRODUCT

03.1 Therapeutic indications

“Treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses (AK) of the face and scalp.

Treatment of superficial, non-recurrent basal cell carcinoma (BCC) of the trunk, limbs and neck. Lesions should previously be confirmed by biopsy.

Treatment of non-pigmented squamous cell carcinoma in situ (Bowen’s disease) in immunocompetent subjects when surgery is not possible. Lesions should previously be confirmed by biopsy and healing should be monitored.”

03.2 Dosage

“Posology

Adults (including the elderly)

Treatment of actinic keratoses. One session of photodynamic therapy should be administered. Treated lesions should be evaluated after three months and if needed, treatment should be repeated with a second therapy session.

Treatment of superficial basal cell carcinoma. One session of photodynamic therapy should be administered. Treated lesions should be evaluated after three months and if needed, two additional sessions should be administered with an interval of one week between sessions.

Treatment of Bowen's disease. Two sessions of photodynamic therapy should be administered with an interval of one week between sessions. Treated lesions should be evaluated after three months and if needed, two additional sessions may be administered with an interval of one week between sessions. Multiple lesions may be treated during the same treatment session.

Method of administration

Before applying METVIXIA cream, the lesion surface should be prepared to remove scales and crusts and roughen the surface of the lesions.

Apply a layer of METVIXIA cream (about 1 mm thick) by using a spatula to the lesion and the surrounding 5-10 mm of normal skin. Cover the treated area with an occlusive dressing for 3 hours.

Remove the dressing, and clean the area with saline and immediately expose the lesion to red light with a continuous spectrum of 570-670 nm and a total light dose of 75 J/cm^2 at the lesion surface. Red light with a narrower spectrum giving the same activation of accumulated porphyrins may be used. The light intensity at the lesion surface should not exceed 200 mW/cm^2.

Only CE marked lamps should be used, equipped with the necessary filters and/or reflecting mirrors to minimize exposure to heat, blue light and UV radiation. It is important to ensure that the correct light dose is administered. The light dose is determined by factors such as the size of the light field, the distance between lamp and skin surface and illumination time. These factors vary with lamp type, and the lamp should be used according to the user manual. The light dose delivered should be monitored if a suitable detector is available.

Patient and operator should adhere to safety instructions provided with the light source. During illumination patient and operator should wear protective goggles which correspond to the lamp light spectrum.

Healthy untreated skin surrounding the lesion does not need to be protected during illumination.

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

04 CLINICALLY RELEVANT COMPARATORS

04.1 Medicinal products

NAME (INN) *Company*	Same TC* Yes / No	Indications	Date of Last Opinion	AB	IAB (Wording)	Reimbursed Yes/No
EFFALA 8 mg, medicated plaster 5-aminolevulinic acid *Spirig Pharma*	Yes	Single-use plaster for the treatment of mild actinic keratoses (AK) of the face and scalp (bald/hairless areas) with a maximum diameter of 1.8 cm.	06/03/2013	Substantial	IAB IV in terms of efficacy compared with cryotherapy.	Yes
EFUDIX 5%, cream 5-fluorouracil *Meda Pharma*	No Pyrimidine analogue antimetabolite	Pre-epitheliomatous keratosis. Bowen's disease, erythroplasia of Queyrat: this treatment may be used when surgery is not possible, but healing should be monitored. Genital warts.	15/02/2006 14/02/2007	Substantial Substantial Substantial	-	Yes
ALDARA 5%, cream Imiquimod *Meda Pharma*	No Chemo-therapeutics for topical use	Clinically typical, non-hypertrophic, non-hyperkeratotic actinic keratoses on the face or scalp in immunocompetent adult patients, when the size or number of lesions limits the efficacy and/or safety of cryotherapy and if other topical treatments are contraindicated or less appropriate. External genital and perianal warts (condylomata to acuminata) in adults. Small superficial basal cell carcinomas (SBCCs) in adults.	10/03/2010	Substantial Substantial Insufficient	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

04.2 Other health technologies

Other, non-medicinal treatments are: cryotherapy (the standard treatment for actinic keratosis), surgery, radiotherapy, CO_2 laser therapy, and electrocoagulation and curettage.

◗ Conclusion

EFFALA, another sensitiser used in photodynamic therapy, is the most relevant comparator.

