HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

18 December 2013

ERIVEDGE 150 mg, capsule

B/28 (CIP: 34009 274 767 7 8)

Applicant: ROCHE

INN	vismodegib
ATC Code (2012):	L01XX43 (antineoplastic agents)
Reason for the request	**Inclusion**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indications concerned	**"Erivedge is indicated for the treatment of adult patients with:** • **symptomatic metastatic basal cell carcinoma (mBCC)** • **locally advanced basal cell carcinoma (laBCC) inappropriate for surgery or radiotherapy."**

Actual Benefit	**The actual benefit of ERIVEDGE is substantial in the Marketing Authorisation indication.**
Improvement in Actual Benefit	**Taking into account both the demonstration level (efficacy data limited to one non-comparative phase II study) and the absence of a valid alternative in the treatment of metastatic basal cell carcinoma and locally advanced basal cell carcinoma where surgery or radiotherapy is inappropriate, the Committee considers that ERIVEDGE provides a minor improvement in actual benefit (level IV) in the treatment strategy of these cancers.**
Therapeutic use	**ERIVEDGE represents a backup treatment for patients suffering from metastatic or locally advanced BCC where surgery or radiotherapy is inappropriate. Implementing this treatment should be decided in the SPC.**
Committee recommendation	**The Committee recommends the inclusion of ERIVEDGE 150 mg, capsule 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 dosage in the Marketing Authorisation.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation	Date initially granted: 12 July 2013 (European centralised procedure) Conditional Marketing Authorisation: • Update of the safety data for the grouped safety population (due date: June 2014), the final analysis of the SHH4476g study (pivotal study) and the interim analysis of the MO25616 study on 500 patients with a potential follow-up of one year. • Additional safety and efficacy data in patients suffering from mBCC (date due: June 2015) Temporary authorisation for use by a named patient [ATU nominative in French] prior to the Marketing Authorisation
Prescribing and dispensing conditions / special status	List I Medicine subject to hospital prescription Prescription restricted to oncologists or doctors with training in oncology.

ATC Classification	2012 L Antineoplastic and immunomodulating agents L01 Antineoplastic agents L01X Other antineoplastic agents L01XX Other antineoplastic agents L01XX43 Vismodegib

02 BACKGROUND

Review of the application for inclusion of the proprietary medicinal product ERIVEDGE 150 mg, capsule, on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use.

ERIVEDGE is a medicine based on vismodegib, a selective Hedgehog pathway inhibitor (Hh), involved in more than 90% of basal cell carcinomas (BCC).

03 THERAPEUTIC INDICATIONS

"Erivedge is indicated for the treatment of adult patients with:
- symptomatic metastatic basal cell carcinoma (mBCC)
- locally advanced basal cell carcinoma (laBCC) inappropriate for surgery or radiotherapy."

04 DOSAGE

"Erivedge should only be prescribed by or under the supervision of a specialist physician experienced in the management of the approved indication.

Posology
The recommended dose is one 150 mg capsule taken once daily.

Missed doses
If a dose is missed, patients should be instructed not to take the missed dose, but to resume with the next scheduled dose.

Duration of treatment
In clinical trials, treatment with Erivedge was continued until disease progression or until unacceptable toxicity. Treatment interruptions of up to 4 weeks were allowed based on individual tolerability.
Benefit of continued treatment should be regularly assessed, with the optimal duration of therapy varying for each individual patient.

Special populations:
Older people
No dose adjustment is required in patients aged 65 and over (see section 5.2 of the SPC). Of a total number of 138 patients in 4 clinical trials of Everidge in advanced basal cell carcinoma, approximately 40% of patients were aged 65 and over. No overall differences in safety and efficacy were observed between these patients and younger patients.

Patients with renal and hepatic impairment
The safety and efficacy of Everidge have not been studied in patients with impaired renal and hepatic function (see section 5.2 of the SPC). No specific dose recommendations for these patient populations are available. Patients with severe renal impairment or moderate to severe hepatic impairment should be carefully monitored for adverse reactions.

Paediatric population
The safety and efficacy of Erivedge in children and adolescents aged below 18 years have not been established. No data are available.
For safety reasons (see sections 4.4 and 5.3 of the SPC), Erivedge should not be used in children and adolescents aged below 18 years.

Method of administration
Erivedge is for oral use. The capsules must be swallowed whole with water, with or without food (see section 5.2 of the SPC). They must not be opened, to avoid unintended exposure to patients and health care providers."

