HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

28 March 2007

METVIXIA 168 mg/g, cream
2 g tube (CIP: 377 198-5)

Applicant: GALDERMA INTERNATIONAL

Methyl aminolevulinate hydrochloride

List I

Date of Marketing Authorisation: September 19, 2006

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Methyl aminolevulinate hydrochloride

1.2. Background

METVIXIA is the first antineoplastic agent activated by photodynamic therapy to be used in dermatology. It acts specifically on cancer cells by causing accumulation of photoactive porphyrins - photoactivation produces cytotoxic agents.

1.3. Indications

Treatment of fine or non-hyperkeratosic 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. The lesions must be confirmed in advance by biopsy.

Treatment of non-pigmented intraepidermal carcinoma (Bowen's disease) in immunoincompetent subjects where surgery is not possible. The lesions must be confirmed in advance by biopsy and check-ups must be performed to monitor healing.

1.4. Dosage

Posology

Adults (including the elderly)

Treatment of actinic keratosis. One session of photodynamic therapy must be given. The lesions treated must be assessed after 3 months and a second session can be given if needed.

Treatment of superficial basal cell carcinoma. One session of photodynamic therapy must be given. The lesions treated must be assessed after 3 months and if needed a two-session treatment may be repeated with a one-week interval in-between.

Treatment of Bowen's disease. Two consecutive sessions of photodynamic therapy should be given with a one-week interval in-between. The lesions treated must be assessed after 3 months and if necessary two additional sessions can be given with a one-week interval in-between. Multiple lesions can be treated simultaneously.

Method of administration

Before applying METVIXIA cream, the surface of the lesions should be prepared in order to remove the scales and crusts and to make the surface of the lesions rough.

Using a spatula, apply a layer of METVIXIA cream (approx. 1 mm thick) to a radius of 5 to 10 mm of healthy skin around the lesion. Cover the treated area with an occlusive bandage for 3 hours.

Remove the bandage and clean the area with a saline solution, then immediately expose the lesion to a continuous spectrum of red light of between 570 and 670 nm so that the total dose of light on the surface of the lesion is 75 J/cm^2. It is possible to use a red light with a narrower spectrum but which activates the accumulated porphyrins in the same way. The intensity of light on the surface of the lesion should not exceed 200 mW/cm^2.

It is essential that only lamps bearing the CE mark are used, equipped with filters and/or reflective mirrors which are necessary to minimize exposure to heat, blue light and UV rays. One must ensure that the dose of light administered is the correct one. The dose of light is determined by several factors, in particular the width of the beam, the distance between the lamp and the surface of the skin and exposure time. These factors vary depending on the type of lamp used and the lamp must be used in accordance with the user manual. The dose of light provided will be controlled if a suitable detector is available.

The patient and the operator must adhere to the safety instructions provided with the light source. During exposure, the patient and operator must wear safety goggles corresponding to the light spectrum of the lamp.

The untreated healthy skin around the lesion does not need to be protected during exposure.

Children and adolescents:
There are no data relating to treatment of patients under 18 years of age.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2007)

L : Antineoplasic agents and immunostimulators
L01 : Antineoplasic agents
L01X : Other antineoplasic agents
L01XD : Agents used in photodynamic therapy
L01XD03 : Methyl aminolevulinate

2.2. Medicinal products in the same therapeutic category

2.2.1. Comparable medicinal products

METVIXIA is the only medicinal product in its pharmacotherapeutic class

2.2.2. Comparisons that have been carried out

Not applicable.

2.3. Medicines with a similar therapeutic aim

Other antineoplasics used in the same indications:

- EFUDIX (5-fluoro-uracil): actinic keratosis and Bowen's disease
- ALDARA (imiquimod): superficial basal cell carcinoma

Other non-drug treatments: surgery (standard treatment for basal cell carcinoma and Bowen's disease), cryotherapy (standard treatment for actinic keratosis), radiotherapy, CO_2 laser, electrocoagulation-curettage.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The laboratory has provided 6 phase III and IV comparative studies on actinic keratosis (AK), basal cell carcinoma (BCC) and Bowen's disease (BD); the principal characteristics are shown in table 1 below.

Table 1: Comparative studies submitted by the laboratory

Study	Methodology	Number of patients	Therapeutic indication	Comparator		
				Placebo	Cryotherapy	5-FU
PC-T306/99	Phase III, randomised, double-blind, parallel-group	80	AK	X		
PC-T305/99	Phase III, non-inferiority, open-label, randomised, parallel-group	204	AK	X	X	
PC-T301/99	Phase III, non-inferiority, open-label, randomised, parallel-group	202	AK		X	
29030	Phase IV, randomised, intra-individual comparison	119	AK		X	
PC-T304/99	Phase III, open, randomised, parallel-group	120	BCC		X	
PC-T309/00	Phase III, non-inferiority, open-label, randomised, parallel-group	225	BD	X	X	X

ACTINIC KERATOSIS

- **Placebo-controlled study: PC-T306/99**

Randomised, double-blind, multicentre study comparing METVIXIA with placebo (excipient of METVIXIA).