05 SUMMARY OF PREVIOUS ASSESSMENTS

Date of Opinion (reason for request)	28 March 2007 (application for inclusion on the list of medicines refundable by National Health Insurance and of medicines approved for hospital use)
Indication	Treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses (AK) of the face and scalp. Treatment of superficial, non-recurrent basal cell carcinoma (BCC) of the trunk, limbs and neck. Lesions should previously be confirmed by biopsy. Treatment of non-pigmented squamous cell carcinoma in situ (Bowen's disease) in immunocompetent subjects when surgery is not possible. Lesions should previously be confirmed by biopsy and healing should be monitored.
AB	**Treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses of the face and scalp.** Actinic keratoses are lesions occurring on areas exposed to the sun, most often in elderly persons. There are often multiple lesions which, in the absence of effective treatment, can develop into skin cancers (squamous cell carcinoma). This proprietary medicinal product is intended as curative therapy. Public health benefit: Although it is a fairly common condition, the public health burden of actinic keratosis is low 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 treatment 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, in particular, the profile of patients treated in current practice 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 METVIXIA is not expected to benefit public health in this indication. The efficacy/adverse effects ratio is high. This proprietary medicinal product may be a first-line therapy for multiple thin and non-pigmented keratosis lesions of the face and scalp. The actual benefit of METVIXIA in this indication is substantial. **Treatment of superficial, non-recurrent basal cell carcinoma of the trunk, limbs and neck.** Basal cell carcinoma is the most common carcinoma of the skin. It can occur anywhere on the skin and may involve multiple sites from the outset. The prognosis for basal cell carcinomas is usually good and they rarely metastasise. Extension to the local subcutaneous tissue and recurrence (the risk factors for

	which are stated in the ANAES [National Health and Accreditation Assessment Agency] guidelines[1]) are poor prognostic factors. This proprietary medicinal product is intended as curative therapy. Public health benefit: The public health burden of small, superficial basal cell carcinomas in adults is low in that this cancer has a good prognosis (recurrence is rare and there is no mortality rate) and the target population (patients in whom surgery is contraindicated) is small. In those rare patients in whom surgery is contraindicated, the availability of a second effective medicinal product may constitute a valuable treatment alternative. However, a public health need cannot be said to exist. In light of the clinical trial data and given the existing treatment alternatives, patients with superficial basal cell carcinoma are not expected to be impacted in terms of morbidity. Consequently, in view of the available data and the existence of non-medicinal alternatives, the proprietary medicinal product METVIXIA is not expected to benefit public health in this indication. The efficacy/safety ratio is high. This medicinal product is a first-line therapy in inoperable patients. The actual benefit of METVIXIA in this indication is substantial. **Treatment of non-pigmented squamous cell carcinoma in situ (Bowen's disease) in immunocompetent subjects when surgery is not possible.** Bowen's disease is a precancerous condition which can occur anywhere on the skin in adults, particularly in the elderly. The lesions tend to spread slowly and to be resistant to local treatment. They may develop into squamous cell carcinoma. This proprietary medicinal product is intended as curative therapy. Public health benefit The public health burden of Bowen's disease is low because of the limited number of patients concerned. In those rare patients in whom surgery is contraindicated, the availability of a second effective medicinal product may constitute a valuable treatment alternative. However, a public health need cannot be said to exist. In light of the clinical trial data and given the existing treatment alternatives, patients with Bowen's disease are not expected to be impacted in terms of morbidity. Consequently, in view of the available data and the existence of non-medicinal alternatives, the proprietary medicinal product METVIXIA is not expected to benefit public health in this indication. The efficacy/adverse effects ratio is high. This medicinal product is a first-line therapy in inoperable patients. The actual benefit of METVIXIA in this indication is substantial.
IAB	**Treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses of the face and scalp** METVIXIA does not provide any improvement in actual benefit (level V) compared with cryotherapy in the treatment of thin or non-hyperkeratotic and non-pigmented facial and scalp actinic keratoses, but it does constitute an additional treatment resource.

[1]Prise en charge diagnostique et thérapeutique du carcinome basocellulaire de l'adulte. ANAES. (2004).