05 THERAPEUTIC NEED

Basal cell carcinoma (BCC) is the most common cancer and represents about 80% of non-melanoma skin cancers. Most of the BCCs are easily treated with surgery or even radiotherapy. Very rarely, these lesions progress towards advanced forms which do not allow recourse to surgery or radiotherapy (locally advanced basal cell carcinoma, or laBCC). Even rarer, these lesions spread to distant sites (metastatic basal cell carcinoma, or mBCC).

The morbidity associated with these advanced forms (mBCC or laBCC inappropriate for surgery or radiotherapy) is major because of their locality, mainly on the face, and other parts which are exposed to rays, the size of the lesions, the local destruction or its spread over a large area for metastatic forms. The consequences as far as function and appearance are concerned may lead to significant deterioration in quality of life (mutilations of part of the face, pain, bleeding, infection and sepsis). These advanced forms can sometimes lead to death.

The objectives of treatment are primarily carcinological efficacy, but also optimal scar tissue and functional results. The decision on the treatment for laBCC and mBCC is taken at a multidisciplinary meeting (SPC).

06 CLINICALLY RELEVANT COMPARATORS

At this stage of the treatment of metastatic basal cell carcinoma (mBCC) and locally advanced basal cell carcinoma (laBCC) where surgery and radiotherapy is inappropriate, there is no valid treatment alternative.

◗ Conclusion

There is no clinically relevant comparator of ERIVEDGE in the treatment of mBCC and laBCC where surgery or radiotherapy is inappropriate.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	Date of MA	Status	Indications
United States	31 January 2012	Marketed	Treatment of mBCC or laBCC in adult patients with relapses after surgery or for whom surgery or radiotherapy is inappropriate.
Mexico	30 October 2012	Marketed	Treatment of adult patients with advanced BCC who are not candidates for surgery.
Israel	13 February 2013	Marketed	Treatment of adult patients with mBCC or laBCC with relapses after surgery or who are not candidates for surgery or radiotherapy.
Switzerland	30 May 2013	Not communicated	Treatment of mBCC or laBCC in adult patients with relapses after surgery or for whom surgery or radiotherapy is inappropriate.
Australia	10 May 2013	Not communicated	Treatment of adult patients with mBCC or laBCC where surgery and/or radiotherapy is inappropriate.
Ecuador	8 May 2013	Not communicated	Treatment of adult patients with advanced BCC where surgery is inappropriate.
South Korea	12 March 2013	Not communicated	Treatment of adult patients with mBCC or laBCC who are not candidates for surgery or radiotherapy (including the patients who are not candidates for surgery or radiotherapy among the patients with relapses of mBCC or laBCC following surgery).

08 ANALYSIS OF AVAILABLE DATA

The record submitted comprises two clinical studies which evaluated vismodegib (ERIVEDGE) in adult patients suffering from metastatic basal cell carcinoma (mBCC) or locally advanced basal cell carcinoma (laBCC) where surgery or radiotherapy was not appropriate:

- ERIVANCE study:[1] phase II pivotal study which evaluated efficacy and safety;
- STEVIE study:[2] phase II study which evaluated safety.

08.1 Efficacy

8.1.1 ERIVANCE study[1]

Methodology

Main objective:
Evaluate the clinical benefit in terms of percentage of objective response to vismodegib in adult patients suffering from mBCC or laBCC where surgery or radiotherapy was inappropriate.

Method:
Non-comparative, two-cohort, phase II pivotal study: mBCC cohort and laBCC cohort.

Among the inclusion criteria:

- age ≥ 18 years;
- mBCC cohort:
  - metastases, confirmed histologically;
  - metastatic stage measured using imaging (CT scan or MRI) according to the RECIST criteria;[3]
- laBCC cohort:
  - confirmed histologically, with at least one lesion ≥ 10 mm in diameter;
  - surgery and radiotherapy are inappropriate (patient considered to be inoperable by a surgeon or with a contraindication to surgery;[4] patient whose disease progressed after radiotherapy or with a contraindication to radiotherapy[5]);
- satisfactory autonomy in activities of daily living (ECOG performance status[6] ≤ 2), satisfactory haematopoietic capacity (haemoglobin > 8.5 g/dl, granulocytes ≥ 1,000/µl and platelets ≥ 75,000/µl) and satisfactory hepatic function (ASAT and ALAT ≤ 3 times the normal upper limit, bilirubin ≤ 1.5 times the normal upper limit or ≤ 3 in the case of Gilbert's syndrome).