Inclusion criteria:
Adult patients suffering from actinic keratosis.
At inclusion, the patients' lesions were classified by the investigator into three groups, according to thickness:

- Grade 1: minor lesion: more palpable than visible,
- Grade 2: moderate lesion: palpable and visible,
- Grade 3: thick lesion.

Grades 1 and 2 incorporate non hyperkeratosic lesions.

Only patients with 4 to 10 grade 1 or 2, previously untreated non-pigmented lesions on their face or neck and with at least one AK lesion at least 3 mm in diameter in size were included .

Treatment:
The patients were treated with photodynamic therapy with METVIXIA (n=42) or placebo (n=38) over 2 sessions with a week's interval in-between. The cream containing methyl aminolevulinate or placebo was applied for 3 hours, then the skin was illuminated by lamp (570-670 nm) at a total dose of approximately 75J/cm^2.

Primary efficacy endpoint: percentage of patients with complete response for 100% of lesions, evaluated 3 months after treatment**.**
The responses were defined as follows:

- complete response: lesion entirely disappeared,
- incomplete response: lesion not entirely disappeared,
- recurrence: recurrence of lesion after complete response 3 months after treatment.

For those patients with a single lesion, efficacy corresponded to the response level of that particular lesion.
For patients with multiple lesions, the complete response level is less that the response level per lesion. A weighting factor was therefore introduced by the number of lesions.

Results:
Characterisation of patients according to skin type: the majority of patients included in the study were of skin type I (24.5%), II (43%) or III (26.5%) according to the classification by Fitzpatrick[1]. The distribution among the groups was homogeneous.

The percentage of patients with a complete response for 100% of lesions was significantly greater in the METVIXIA group compared with that in the placebo group (ITT analysis: 79% vs 21%, p<0.0001).

- **Studies versus cryotherapy:**

PC-T301/99 and PC-T305/99 studies
Open-label, non-inferiority studies comparing METVIXIA with cryotherapy, and with placebo in study PC-T301/99.

Inclusion criteria:
Adult patients with actinic keratosis lesions that warranted cryotherapy treatment.
In study PC-T301/99, the lesions could be grade 1, 2 or 3, on the face, scalp and other locations. Patients with more than 10 lesions were not included.

Comment: patients with grade 3 lesions or whose lesions are situated in a location other than the face and the scalp do not correspond to the indication on the Marketing Authorisation.

In study PC-T305/99, the lesions could be grade 1 or 2, on the face and scalp. Patients with more than 10 lesions were not included.

Treatment:

Study PC-T301/99:

[1] According to Fitzpatrick's classification, there are 7 different phototypes :

Classification de Fitzpatrick

Phototype	Colour of skin not exposed to light	Minimum dose provoking erythema in MJ/cm²	Sensitivity to UV	Sunburn/tanning
I	White	15-30	Very sensitive	Always burns, never tans
II	White	25-40	Very sensitive	Always burns, tans slightly
III	White	30-50	Sensitive	Burns sometimes, slight uniform tan (light brown)
IV	Slightly brown	40-60	Moderately sensitive	Burns sometimes, tans (brown)
V	Brown	60-90	Very slightly sensitive	Rarely burns (dark brown)
VI	Dark brown/black	90-150	Not sensitive or only slightly sensitive	No sunburn (black)

- METVIXIA: 1 session of photodynamic therapy for lesions on the face and scalp, 2 sessions with a week's interval in-between for other locations.
- Cryotherapy: double freezing-thawing

Study PC-T305/99:
- METVIXIA : 2 sessions of photodynamic therapy with a week's interval in-between
- Cryotherapy: single freezing
  Placebo: 2 sessions of photodynamic therapy with a week's interval in-between

Primary efficacy endpoint:

Study PC-T301/99: percentage of patients with a complete response for 75 - 100% of treated lesions 3 months after treatment.
METVIXIA was considered to be non-inferior to cryotherapy if the lower limit of the 90% confidence interval of the difference between treatments (METVIXIA - cryotherapy) was greater than -15% (pre-specified non-inferiority threshold).

Study PC-T305/99: percentage of overall response per patient, weighted by the number of lesions per patient 3 months after treatment. The response of each lesion was classified as either complete (total disappearance of lesion, visually and on palpation) or incomplete (incomplete disappearance of lesion).
METVIXIA was considered to be non-inferior to cryotherapy if the lower limit of the 90% confidence interval in the difference between treatments (METVIXIA - cryotherapy) was greater than -15% (pre-specified non-inferiority threshold).