	Treatment of superficial, non-recurrent basal cell carcinoma of the trunk, limbs and neck In the treatment of superficial, non-recurrent basal cell carcinoma of the trunk, limbs and neck, METVIXIA provides a minor improvement in actual benefit (level IV) in the therapeutic management of patients who cannot be treated with surgery. **Treatment of non-pigmented squamous cell carcinoma in situ (Bowen's disease) in immunocompetent subjects when surgery is not possible** In the treatment of non-pigmented squamous cell carcinoma in situ (Bowen's disease) in immunocompetent subjects, METVIXIA provides a minor improvement in actual benefit (level IV) in the therapeutic management of patients who cannot be treated with surgery.
Studies Requested	The Transparency Committee would like a follow-up study to be conducted in patients treated with METVIXIA in order to determine the following: - the population treated with METVIXIA (indications, clinical picture, size of lesions, single or multiple lesions, histology, recurrence, etc.), - METVIXIA's conditions of use (dosages, treatment frequency and duration, concomitant treatments, role in the therapeutic strategy, etc.), - the existence of any histological testing (at the time of diagnosis or follow-up), - patients' clinical course, - the impact of tolerability on continuation with the treatment. The length of the study, determined by an independent scientific committee, must be justified and sufficient to respond to the Committee's request.

06 ANALYSIS OF AVAILABLE DATA

06.1 Efficacy

The company has not provided any new clinical efficacy data for the use of METVIXIA under the conditions approved by the Marketing Authorisation.

06.2 Safety/adverse effects

New safety data have been provided: PSUR covering the period from 15 June 2005 to 30 June 2012.

These data led to the "Special warnings and precautions for use" section being changed (31 January 2008) to include information on allergic contact dermatitis and the results of a clinical trial in immunocompromised patients which did not identify any new safety concerns.

The PSUR data documented the risks of developing angioedema, oedema of the eyelids, facial oedema (facial swelling) and pustular rash (pustules on the application site). An amendment to the SPC regarding these adverse effects is currently being assessed by the ANSM [National Medicines and Health Products Safety Agency].

In addition, eye disorders, skin carcinomas, cutaneous allergic reactions and cerebral vascular events are still subject to special monitoring.

06.3 Usage/prescription data

Post-inclusion study: "France-PDT" observational study (OPDT)[2]

In its opinion of 28/03/2007, the Transparency Committee requested a follow-up study to be conducted in patients treated with METVIXIA in everyday clinical practice, aiming to determine the characteristics of patients treated, the conditions of use, the existence of any histological testing (at the time of diagnosis or follow-up), patients' clinical course and the impact of tolerability on continuation with the treatment.

In response to the Committee's request, the company set up a national non-comparative observational cohort study carried out in hospital dermatology departments and private dermatology practice, in patients treated with METVIXIA for any indication between 30 April and 31 July 2010 and followed up for 3 or 6 months.

OBJECTIVES AND METHOD
The primary objective of this observational study was to describe the population reached by METVIXIA (in terms of indications and patient characteristics) and how the product is used.
The secondary objectives were:

- to describe the clinical course and clinical follow-up, particularly whether histological testing was carried out in patients during follow-up;
- to estimate the proportion of early and/or late discontinuations of treatment with METVIXIA due to intolerance or for other reasons.

[2] Farhi D, Bedane C, Savary J, Basset-Seguin N. The France-PDT study: a national prospective observational cohort survey on the use of methyl-aminolevulinate photodynamic therapy in France, with up to 6-month follow-up. Eur J Dermatol. 2013; 23: 68-76.

This study was conducted in a sample of hospital and private dermatologists practising in Metropolitan France and identified as using the technique from a list of all providers maintained by the company for the purposes of training in the technique and provision of equipment (whether they use the lamp supplied by the company or not).

The cohort was made up of patients treated with METVIXIA for the first time, irrespective of treatment indication or the type of lamp used.
Patients who had previously been treated with METVIXIA were specifically excluded.

Because of differences in the prevalence of each of the diseases treated using this product, and in order to include a sufficient number of patients for each indication, each dermatologist included, consecutively, the first 10 patients treated with METVIXIA and then, from the 11th patient onwards, all consecutive patients treated with METVIXIA excluding the indication for actinic keratosis.

Data were collected by the dermatologists during the first cycle of treatment, then at 3 months during the follow-up visit and at 6 months if a new session was administered.
Patients were also asked about pain experienced (visual analogue scale) and about their tolerance of the technique following photodynamic therapy sessions.

The primary endpoint was the percentage of patients in whom misuse was observed, using an algorithm based on non-compliance with the dosage, method of administration, and special warnings and precautions for use as described in the Summary of Product Characteristics.