[1] Sekulic A, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. N Engl J Med. 2012; 366(23): 2171-9. (ERIVANCE study: published data).

[2] Starnawski M, et al. A single-arm, open-label, phase II, multicenter study to assess the safety of vismodegib (GDC-0449) in patients with locally advanced or metastatic basal cell carcinoma. [Unpublished] (STEVIE study: interim protocol and reports for 150 and 300 patients).

[3] Eisenhauer E, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45(2): 228-47. (RECIST criteria, Response Evaluation Criteria In Solid Tumors).

[4] relapse of laBCC occurring at the same site after two surgical procedures or more and complete curative exeresis considered unlikely; risk of significant morbidity and/or risk of post-surgical mutilation (ablation of all or part of the face: nose, ear, eyelid, eye; amputation of a limb).

[5] hypersensitivity to radiation because of a genetic syndrome: Gorlin syndrome; some tumour sites; overexposure to radiotherapy.

[6] Oken M, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5(6): 649-55. (ECOG performance status, Eastern Cooperative Oncology Group).

Among the non-inclusion criteria:

- life expectancy ≤ 12 weeks;
- a history of other tumours in the 3 years preceding D1, apart from tumours with a minimum risk of metastasis or death (correctly treated squamous cell carcinoma, *in situ* breast carcinoma, *in situ* cervical cancer) and other diseases contraindicating the use of the study treatment (metabolic dysfunction);
- a history of treatment with vismodegib or other Hh signalling antagonists;
- other anticancer treatment (chemotherapy, other targeted therapy, topical fluorouracil or imiquimod treatment, radiotherapy, photodynamic therapy);
- inability to swallow capsules.

Treatment groups:

In the two cohorts (mBCC cohort and laBCC cohort), the patients received vismodegib orally at a dose of 150 mg/d, from D1 and until the disease progressed, unacceptable toxicity potentially linked to the treatment or withdrawal from the study.

No change to the dose was authorised during the study.

The treatment could be interrupted for up to 4 weeks so as to evaluate whether there was any intolerable toxicity or if the patient was temporarily unable to swallow the tablets, and up to 8 weeks in the event of any scheduled surgical procedure.

Primary efficacy endpoint:

Percentage of objective response, evaluated by an independent review committee.

Definition of the objective response:

- mBCC cohort: reduction in the size of the target lesions ≥ 30%, measured by imaging (CT or MRI) according to the RECIST criteria,[3] compared with what it was at baseline;
- laBCC cohort: no progression of the disease compared with how it was at baseline and at least one of the following criteria:
    - reduction in the size of the target lesions ≥ 30 %, measured by imaging (CT or MRI) according to the RECIST criteria;[3]
    - reduction in the size of the external visible part of the target lesions ≥ 30%, seen on photographs ± biopsy;
    - complete disappearance of ulcerations from all the target lesions, seen on photographs.

Among the secondary endpoints:

- percentage of objective response, evaluated by the investigator;
- median duration of the objective response, evaluated by the independent review committee on the one hand and by the investigator on the other hand;
- progression-free survival (median duration), evaluated by the independent review committee on the one hand and by the investigator on the other hand;
- overall survival (median duration), evaluated by the investigator;
- quality of life, evaluated by the SF-36 questionnaire.[7]

Statistical analysis:

A clinical benefit was considered as significant if the percentage of objective response (primary efficacy endpoint) was > 10% in patients suffering from mBCC and > 20% in patients suffering from laBCC (95% CI determined according to the Blyth-Still-Casella method, and with α risk = 0.025).

[7] Ware J, et al. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992; 30(6): 473-83.

Population of analysis:
All the patients included in the study received at least one dose of vismodegib (evaluable population in terms of safety) with confirmation of the mBCC or laBCC diagnosis by an independent pathologist (evaluable population in terms of efficacy).

Results of the main analysis

Number of patients included:
A total of 104 patients were included in the study and they received at least one dose of vismodegib:

- mBCC cohort: 33 patients (all evaluable in terms of efficacy);
- laBCC cohort: 71 patients (63 of whom were evaluable in terms of efficacy with 8 patients being excluded from the main analysis as there was no confirmation of their diagnosis by an independent pathologist).

Average duration of exposure to treatment:

- mBCC cohort: 9.7 months;
- laBCC cohort: 9.7 months.