Results :

- **Table 2: Principal characteristics of patients included**

Characteristics of patients	**PC-T301/99**		**PC-T305/99**		
	PDT-METVIXIA® 1 session	**Cryotherapy Double freezing-thawing**	**PDT-METVIXIA® 2 sessions**	**Cryotherapy Single freezing**	**Placebo**
Number of patients : ITT	102	100	91	90	23
PP	98	95	87	86	19
Skin type (Fitzpatrick)(%)					
- I	5	5	34	35	52
- II	65	67	48	44	26
- III	26	24	16	20	17
- IV	4	3	3	1	4
Distribution per patient of number of lesions (%)					
- 1	20	32	25	22	31
- 2-4	48	37	49	45	48
- 5-9	27	30	18	17	17
- 10+	5	1	8	16	4
Location (%)					
- face	65	61	76	67	84
- scalp	26	30	24	33	16
- other	9	8	-	-	-
Thickness of lesion (%) :					
- thin	39	42	58	55	47
- moderate	55	49	42	45	53
- thick	6	9	-	-	-

In study PC-T301/99, the photo skin type was predominantly type II or III, with the lesions being mainly located on the face and scalp and predominantly grade 1 and 2.

In study PC-T305/99, the photo skin type was predominantly type I, II or III, with the lesions being mainly located on the face and scalp and approximately equally distributed between grade 1 and 2.

- **Table 3: Primary efficacy endpoint results of studies PC-T301/99 and PC-T305/99**

	PC-T301/99		PC-T305/99		
	METVIXIA 1 session	**Cryotherapy** Double freezing-thawing	**METVIXIA** 2 sessions	**Cryotherapy** Single freezing	**Placebo**
N (PP)	98	95	77	86	19
Assessment criteria	**Patients with CR* for 75%-100% of lesions**		**Level of response per patient**		
Value in %	55	72	90.5	68.3	13
	$CI_{95\%}$ =[45; 64]	$CI_{95\%}$ =[62; 80]	± 2.2	± 3.6	± 7.5
Difference METVIXIA - cryotherapy 90%CI	-16.5 [-27.7: -5.2]		10.7 [3.6; 17.7]		

*: complete response

In the PC-T301/99 study, the lower limit of the 90% confidence interval is less than the non-inferiority limit of –15%. As a result, the non-inferiority of METVIXIA (1 session of dynamic phototherapy) compared with cryotherapy (double freezing-thawing), in terms of the percentage of patients with a complete response for 75 to 100% of lesions treated could not be demonstrated.

In study PC-T305/99, the lower limit of the 90% confidence interval is greater than the non-inferiority limit of –15%. As a result, METVIXIA (2 sessions of dynamic phototherapy) was non-inferior to cryotherapy (single freezing), in terms of level of response per patient weighted by the number of lesions per patient.

Comment: This result should be interpreted with caution insofar as a significant number of patients with more than 10 lesions was included contrary to what was specified in the protocol. These patients were not distributed uniformly between the groups (16% of patients in the cryotherapy group versus 8% in the METVIXIA group).

Study 29030

Phase IV, randomised study with intraindividual comparison between METVIXIA (1 session repeated after an interval of three months in the event of an incomplete response) and cryotherapy (1 session repeated after an interval of three months in the event of an incomplete response).

Inclusion criteria:

Adult patients with actinic keratosis lesions of the same severity (grade 1 and 2) on both sides of the face and scalp. The patients had to have at least 3 lesions and the ratio of the number of lesions between the 2 sides could not be greater than 2.

The lesions should not have been treated with a topical treatment in the 3 months preceding the study. The presence of thick or pigmented lesions was an exclusion criterion.

Treatment:

Each patient included in the study (n=119) had one session of treatment with METVIXIA on one side of the face and one treatment of double freezing-thawing on the other side. The randomisation related to the side of the face. Any lesions that did not respond 3 months after treatment were re-treated with the same treatment.

Primary efficacy endpoint:

- Preference of patient evaluated after 6 months on a 5-point scale ranging from -2 (the left side much better than the right) to 2 (the right side much better than the left). The preference was judged on the basis of cosmetic appearance, efficacy and feeling of discomfort on the skin;
- Reduction, in percent, of number of lesions after 6 months.

Results:
The patients included had an average of 6 lesions per side (maximum 20 per side) distributed uniformly over the face and scalp. The lesions were grade 1 lesions in 60% of cases and grade 2 lesions in 40% of cases. The surface of the lesions averaged 73 mm^2 in size.

80% of cases initially treated with cryotherapy were retreated and 90% of cases initially treated with METVIXIA were retreated.

49.2% of patients preferred METVIXIA to cryotherapy, 30.4% of patients had no preference and 20.6% of patients preferred cryotherapy ($p<0.001$).

No difference was observed between METVIXIA and cryotherapy as far as percentage reduction in number of lesions after 6 months was concerned (86.7 ± 23.5% and 83.9 ± 23.5% respectively).

BASAL CELL CARCINOMA

Study versus cryotherapy: PC-T304/99

Open-label, randomised study comparing METVIXIA with cryotherapy in the treatment of superficial basal cell carcinoma (BCC).

Comment: the standard treatment in this indication is surgery.

Inclusion criteria:
Adult patients with a histologically confirmed diagnosis of primary superficial non-pigmented BCC, with fewer than 10 lesions not located within the facial H zone. The greatest diameter of the lesion should not be less than 6 mm, or greater than 15 mm on the face, 20 mm on the limbs and neck and 30 mm on the trunk. The lesions could be treated with cryotherapy.