Description of the “France-PDT” observational study:

Of the 174 providers of photodynamic therapy (PDT) identified in France, 71 agreed to take part and only 56 (comprising 41% hospitals, 32% mixed and 27% private practice), who had been using the technique for a median duration of one year, included at least one patient, i.e. 32%.
On 19 September 2011 (the date the database was frozen), out of a total of 583 patients considered to be eligible, only 456 patients (78.2%) who conformed to the inclusion and non-inclusion criteria and had an inclusion questionnaire were analysed.

Of these 456 patients, 203 (44.5%) were treated with METVIXIA for actinic keratosis (AK), 130 (28.5%) for basal cell carcinoma (BCC), 69 (15.1%) for Bowen’s disease, 32 (7.0%) for multiple tumours (BCC + AK, Bowen’s + CA, CA + Bowen’s) and 22 (5%) for other reasons (porokeratosis, warts, granuloma, folliculitis, etc.).

These patients’ main characteristics on inclusion are listed in Table 1.

Table 1: Patient characteristics and lesion characteristics on inclusion (n, %)

	Basal Cell Carcinoma (N=130)	Actinic Keratosis (N=203)	Bowen's Disease (N=69)	Multiple (N=32)	Other (N=22)	Total (N=456)
Female	67 (51.9)	50 (24.6)	46 (66.7)	18 (58.1)	12 (54.5)	193 (42.3)
Median age (years)	66.2	77.4	78.3	75.8	58.9	74.3
Skin phototype						
• Type I	7 (5.4)	18 (8.9)	3 (4.3)	0	0	28 (6.2)
• Type II	61 (46.9)	97 (48.0)	37 (53.6)	12 (37.5)	3 (13.6)	210 (46.2)
• Type III	49 (37.7)	70 (34.7)	24 (34.8)	15 (46.9)	14 (63.6)	172 (37.8)
• Type IV to VI	13 (10.0)	17 (8.4)	5 (7.2)	5 (15.6)	5 (22.7)	45 (10.0)
History						
• Cardiovascular	47 (36.4)	111 (55.2)	33 (49.3)	19 (61.3)	4 (18.2)	214 (47.6)
• Diabetes	4 (3.1)	24 (12.1)	4 (6.2)	7 (24.1)	1 (4.5)	40 (9.0)
• Respiratory	6 (4.7)	17 (8.6)	2 (3.0)	5 (16.7)	4 (18.2)	38 (8.6)
• Haematological	5 (4.0)	11 (5.6)	2 (3.0)	3 (9.7)	0	21 (4.8)
• Immunodeficiency	6 (4.8)	17 (8.6)	7 (10.6)	3 (4.8)	0	22 (5.0)
Immunosuppressants						
• Yes	6 (4.9)	17 (8.6)	7 (10.6)	4 (13.3)	0	34 (7.8)
Previous treatments						
• Surgery	13 (56.5)	24 (15.4)	7 (30.4)	7 (33.3)	1 (5.0)	52 (21.4)
• Cryotherapy	12 (52.2)	141 (90.4)	10 (43.5)	19 (90.5)	4 (20.0)	186 (76.5)
• Radiotherapy	2 (8.7)	1 (0.6)	0	0	0	3 (1.2)
• Electrocoagulation and curettage	0	7 (4.5)	0	1 (4.8)	0	8 (3.3)
• Laser therapy	2 (8.7)	6 (3.8)	2 (8.7)	1 (4.8)	6 (30.0)	17 (7.0)
• Medicinal treatment	10 (43.5)	74 (47.5)	8 (34.8)	10 (47.6)	4 (20.0)	106 (43.6)
• Other	1 (4.3)	7 (4.5)	1 (4.3)	2 (9.5)	14 (70.0)	25 (10.3)
• No treatment	106 (81.5)	47 (23.2)	43 (62.3)	11 (34.4)	2 (9.1)	209 (45.8)
Location of lesions						
• Face	35 (26.9)	106 (52.2)	22 (31.9)	22 (68.8)	7 (31.8)	192 (42.1)
• Scalp	5 (3.8)	93 (45.8)	3 (4.3)	7 (21.9)	1 (4.5)	109 (23.9)
• Neck	8 (6.2)	9 (4.4)	1 (1.4)	1 (3.1)	0	19 (4.2)
• Anterior thorax	26 (20.0)	5 (2.5)	3 (4.3)	3 (9.4)	2 (9.1)	39 (0.9)
• Abdomen	4 (3.1)	0	0	0	0	4 (0.1)
• Back	59 (45.4)	0	0	1 (3.1)	0	60 (13.2)
• Upper limbs	15 (11.5)	7 (3.4)	9 (13.0)	2 (6.3)	4 (18.2)	37 (8.1)
• Lower limbs	8 (6.2)	6 (3.0)	26 (37.7)	7 (21.9)	5 (22.7)	52 (11.4)
• Back of hands	2 (1.5)	11 (5.4)	0	2 (6.3)	0	15 (3.3)
• Other	3 (2.3)	3 (3.0)	9 (13.0)	1 (3.1)	5 (22.7)	24 (5.3)
Mean number of lesions treated with METVIXIA (SD)	2.4 (±2.8)	13.4 (±13.6)	1.8 (±2.1)	6.5 (±5.8)	7.0 (±12.2)	7.4 (±10.8)
Mean maximum thickness (mm)	1.2 (±1.0)	1.9 (±1.4)	1.7 (±1.6)	1.9 (±1.3)	1.7 (±1.4)	1.7 (±1.3)
Pigmentation	5 (4.0)	16 (8.6)	2 (3.0)	3 (9.7)	2 (9.5)	28 (6.5)
Diagnosis on evaluation						
• Clinical	29 (22.3)	151 (77.4)	3 (4.3)	11 (34.4)	3 (13.6)	197 (43.2)
• Histological	99 (76.2)	34 (16.7)	64 (92.8)	21 (65.6)	16 (72.7)	234 (51.3)
Other lesions present	42 (32.3)	89 (44.3)	14 (20.3)	18 (58.1)	9 (40.9)	172 (38.0)