Median duration of patient follow-up:

- mBCC cohort: 11.6 months (95% CI = [10.48; 13.01] months);
- laBCC cohort: 11.7 months (95% CI = [10.28; 12.91] months).

Characteristics of patients on inclusion:

Characteristics of patients on inclusion	mBCC cohort (n=33)	laBCC cohort (n=63)
Age (years)		
Mean (standard deviation)	61.6 (11.4)	61.4 (16.9)
Median	62.0	62.0
Min - Max	38 – 92	21 – 101
Gender		
Male	24 (72.7%)	35 (55.6%)
Female	9 (27.3%)	28 (44.4%)
ECOG performance status		
0	13 (39.4%)	48 (76.2%)
1	19 (57.6%)	13 (20.6%)
2	1 (3.0%)	2 (3.2%)
Number of target lesions		
1	9 (27.3%)	40 (63.5%)
2	4 (12.1%)	12 (19.1%)
3	9 (27.3%)	6 (9.5%)
> 3	11 (33.3%)	5 (7.9%)
Main lesion sites		
Lung	22 (66.7%)	-
Lymph nodes	7 (21.2%)	-
Mediastinum	3 (9.1%)	-
Scalp	-	18 (28.6%)
Forehead	-	15 (23.8%)
Nose	-	9 (14.3%)
Cheek	-	8 (12.7%)
Ear	-	8 (12.7%)

Results on the primary efficacy endpoint:

Primary efficacy endpoint:	mBCC cohort (n=33)	laBCC cohort (n=63)
Percentage of objective response - evaluated by an independent review committee	**10 (30.3%)**	**27 (42.9%)**
95% CI	[15.6%; 48.2%]	[30.5%; 56.0%]
p	0.0011	< 0.0001

In the mBCC cohort, the percentage of objective response evaluated by an independent review committee was 30.3% higher than the percentage of 10% fixed as the threshold for clinical benefit in this cohort.
In the laBCC cohort, the percentage of objective response evaluated by an independent review committee was 42.9% higher than the percentage of 20% fixed as the threshold for clinical benefit in this cohort.

Results of the secondary endpoints:

Secondary endpoints	mBCC cohort (n=33)	laBCC cohort (n=63)
Percentage of objective response - evaluated by the investigator	15 (45.5%)	38 (60.3%)
Median duration of the objective response - evaluated by an independent review committee - evaluated by the investigator	7.6 months 12.9 months	7.6 months 7.6 months
Progression-free survival (median duration) - evaluated by an independent review committee - evaluated by the investigator	9.5 months 9.2 months	9.5 months 11.3 months
Overall survival (median duration) - evaluated by the investigator	Not evaluable	Not evaluable
Quality of life - PCS score (physical health) - MCS score (psychological health)	– 1.9 points + 2.3 points	

08.2 Safety/Adverse effects

8.2.1 ERIVANCE study[1]

The most common adverse events:
The 104 patients included in the study all received at least one dose of vismodegib and all reported at least one adverse event.

The most common adverse events	mBCC cohort (n=33)	laBCC cohort (n=71)
Muscle spasms	21 (63.6%)	50 (70.4%)
Alopecia	19 (57.6%)	47 (66.2%)
Dysgeusia	21 (63.6%)	32 (41.0%)
Weight loss	13 (39.4%)	35 (49.3%)
Fatigue	14 (42.4%)	23 (32.4%)
Nausea	7 (21.2%)	23 (32.4%)
Loss of appetite	8 (24.2%)	16 (22.5%)
Diarrhoea	7 (21.2%)	16 (22.5%)
Constipation	6 (18.2%)	11 (15.5%)
Arthralgia	3 (9.1%)	13 (18.3%)
Cough	8 (24.2%)	8 (11.3%)
Vomiting	5 (15.2%)	10 (14.1%)
Headaches	3 (9.1%)	10 (14.1%)
Squamous cell carcinoma	3 (9.1%)	9 (12.7%)
Ageusia	2 (6.1%)	10 (14.1%)
Hypogeusia	3 (9.1%)	8 (11.3%)

Severity of adverse effects:
Among the 104 patients included in the study, 56.7% reported adverse events of grades 1 to 2, 35.6% reported adverse events of grades 3 to 4 and 6.7% reported adverse events of grade 5.
Serious adverse events were reported in 25.0% of patients and were related to the treatment in 3.8% of patients.