The lesions should not have been treated previously.

Treatment:
The patients were treated once with METVIXIA or cryotherapy. If the response was incomplete after 3 months, the treatment was repeated twice more and the response evaluated again after 3 months.

Primary efficacy endpoint: evaluation after 3 months or 6 months (in the event of retreatment) of response to treatment of each lesion according to whether complete (total disappearance of lesion) or incomplete (incomplete disappearance of lesion).

Comment: a histological evaluation of the area treated was desirable in order to avoid mistakenly concluding a complete response.

Results:
The patients included (n=120) predominantly had lesions on the face (75% of lesions) and limbs (20% of lesions). The majority of patients had 1 lesion (65%), 2 lesions (15%) or 3 lesions (10%). The skin type was predominantly type II (60%) or type III (30%).

A complete response was obtained for 96% of lesions treated with METVIXIA and 90% of lesions treated with cryotherapy (ITT population).

A complete response for 100% of lesions was obtained in 92% of patients treated with METVIXIA and 90% of patients treated with cryotherapy (ITT population).

Comment: As these results were not statistically analysed, this study does not allow either treatment to be declared superior, neither can one state that there is no significant difference between the 2 treatments. Nevertheless, one can state that the results obtained for METVIXIA and cryotherapy are of the same order.

BOWEN'S DISEASE

Study PC-T309/00

Open-label, randomised, non-inferiority study comparing METVIXIA with cryotherapy or 5-FU or to placebo.

Comment: Cryotherapy and 5-FU are not standard treatments in this indication – surgery is.

Inclusion criteria:
Adult patients with Bowen's disease confirmed by biopsy within the previous 5 months and, if the lesion has shown no progression in the meantime, a biopsy at the examination. Patients should not have received treatment for their lesion within the last three months or be on immunosuppressant treatment. Strongly pigmented lesions, lesions less than 6 mm or greater than 40 mm in size and lesions located on the genitals were also excluded.

Treatment:
The patients were divided into 3 groups by the investigator: METVIXIA, cryotherapy or 5-FU and placebo (excipient of METVIXIA). The treatment methods were as follows:

- METVIXIA (n=96) and placebo (n=17): one cycle of 2 sessions of dynamic phototherapy with a week in-between, the cycle was repeated after 3 months if the response was incomplete.
- Cryotherapy (n=82): 1 session of freezing repeated after 3 months if the response was incomplete.
- 5-FU, cream (n=30): one cycle of 1 application per day for 1 week then twice a day for 3 weeks, the cycle was repeated after 3 months if the response was incomplete.

Primary efficacy endpoint: % of patients with complete response for 100% of lesions.
METVIXIA was considered to be non-inferior to standard treatment if the lower limit of the 95% confidence interval in the difference between treatments (METVIXIA – cryotherapy or %-FU) was greater than -15% (pre-specified non-inferiority threshold).

Comment: a histological evaluation of the area treated was desirable in order to avoid mistakenly concluding a complete response.

Results:
The patients included had a photo skin type that was predominantly type I (10%), II (47%) and III (37%). The majority had a single lesion (88%) and the lesions were predominantly located on the limbs (63%) and face (19%).
The majority of patients were treated with a single cycle of METVIXIA or cryotherapy. The patients treated with 5-FU were treated with a single cycle for 4 weeks (70%) or 2 4-week cycles (30%).

Table 4: Results – percentage of patients with a complete response for 100% of lesions

	METVIXIA	**Standard treatment (Cryotherapy or 5-FU)**
N (PP)	91	103 (77 + 26)
% patients with CR*	91.2	85.4
$CI_{95\%}$	[83.4 ; 96.1]	[77.1 ; 91.6]
METVIXIA - standard treatment	6.34	
$CI_{95\%}$	[-2.61 ; 15.28]	

* : complete response for 100% of lesions

The lower limit (-2.61%) of the 95% confidence interval of the difference between METVIXIA and the cryotherapy or 5-FU treatment is greater than the non-inferiority threshold of–15%. As a result, METVIXIA was non-inferior to treatment with cryotherapy or 5-FU.

3.2. Adverse events

Between 60% and 80% of patients included in the clinical trials had a local reaction at the treatment site which was attributed to the toxic effects of photodynamic therapy (phototoxicity) or to the preparation of the lesion. Normally these symptoms start as soon as the skin is exposed to light or immediately afterwards, last several hours and generally disappear the day of treatment.
The most common symptom was painful skin. The intensity of symptoms was generally weak to moderate, but in rare cases required that the light be turned off prematurely.
Other common signs of phototoxicity were erythema and oedema which could persist for one to two weeks, sometimes longer.

3.3. Conclusion

In fine or non-hyperkeratosic and non-pigmented actinic keratosis of the face and scalp, dynamic phototherapy with METVIXIA was evaluated in three comparative studies, one against placebo (excipient of METVIXIA) and two against cryotherapy (1 with a placebo arm). Different treatment methods were used in each study, but only one study (phase IV against cryotherapy) was carried out according to the dosage scheme in the METVIXIA Marketing Authorisation, i.e. 1 session of dynamic phototherapy that could be repeated after an interval of 3 months.