Description of lesions treated with PDT:

- Actinic keratoses: a mean number of 13.4 lesions (SD ±13.6) were treated with PDT. These were primarily non-pigmented (89.7%), moderate (46.5%) or thick (25.7%). They were most commonly located on the face and scalp (80.6%). In 23% of cases, a cancerous zone was treated.
- Basal cell carcinoma: lesions were mainly superficial (93.8%), primary (97.4%) and had a good prognosis (92.7%). They were most commonly located on the back and chest (51.2%) but also on the face (21%). Diagnosis was based on a histological assessment in 3 out of 4 cases before PDT was administered.
- Bowen's disease: lesions were mainly superficial (94%) and non-pigmented (97%). They were most commonly located on the limbs and face (65.8%). Diagnosis was based on a histological assessment in 9 out of 10 cases before PDT was administered.

Therapeutic strategy:
Treatment of lesions with other techniques before resorting to PDT was common for actinic keratosis (76.8%) but less common for basal cell carcinoma (18%) and Bowen's disease (35%):

- Actinic keratoses: at least one previous treatment with cryotherapy was reported in 90.4% of patients and with medicinal products in 47.4% of patients.
- Basal cell carcinoma: at least one previous treatment with surgery was reported in 56.5% of patients, with cryotherapy in 52.2% and with medicinal products in 43.5%.
- Bowen's disease: at least one previous treatment was reported with cryotherapy in 43.5% of patients, with medicinal products in 34.8% and with surgery in 30.4%.

Surgery was reported to be technically difficult (awkward area to operate on, large lesion, multiple lesions) in 84% of patients with basal cell carcinoma and 78.6% with Bowen's disease; 5.3% and 9.5% of patients respectively had a genuine contraindication to surgery.

Description of treatment sessions during the first cycle (on inclusion):
In the majority of cases (86.2%), a single session was performed on inclusion for the treatment of actinic keratoses, whereas 39.2% of patients with basal cell carcinoma received two sessions at a mean interval of 20 days. 84.1% of patients with Bowen's disease received two sessions at a maximum interval of 10 days on average.
One tube of METVIXIA was generally used, applied for a median duration of three hours.
The subsequent illumination lasted for a mean period of 10 minutes, with a healthcare professional present in 98% of cases.

RESULTS

Of the 456 patients included, 377 patients (82.7%) were followed up at 3 months and 60 patients at 6 months.

Results for correct usage and conditions of use

During the first cycle of PDT session(s), misuse was observed in terms of duration of application, duration of illumination and use of the lamp, number of sessions, interval between sessions and existence of a follow-up visit in 41.6%, 25.6% and 23.4% of patients with basal cell carcinoma, actinic keratoses and Bowen's disease respectively.
The most common deviation concerned the number of sessions carried out on inclusion: two sessions rather than the single session recommended for basal cell carcinoma (39.2%) and actinic keratosis (13.8%).

During the second cycle of PDT session(s) at 3 months, misuse was observed in 42.1%, 49.3% and 36.8% of patients with basal cell carcinoma, actinic keratoses and Bowen's disease respectively.