Adverse events, grades 3 to 5	Total population (n=104)
Weight loss	5 (4.8%)
Muscle spasms	4 (3.8%)
Fatigue	4 (3.8%)
Loss of appetite	3 (2.9%)

Adverse events, grade 5	Total population (n=104)
Death from unknown cause	3 (2.9%)
Myocardial infarction	1 (<1.0%)
Acute myocardial ischaemia	1 (<1.0%)
Meningeal disease	1 (<1.0%)
Hypovolaemic shock	1 (<1.0%)

Serious adverse events related to the treatment	Total population (n=104)
Pulmonary embolism	2 (1.9%)
Heart failure with pneumonia	1 (<1.0%)
Cholestasis	1 (<1.0%)
Syncope with dehydration	1 (<1.0%)

Number and causes of drop-outs:
Among the 104 patients included in the study, 51.9% discontinued their treatment.

Causes of drop-outs	mBCC cohort (n=33)	laBCC cohort (n=71)
Patient's decision	2 (6.1%)	18 (25.4%)
Adverse event	1 (3%)	11 (15.5%)
Disease progression	6 (18.2%)	5 (7.0%)
Death	1 (3.0%)	2 (2.8%)
Medical decision	2 (6.1%)	1 (1.4%)
Lost to follow-up	2 (6.1%)	1 (1.4%)
Not specified	0 (0.0%)	1 (1.4%)
Total	**14 (42.4%)**	**39 (54.9%)**

An analysis carried out with six additional months of follow-up listed a percentage of drop-out from treatment because of adverse events of 16.3% in the overall study population (17/104) and a frequency of adverse events of grades 3 to 5 of 48.1% (50/104).

Death:
Among the 104 patients included in the study, 15.4% died during the study. The relation between the deaths and the treatment is not known.

Causes of death	mBCC cohort (n=33)	laBCC cohort (n=71)
Disease progression	5 (15.2%)	2 (2.8%)
Acute myocardial ischaemia	-	1 (1.4%)
Stroke	-	1 (1.4%)
Meningeal disease	-	1 (1.4%)
Hypovolaemic shock	-	1 (1.4%)
Unknown cause	2 (6.1%)	3 (4.2%)
Total	**7 (21.2%)**	**9 (12.7%)**

Further analysis (carried out 6 months after the main analysis) revealed 5 additional deaths, including 4 caused by the disease progressing and 1 caused by a melanoma. In all, 20.2% of patients died during the study (main analysis and further analysis).

8.2.2 Grouped data

Vismodegib was also studied in two phase I studies. The grouped safety data concerned a total of 138 patients, including the 104 patients included in the ERIVANCE study[1] and 34 patients included in the two phase I studies.
All 138 patients reported at least one adverse event and 55.1% of patients reported adverse events of grades 1 to 2.
The most common adverse events were muscle spasms (71.7%), alopecia (63.8%), dysgeusia (55.1%), weight loss (44.9%), fatigue (39.9%) and nausea (30.4%).

8.2.3 STEVIE study[2] (MO25616 study)

Phase II, non-comparative study, the main objective of which is to evaluate the safety of vismodegib in adult patients suffering from mBCC or laBCC where surgery or radiotherapy was inappropriate.
The results available are those of the second interim analysis (on the basis of the first 300 patients, including 22 suffering from mBCC and 278 suffering from laBCC), which showed that 93% of patients reported at least one adverse event, 85% of patients reported grade 1 adverse events and 66% of patients reported grade 2 adverse events.
The most common adverse events were muscle spasms (59%), alopecia (49%), dysgeusia (41%), ageusia (26%), asthenia (23%), weight loss (16%), loss of appetite (16%), nausea (14%) and fatigue (13%).

Serious adverse events were reported in 17.7% of patients and were related to the treatment in 5.1% of patients.
Among the 22 patients suffering from mBCC, 31.8% discontinued their treatment because of the disease progressing (13.6%), death (9.1%), patient's request (4.5%) and being lost from sight (4.5%).
Among the 278 patients suffering from laBCC, 45% discontinued their treatment, mainly because of adverse events (12.6%), patient's request (12.6%), the disease progressing (5.4%) and death (8.9%).
Among the first 300 patients included, 4.3% died, including 3.3% because of adverse events (pneumonia, COPD, myocardial infarction, multi-organ failure, rectal cancer, non Hodgkin's lymphoma, cardiopulmonary failure, cardiac arrest and sudden death), 0.7% because of the disease progressing and 0.3% because of multi-organ failure.