In the study against placebo (PC-T306/99, randomised, double-blind), the patients were treated with 2 sessions of dynamic phototherapy with a week in-between. The patients included (n=80) had 4-10 previously untreated, grade 1 or 2, non-pigmented lesions on the face or neck, with at least one lesion of AK of a minimum diameter of 3 mm. The percentage of patients with a complete response for 100% of lesions was significantly greater in the METVIXIA group than in the placebo group (ITT analysis: 79% vs 21%, $p<0.0001$).

In the study against cryotherapy (PC-T305/99 randomised, open-label), the patients were treated with 2 sessions of dynamic phototherapy with METVIXIA with a week's interval in-between or by cryotherapy (1 session of freezing). The patients included (n=204) had grade 1 or 2 AK lesions on their face and scalp. Patients with more than 10 lesions were not included. The per patient response rate, weighted by the number of lesions per patient, was 90.5% for METVIXIA and 68.3% for cryotherapy. METVIXIA was non-inferior to cryotherapy.

In the phase IV study (29030, randomised, with intra-individual comparison), METVIXIA (1 session repeated after an interval of 3 months if the response was incomplete, scheme recommended in the Marketing Authorisation) was compared with cryotherapy (1 session repeated after an interval of 3 months if the response was incomplete). The patients included (n=119) had AK lesions of the same severity (grade 1 and 2) on both sides of their face and scalp. METVIXIA was preferred to cryotherapy by 49.2% of patients, 30.4% showed no preference and 20.6% preferred cryotherapy (significant difference: $p<0.001$).

No difference was observed in the percentage reduction in number of lesions 3 months after the last treatment between METVIXIA (86.7 ± 23.5%) and cryotherapy (83.9 ± 23.5%).

In non-recurrent, superficial BCC of the trunk, limbs and neck, an open-label, randomised study compared METVIXIA (1 or 2 treatments with a 3-month interval in-between) to cryotherapy (1 or 2 sessions with a 3-month interval in-between) in patients with a histologically confirmed diagnosis of superficial, primary, non-pigmented BCC with fewer than 10 lesions not located in the H zone of the face.

A complete response was obtained for 96% of lesions treated with METVIXIA and 90% of lesions treated with cryotherapy (ITT population).

A complete response for 100% of lesions was obtained in 92% of patients treated with METVIXIA and 90% of patients treated with cryotherapy (ITT population).

No statistical analysis was carried out, however the results observed for each of these treatments are of the same order of magnitude.

In Bowen's disease, METVIXIA was compared with cryotherapy or 5-FU (according to a decision made by the investigator) in an open-label, randomised, non-inferiority study. The patients had Bowen's disease histologically confirmed; lesions that were very pigmented, and were less than 6 mm or greater than 40 mm in size or located in the genital region were excluded. A complete response for 100% of lesions was obtained for 91.2% of patients on METVIXIA (1 cycle of 2 sessions with a week's interval in-between, repeated after 3 months) and 85.4% of patients treated with cryotherapy or 5-FU,and the non-inferiority was demonstrated.

For all indications as a whole, dynamic phototherapy with METVIXIA showed a similar efficacy to cryotherapy.
The adverse events were mainly local (painful skin, erythema, oedema) and linked to phototoxicity from dynamic phototherapy.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

4.1.1. Treatment of fine or hyperkeratosic and non-pigmented actinic keratosis of the face and scalp

Actinic keratoses are lesions that occur on areas of skin exposed to the sun, most commonly in the elderly. There are normally multiple lesions which, in the absence of effective treatment can evolve into skin cancers (spinocellular carcinoma).

METVIXIA is intended as a curative treatment.

Public health benefit:

As far as public health is concerned, although quite common, the burden imposed by actinic keratoses (AK) is small since this condition has a good prognosis.

Improving the management of AK is not a public health necessity (non-drug alternatives are effective in preventing the onset of cancer). In the case of actinic keratoses with multiple lesions, this therapeutic alternative may be of interest.

In view of the clinical trial data and given the existing therapeutic alternatives, no impact is anticipated in terms of morbidity for the patients suffering from AK.
In addition, transposability of these results to clinical practice is not guaranteed inasmuch as the profile of the patients treated will probably differ from that of patients in studies.

As a result, given the available data and the existence of non-drug alternatives, no public health benefit is expected for METVIXIA in this indication.

The efficacy/safety ratio is high.

METVIXIA can be used as a first-line treatment in multiple lesions of fine and non-pigmented keratosis of the face and scalp.

The actual medical benefit of METVIXIA in this indication is substantial.

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

BCCs are the most common form of skin cancers. They can occur anywhere on the skin and from the outset can occur in multiple locations. The prognosis of BCC is usually good, they rarely metastasise. Factors such as recurrence or spread to local subcutaneous structures (the risk factors are detailed in the ANAES[2] recommendations) have a poor prognosis.
METVIXIA is intended as a curative treatment.