Compliance with the Marketing Authorisation for METVIXIA, including compliance regarding the indication, location of lesions, type of lesions (in terms of thickness, pigmentation, histological type, prognosis and form) and the use of biopsy at diagnosis was observed in 47.8% of patients during the first cycle of PDT session(s).

The most common deviations concerned basal cell carcinoma lesions located on the face (26.9% of cases), the thickness of lesions (26.9% of actinic keratoses) and a lack of biopsy at diagnosis (23% of basal cell carcinomas).

Results for maintenance of clinical benefit

In the 377 patients reviewed at M3, response was considered as complete by the physician in only 46.7% of cases: 65.5% for basal cell carcinoma, 31.9% for actinic keratoses and 59.3% for Bowen's disease. Further sessions were offered to 25% of patients.
Histological confirmation that the lesions had disappeared was only performed in 6.8% of cases for basal cell carcinoma and in 12.3% of cases for Bowen's disease.

At the follow-up visit, 89/377 patients (23.6%) received a new session of PDT at 3 months and 14/60 patients at 6 months.

Tolerability results

During treatment sessions in the first cycle (on inclusion), use of a water spray or ventilation was reported in 63.1% and 40.7% of sessions respectively.
Use of analgesics was planned for 42.7% of sessions.
Treatment was temporarily or provisionally stopped in 19.2% of the 759 PDT sessions for a mean duration of 5 minutes. It was permanently stopped in 4.5% of cases.
The mean maximum pain experienced during illumination (on a visual analogue scale from 0 to 100) was 44.5 (± 28.9).
More than a third of patients were prescribed an analgesic after the procedure.

Three deaths occurred during the study (one mantle cell lymphoma, one acute leukaemia, one death during sleep) and one hospital admission for cerebral vascular accident. None of these events was deemed to be related to the PDT treatment.

06.4 Summary & discussion

No new clinical efficacy data is available for METVIXIA used in the context of its Marketing Authorisation. Pharmacovigilance data have indicated allergic-type adverse effects. These data are currently being assessed by the ANSM.

In its opinion of 28/03/2007, the Transparency Committee had requested a follow-up study examining conditions of use and clinical course to be conducted in patients treated with METVIXIA in everyday clinical practice.

The "France-PDT" observational study carried out between April and July 2010 allowed 456 patients to be analysed, of whom 377 were followed up at 3 months and 60 at 6 months.
The results show:

- The guidelines for use of METVIXIA are insufficiently followed in 32.7% of patients across all indications. In everyday clinical practice, METVIXIA is used outside the strict framework of its Marketing Authorisation (indications, lesion location, diagnosis circumstances, treatment regimen, follow-up) in 52.2% of cases; deviations relate primarily to the location and type of lesions, insufficient histological testing and the number of treatment sessions (two rather than one) in basal cell carcinoma and actinic keratoses.
- Complete response at 3 months was reported in 46.7% of cases (65.5%, 31.9% and 59.3% for basal cell carcinoma, actinic keratoses and Bowen's disease respectively).
- Photodynamic therapy using METVIXIA as a photosensitiser was poorly tolerated, with significant pain causing sessions to be temporarily (19.2%) or permanently stopped (4.7%) or resulting in the use of analgesics (42.7%).

07 THERAPEUTIC USE

Actinic keratoses

Actinic keratosis is a skin condition associated primarily 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 to other physical or chemical triggers (ionising radiation).

The aim of treatment is to destroy the lesions, followed by regular post-treatment monitoring to screen for any recurrences. The available therapies are surgery, cryotherapy (destruction with nitrogen), radiotherapy, electrocoagulation and curettage, dermabrasion, CO_2 laser therapy, topical cytostatics (5-FU and imiquimod), topical diclofenac (not refundable in actinic keratosis), and photodynamic therapy using METVIXIA (methyl aminolevulinate hydrochloride cream) or EFFALA (5-aminolevulinic acid plaster) as the sensitising agent.

When the lesions are few in number, the standard treatment is cryotherapy, a simple and rapid technique that does not require any specific equipment. In case of doubt with squamous cell carcinoma, a biopsy should be carried out prior to cryotherapy.

Photodynamic therapy with METVIXIA or EFFALA is a first-line therapy as an alternative to cryotherapy. It is particularly useful for the treatment of multiple superficial and non-pigmented actinic keratosis lesions of the face and/or (bald) scalp because it enables 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 been shown to be superior to cryotherapy.

When the 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 therapy and electrocoagulation and curettage may also be treatment options.

Basal cell carcinoma

According to the ANAES guidelines (2004), surgery is the standard treatment for basal cell carcinomas. The excision margins should be examined histologically. However, the treatment decision is also based on prognostic criteria for the lesions, patient preference, general health and life expectancy, concomitant treatments and comorbidities, the techniques available and the practitioner's skills. In rare cases, cryosurgery, electrocoagulation and curettage and radiotherapy may be offered as second-line therapies. Imiquimod is only indicated in superficial basal cell carcinomas with a diameter < 2 cm.

Photodynamic therapy with METVIXIA may be used for superficial, non-recurrent, biopsy-confirmed basal cell carcinoma with a good prognosis when surgery is not possible (due to multiple or extensive lesions or a location that is difficult to access surgically). METVIXIA's indication in basal cell carcinoma is restricted to lesions located on the limbs, trunk and neck.

In its 2004 guidelines, ANAES recognised that in the absence of medicinal products with Marketing Authorisation in France, BCCs could benefit from this technique.

The British Association of Dermatologists (2002) and the National Institute for Health and Clinical Excellence (NICE, 2006) recommend photodynamic therapy for treating large and/or multiple superficial lesions.

Bowen's disease

According to French experts, surgery is the standard treatment for Bowen's disease. The excision margins should be 3 to 5 mm and histological testing should be performed to check the margins and confirm that the lesion is non-invasive. The second-line therapies are cryotherapy, electrocoagulation and curettage, laser therapy, photodynamic therapy and 5-FU. Radiotherapy is used less and less frequently.

In their guidelines, British experts from the British Association of Dermatologists considered that:

- there was limited evidence for the efficacy of surgery;

- for all available treatments, the recurrence rate was between 5% and 10%;
- no one treatment appeared to be superior to the others across all clinical situations.

METVIXIA's indication is limited to non-pigmented lesions when surgery is not possible (due to multiple or extensive lesions or a location that is difficult to access surgically) in immunocompetent patients. Lesions should previously be confirmed by biopsy and healing should be monitored.

The British Association of Dermatologists (2002) recommends using photodynamic therapy to treat superficial lesions that are large and/or multiple and/or located in areas with a poor healing potential.
NICE (2006) recommends using photodynamic therapy to treat large and/or multiple superficial lesions.

Summary:

- **In actinic keratosis, METVIXIA is a first-line therapy as an alternative to cryotherapy for multiple thin or non-hyperkeratotic and non-pigmented lesions of the face and scalp.**

- **In superficial, non-recurrent basal cell carcinoma of the trunk, limbs and neck, METVIXIA is a second-line therapy when surgery is impossible in cases of extensive or multiple lesions or lesions that are difficult to access for surgery. Lesions should previously be confirmed by biopsy.**

- **In non-pigmented squamous cell carcinoma in situ (Bowen's disease), METVIXIA is a second-line therapy in immunocompetent subjects when surgery is not possible in cases of extensive or multiple lesions or lesions that are difficult to access surgically. Lesions should previously be confirmed by biopsy and healing should be monitored.**

08 TRANSPARENCY COMMITTEE CONCLUSIONS

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

08.1 Actual benefit

8.1.1 Treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses of the face and scalp

◗ Actinic keratoses are lesions occurring on areas exposed to the sun, most often in elderly persons. There are often multiple lesions which, in the absence of effective treatment, can develop into skin cancers (squamous cell carcinoma).
This proprietary medicinal product is intended as curative therapy.

◗ The efficacy/adverse effects ratio is modest.

◗ This medicinal product is a first-line therapy, as an alternative to cryotherapy, for multiple thin or non-hyperkeratotic and non-pigmented actinic keratosis lesions of the face and scalp.

◗ Public health benefit:
Although it is a fairly common condition, the public health burden of actinic keratosis is low inasmuch as the condition has a good prognosis.

Improving the management of actinic keratoses does not constitute a public health priority (caution regarding sun exposure and photoprotection are effective measures for preventing the onset of squamous cell carcinoma).

In light of data from clinical trials and the "France-PDT" observational study, no additional impact is expected on morbidity in comparison with the existing alternative treatments.

Consequently, the proprietary medicinal product METVIXIA does not benefit public health in this indication.

Taking account of these points, the Committee considers that the actual benefit of METVIXIA is moderate in the treatment of multiple thin or non-hyperkeratotic and non-pigmented actinic keratosis lesions of the face and scalp.