[2] Recommendations for the diagnosis and therapeutic management of basal cell carcinomas in adults. ANAES. (2004)

Public health benefit:

As far as public health is concerned, the burden imposed by small superficial BCC in adults is small since this cancer has a good prognosis (recurrences are rare and nobody has died from it) and the target population, i.e. patients in whom surgery is contraindicated, is small.

In the rare patients for whom surgery is contraindicated, the availability of a second effective treatment may constitute an interesting therapeutic alternative. Nevertheless, one cannot consider that there is a public health need.

In view of the clinical trial data and given the existing therapeutic alternatives, no impact is expected in terms of morbidity for patients suffering from superficial BCC.

As a result, given the available data and the existence of non-drug alternatives, no public health benefit is expected for METVIXIA in this indication.

The efficacy/safety ratio is high.
METVIXIA is a first-line treatment in inoperable patients.

The actual medical benefit of METVIXIA in this indication is substantial.

4.1.3. Treatment of non-pigmented intraepidermal carcinoma (Bowen's disease) in immunocompetent subjects when surgery is not possible.

Bowen's disease is a precancerous condition that occurs anywhere on the skin of adults, and especially in the elderly. The lesions have a tendency to spread slowly and to resist local treatment. They can evolve into spinocellular carcinomas.

METVIXIA is intended as a curative treatment.

Public health benefit:

As far as public health is concerned, the burden imposed by Bowen's disease is small given the small numbers of patients affected.

In the rare patients for whom surgery is contraindicated, the availability of a second effective treatment may constitute an interesting therapeutic alternative. Nevertheless, one cannot consider that there is a public health need.

In view of the clinical trial data and given the existing therapeutic alternatives, no impact is expected in terms of morbidity for patients suffering from Bowen's disease.

As a result, given the available data and the existence of non-drug alternatives, no public health benefit is expected for the speciality drug METVIXIA in this indication.

The efficacy/safety ratio is high.

METVIXIA is a first-line treatment in inoperable patients.

The actual medical benefit of METVIXIA in this indication is substantial.

4.2. Improvement in actual benefit

4.2.1. Treatment of fine or non hyperkeratosic non-pigmented AK of the face and scalp

METVIXIA does not provide any improvement in actual benefit (level V) compared to cryotherapy in the treatment of fine or non hyperkeratosic non-pigmented AK of the face and scalp however it does constitute an additional means of therapy.

4.2.2. Treatment of superficial, non-recurrent BCC of the trunk, the limbs and the neck

METVIXIA provides a minor improvement in actual benefit (level IV) for the treatment of superficial, non-recurrent BCC of the trunk, the limbs and the neck in the management of patients who cannot be treated surgically.

4.2.3. Treatment of non-pigmented intraepidermal carcinoma (Bowen's disease) in immunocompetent subjects when surgery is not possible.

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

4.3. Therapeutic use [2, 3, 4, 5, 6, 7, 8, 9]

Actinic keratoses, basal cell carcinomas and Bowen's disease are dermatological conditions that are principally associated with exposure to ultraviolet light. However, these skin lesions can be prevented by avoiding exposure to ultraviolet light (natural or artificial) or other triggering physical or chemical factors (ionising radiation, arsenic in the case of Bowen's disease).

The objective of treatment is to destroy the lesions and prevent their recurrence by regular monitoring after treatment. Several techniques are available: surgery, cryotherapy, radiotherapy, curettage/electrocoagulation, laser CO_2 and topical cytostatics (5-FU in AK, imiquimod in BCC and diclofenac in AK, not reimbursed). Dynamic phototherapy with METVIXIA is a new treatment in France for these conditions.

Actinic keratosis

Actinic keratoses are commonly treated with cryotherapy, which is considered to be the standard treatment when there are few lesions. Cryotherapy treatment is simple, quick and does not require any specific materials. If there is any doubt of a spinocellular carcinoma, a biopsy should be taken before destroying the lesion with nitrogen. Surgery is sometimes performed if the lesions are large; this can be followed by a graft if the area being treated is extensive. Topical 5-FU and mechanical dermabrasion are used in multiple keratoses. Alternative options for treatment include vaporising the lesions by laser CO_2 and curettage/electrocoagulation.

Role of METVIXIA:

[3] Dubertret et al. Dermatological treatments. Médecine Sciences Flamarion (2001)
[4] Skin Cancer (PDQ®) : Treatment Health Professional Version. National Cancer Institute (2006). www.cancer.gov
[5] Saurat J.-H. et al. Dermatology and sexually transmitted infections (MASSON, 4th edition)
[6] De Berker D. et al. Guidelines for the management of actinic keratoses. *British Journal of Dermatology* 2007;156:222-30
[7] Cox N.H. et al. on behalf Guidelines for management of Bowen's disease: 2006 update. *British Journal of Dermatology* 2007;156:11-21
[8] Morton C.A. et al. Guidelines for topical photodynamic therapy:. *British Journal of Dermatology* 2002;146:552-67
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Dynamic phototherapy with METVIXIA is one alternative to cryotherapy; its value lies in the treatment of multiple AK lesions of the face and/or scalp (especially in people with alopecia) as it enables all the lesions to be treated together in 1 session, resulting in less scarring. However, METVIXIA has only proven to be of interest in the treatment of superficial and non-pigmented lesions.

Basal cell carcinoma

According to the ANAES recommendations (2004), surgery is the standard treatment for BCC. The margins of the ablation will need to be histologically checked. However, the decision regarding treatment will also be based on the prognosis of the lesions, patient choice, the patient's general condition and life expectancy, accompanying treatments and illnesses, availability of techniques and the competence of the practitioner. In rare cases, cryosurgery, curettage/electrocoagulation and radiotherapy can be proposed as second-line therapy. Imiquimod is only indicated for superficial BCC of <2 cm diameter.

Role of METVIXIA:

Surgical treatment remains the standard treatment as it is the only treatment where a cure can be histologically verified. Dynamic phototherapy with METVIXIA could be used in superficial, non-recurrent BCC which has a good prognosis and has been histologically confirmed where it is not possible to operate. The indication for METVIXIA in BCC is limited to localised lesions on the limbs, trunk and neck.

In its recommendations, ANAES acknowledged in 2004 that in the absence of medications with a Marketing Authorisation in France, BCC could benefit from this technique.
The British Association of Dermatologists (2002) and NICE (National Institute for Health and Clinical Excellence, 2006) recommend dynamic phototherapy in the treatment of extensive and/or multiple superficial lesions.

Bowen's disease

According to French experts, surgery is also the standard treatment for Bowen's disease. The margins of the ablation are 3 to 5 mm and the margins should be histologically checked to ensure that the lesion is non-invasive. Other possible second-line treatments include cryotherapy, curettage-electrocoagulation, laser and chemotherapy with 5-FU. Radiotherapy is used less and less.
In their recommendations, British experts from the British Association of Dermatologists concluded that:

- there is limited evidence to suggest that surgery is effective,
- the rate of recurrence is 5-10% for available treatments as a whole
- none of the treatments appeared to be superior to the others across the range of clinical situations.

Role of METVIXIA:

Surgical treatment remains the standard treatment as it is the only treatment where a cure can be histologically verified. Dynamic phototherapy with METVIXIA can be used where it is not possible to operate. The indication for METVIXIA is limited to non-pigmented lesions in immunocompetent subjects. The lesions must be confirmed by biopsy in advance and monitored to ensure they are cured.

The British Association of Dermatologists (2002) recommends the use of dynamic phototherapy to treat extensive and/or multiple superficial lesions and/or lesions that are located in areas unlikely to scar.
NICE (2006) recommends the use of dynamic phototherapy to treat extensive and/or multiple superficial lesions.

4.4. Target population

Actinic keratosis

The target population of METVIXIA in this indication is defined by patients suffering from superficial (non-hyperkeratosic), non-pigmented AK lesions of the face and scalp.

There is little epidemiological data on AK. British[10,11] and Irish[12] data have revealed an incidence for AK of the order of 19% to 24% in the over-60s. In the Irish study, the incidence was estimated as 13.6% in males and 7.6% in females over the age of 21. Extrapolating these values to the French population (INSEE 2007 data), the number of people suffering from AK can be estimated as between 3 and 5 million.

According to the study by Frost[13] (1994), the lesions are located on the face in 20 to 60% of cases, which would reduce the population to 0.6 to 3 million people.

There is little epidemiological data that allows an estimate to be made of the proportion of superficial AK lesions. In the PC-T301/99 study which included patients with grade 1, 2 and 3 lesions, approximately 90% of the lesions were non-hyperkeratosic (grade 1 and 2).

As a result, the target population for METVIXIA in this indication can be estimated as between 0.5 and 2.7 million people.

However, not all of this population is likely to be treated with METVIXIA insomuch as cryotherapy remains the standard treatment and there are alternatives available. Moreover, the current recommendations (see §4.3) tend to reserve this treatment for extensive or multiple AKs.

Basal cell carcinoma

The target population of METVIXIA in this indication is defined by patients suffering from non-recurrent superficial BCC lesions of the trunk, limbs and neck who cannot be treated surgically.

According to the French epidemiological data[14,15,16,17], the standardised annual incidence of BCC was of the order of 70 to 80 per 100,000 inhabitants and the gross annual incidence of the order of 120 per 100,000 inhabitants over the period 1997-1999. Taking into account an annual increase in incidence of approx. 3% [14,17], and the results of a more recent study carried out in the French department Loire[18] (2005) which revealed a gross incidence of 150-160 per 100,000 inhabitants, currently the standardised incidence for the French population can be considered to be approx. 100 per 100,000 inhabitants. Extrapolating this for the

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[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

[12] O'Beirn SFO, Judge P, Maccon CF.
Skin cancer in County Galway, Ireland. In: Proceedings of Sixth National Cancer Conference, sponsored by the American Cancer Society Inc. and the National Cancer Institute, September 1968. Philadelphia : Lippincott, 1970 : 489-500

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

[14] Haut-Rhin cancer registry (1997/1998/1999).