8.1.2 Treatment of superficial, non-recurrent basal cell carcinoma of the trunk, limbs and neck

◗ Basal cell carcinoma is the most common carcinoma of the skin. It can occur anywhere on the skin and may involve multiple sites from the outset. The prognosis for basal cell carcinomas is usually good and they rarely metastasise. Extension to the local subcutaneous tissue and recurrence (the risk factors for which are stated in the ANAES guidelines[3]) are poor prognostic factors.

◗ This proprietary medicinal product is intended as curative therapy.

◗ The efficacy/adverse effects ratio is modest.

[3] Prise en charge diagnostique et thérapeutique du carcinome basocellulaire de l'adulte. ANAES. (2004).

◗ This medicinal product is a second-line therapy for superficial, non-recurrent basal cell carcinoma of the trunk, limbs and neck when surgery is not possible in cases of extensive or multiple lesions or lesions that are difficult to access surgically. Lesions should previously be confirmed by biopsy.

◗ Public health benefit:
The public health burden of superficial basal cell carcinoma in adults is low in that this cancer has a good prognosis (recurrence is rare and there is no mortality rate) and the target population (patients in whom surgery is contraindicated) is small.

Improving the management of superficial basal cell carcinoma does not constitute a public health priority.

In light of data from clinical trials and the "France-PDT" observational study, no additional impact is expected on morbidity in comparison with the existing alternative treatments.

Consequently, the proprietary medicinal product METVIXIA does not benefit public health in this indication.

Taking account of these points, the Committee considers that the actual benefit of METVIXIA in the treatment of superficial non-recurrent basal cell carcinoma of the trunk, limbs and neck when surgery is:

- **substantial in inoperable patients with extensive or multiple lesions or lesions that are difficult to access surgically;**
- **moderate in other cases.**

8.1.3 Treatment of non-pigmented squamous cell carcinoma in situ (Bowen's disease) in immunocompetent subjects when surgery is not possible

◗ Squamous cell carcinoma in situ (Bowen's disease) is a precancerous condition which can occur anywhere on the skin in adults, particularly in the elderly. The lesions tend to spread slowly and to be resistant to local treatment. They may develop into squamous cell carcinoma.

◗ This proprietary medicinal product is intended as curative therapy.

◗ The efficacy/adverse effects ratio is modest.

◗ This medicinal product is a second-line therapy in non-pigmented squamous cell carcinoma in situ (Bowen's disease) in immunocompetent subjects when surgery is not possible in cases of extensive or multiple lesions or lesions that are difficult to access surgically. Lesions should previously be confirmed by biopsy and healing should be monitored.

◗ Public health benefit:
The public health burden of Bowen's disease is low because of the limited number of patients concerned.

Improving the management of Bowen's disease does not constitute a public health priority.

In light of data from clinical trials and the "France-PDT" observational study, no additional impact is expected on morbidity in comparison with the existing alternative treatments.

Consequently, the proprietary medicinal product METVIXIA does not benefit public health in this indication.

Taking account of these points, the Committee considers that the actual benefit of METVIXIA is substantial in the treatment of non-pigmented squamous cell carcinoma in situ (Bowen's disease) in immunocompetent patients when surgery is not possible.

The Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indications and at the dosages in the Marketing Authorisation.

◗ Proposed reimbursement rate: 65%

08.2 Improvement in actual benefit (IAB)

8.2.1 Treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses of the face and scalp

METVIXIA does not provide any improvement in actual benefit (level V, non-existent) in the treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses of the face and scalp.

8.2.2 Treatment of superficial, non-recurrent basal cell carcinoma of the trunk, limbs and neck

In superficial, non-recurrent basal cell carcinoma of the trunk, limbs and neck, METVIXIA:
- provides a minor improvement in actual benefit (level IV) in inoperable patients with extensive or multiple lesions or lesions that are difficult to access surgically;
- does not provide any improvement in actual benefit (level V) in other cases.

8.2.3 Treatment of non-pigmented squamous cell carcinoma in situ (Bowen's disease) in immunocompetent subjects when surgery is not possible

METVIXIA provides a minor improvement in actual benefit (level IV) in the treatment of non-pigmented squamous cell carcinoma in situ (Bowen's disease) in immunocompetent subjects when surgery is not possible.

09 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

Appropriate for the prescribing conditions as regards the indication, dosage and treatment duration.