[15] Bernard P.,et al. Etude prospective de l'incidence des cancers cutanés dépistés en pratique dermatologique dans la région de Champagne-Ardenne – Prospective study of the incidence of skin cancers detected in dermatological practice in the Champagne-Ardennes region.
Ann Dermatol Venereol. 2001; 128: 883-7.

[16] Langlois C.,., et *al.*
Descriptive epidemiology of basal cell carcinomas.
XXVIII meeting of the epidemiology and cancer registry group in Latin-speaking countries.

[17] Serre D. Basal cell carcinomas in the Loire in 2005. Epidemiological survey carried out by the Association of Dermatologists of the Loire -*Nouv. Dermatol.* 2006; 25: 242.

French population (INSEE 2007 data), the population of people suffering from BCC can be estimated at approximately. 63,000 new cases per year.
In 30-60% of cases, the lesions are on the neck, trunk and limbs (French[18] and European epidemiological data[18,19,20,21,22,23]) or 18,900 to 37,800 new cases per year.
The superficial lesions are mainly on the trunk and limbs (Bastiaens, 1998 and Lovatt[24], 2005). The localisation is superficial for 30-60% of lesions, i.e. 5,600 to 22,600 new cases per year.
There are no data that enable an estimate to be made of the percentage of non-recurrent BCC.
According to expert opinion and a recent French study (unpublished), 10 to 30% of superficial carcinomas are inoperable (extensive, multiple lesions, site of lesion making surgery difficult).
As a result, the target population for METVIXIA may be estimated at between 560 and 6,780 new patients per year.

Bowen's disease
In intra-epidermoid carcinomas (Bowen's disease), the target population for METVIXIA is defined by immunocompetent patients with non-pigmented lesions who cannot be surgically treated.
According to the French epidemiological data[14,15], the incidence of Bowen's disease is approx. 10 to 30 times less than that of BCC (100 per 100,000 inhabitants), which would correspond to a population of 2,000 to 6,000 patients per year. There are no data that enable an estimate to be made of the percentage of inoperable lesions. However, according to various published recommendations, non-surgical treatments are recommended in the event of multiple lesions (not common in Bowen's disease), extensive lesions or lesions in a location that make surgery difficult. The studies by Casacajo[25] (1996) and Degos[26] (1976) revealed that 10-20% of patients with Bowen's disease had multiple lesions.

[18] Revenga Arrantz F.,et al
Descriptive epidemiology of basal cell carcinoma and cutaneous squamous cell carcinoma in Soria (Spain) 1998-2000: a hospital-based survey
European Academy of Dermatology and Venerology *JEADV* 2004; 18: 137-41
[19] Katalinic A., Kunze U. and Schäfer T.
Epidemiology of cutaneous melanoma and non-melanoma skin cancer in Schleswig-Holstein, GermanyBritish Journal of Dermatology 2003; 149: 1200-1206
[20] Scrivener Y., Grosshans E., Cribier B.
Variations of basal cell carcinomas according to gender, age, location and histological subtype.
Br J Dermatol. 2002; 147 (1): 41-7.
[21] Boi S, Cristofolini M, et al
Epidemiology of skin tumors: data from the cutaneous cancer registry in Trentino, Italy.
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[22] Franceschi S. et al.
Site distribution of different types of skin cancer: new aetiological clues
Int J Cancer 1996 Jul 3 ; 67(1) : 24-8
[23] De Vries E et al
Rapid and cutaneous increases in incidence rates of basal cell carcinoma in the southeast Netherlands since 1973.
J Invest Dermatol 2004; 123:634-38
[24] Lovatt TJ, et al.
Associations between ultraviolet radiation, basal cell carcinoma site and histology, host characteristics, and rate of development of further tumors.
[25] Casacajo CD, Reichel M, Sanchez JL.
Malignant neoplasms associated with seborrheic keratoses. An analysis of 54 cases
Am J Dermatopathol, 1996, 18 : 278-282
[26] Degos R, Civatte J, Letessier S.
Maladie de Bowen cutanée ou muqueuse – cutaneous or mucous Bowen's disease.
Ann Dermaol Vénérol, 1976, 103 : 5-14

As a result, the target population for METVIXIA in this indication can be estimated as between 200 and 1,200 new cases per year.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for hospital use and various public services in the Marketing Authorisation.

The Transparency Committee would like a follow-up study to be carried out on patients treated with METVIXIA; the aims of this study would be to describe:

- the population treated with METVIXIA (indications, clinical symptoms, size of lesions, single or multiple locations, histology, recurrence…),
- METVIXIA administration methods (dosage, frequency and duration of treatment, accompanying treatment, role in the medical care strategy…),
- whether any histological examinations are performed (during diagnosis or follow-up),
- the clinical progress of the patients,
- the impact of tolerability on continuing treatment.

The study duration determined by the independent scientific committee will have to be justified, and must be long enough to satisfy the requirements of the Committee.

4.5.1. Packaging

Appropriate for the prescription conditions.

4.5.2. Reimbursement rate: 65%