08.3 Summary & discussion

Vismodegib (ERIVEDGE) obtained a conditional Marketing Authorisation in the treatment of symptomatic metastatic basal cell carcinoma (mBCC) or locally advanced basal cell carcinoma (laBCC) where surgery or radiotherapy is inappropriate.
This Marketing Authorisation is primarily based on a non comparative pivotal study including adult patients suffering from mBCC or locally advanced basal cell carcinoma (laBCC) where surgery or radiotherapy (ERIVANCE study[1]) was inappropriate. The patients, whose median age was 62, were included in two cohorts (mBCC cohort and laBCC cohort) and received vismodegib orally at a dose of 150 mg/d.
The percentage of objective response (reduction in the size of the target lesions ≥ 30%) was the primary efficacy endpoint of the study.
A total of 104 patients were included in the study (33 patients in the mBCC cohort and 71 patients in the laBCC cohort). The average duration of exposure to treatment was 9.7 months in the two cohorts and the median duration of patient follow-up was 11.6 months in the mBCC cohort and 11.7 months in the laBCC cohort.
In the mBCC cohort, the percentage of objective response evaluated by an independent review committee was 30.3% higher than the percentage of 10% fixed as the threshold for clinical benefit in this cohort.
In the laBCC cohort, the percentage of objective response evaluated by an independent review committee was 42.9% higher than the percentage of 20% fixed as the threshold for clinical benefit in this cohort.
The median duration of the objective response was 7.6 months in the two cohorts according to the independent review committee.

A safety analysis carried out with 6 additional months of follow-up compared with the main efficacy analysis listed a percentage of drop-outs because of an adverse event of 16.3% in the overall study population (17/104) and a frequency of adverse events of grades 3 to 5 of 48.1% (50/104); these events were primarily muscle spasms (63.8%), weight loss (46.2%), loss of appetite, fatigue (35.6%), alopecia (63.5%), and dysgeusia (51.0%). Moreover, the monitoring of the occurrence of tumours is part of the RMP. This product is teratogenic and requires contraception during the treatment and for 2 years after it has been discontinued in women and 2 months after it has been discontinued in men.

08.4 Planned studies

8.4.1 Conditional Marketing Authorisation: additional clinical studies or follow-up studies

A conditional Marketing Authorisation having been granted by the EMA, the company should complete the following measures, according to the schedule indicated:

- June 2014: send an update of the safety data for the grouped safety population, the final analysis of the SHH4476g study (ERIVANCE pivotal study) and the interim analysis of the MO25616 study (STEVIE study) on 500 patients with a potential follow-up of one year;
- June 2015: provide additional safety and efficacy data in patients suffering from mBCC, from the final analysis of the MO25616 study (STEVIE study).

8.4.2 Risk management plan (RMP):

The Risk Management Plan (RMP) essentially aims to monitor the population of women of childbearing age treated by ERIVEDGE or female partners of men treated by ERIVEDGE. Minimisation efforts focus on the prevention of fetal exposure to ERIVEDGE because of the risk of severe malformations (midline craniofacial, limbs). This risk was identified in several animal species.
Before prescribing or dispensing, all healthcare professionals able to prescribe and dispense ERIVEDGE receive educational material, in agreement with the ANSM, containing the following:

- brochure for healthcare professionals prescribing ERIVEDGE
- information card for healthcare professionals prescribing ERIVEDGE
- treatment and contraception consent form
- declaration of pregnancy form
- brochure for patients
- information card for patients
- SPC, package leaflet and labelling

The company should implement a Pregnancy Prevention Programme (PPP).

09 THERAPEUTIC USE[8,9]

Basal cell carcinoma is the most common skin cancer. Its malignancy is local. The standard treatment is surgical excision; cryosurgery or radiotherapy may be alternatives in multiple or locally advanced forms. Metastatic forms are the exception. On the other hand, multiple or locally advanced forms are much more common. The case of Gorlin syndrome is a specific case secondary to patched gene mutations which results in patients who are suffering from multiple carcinomas that have occurred prematurely. These patients undergo multiple surgical procedures resulting in deterioration and them requesting alternative treatments.
When surgery or radiotherapy are no longer effective, the treatment for locally advanced or metastatic basal cell carcinoma focuses on local or general chemotherapy (platinum salts 5 FU) often poorly tolerated in elderly patients and not completely effective.
Vismodegib (ERIVEDGE) is the first selective Hedgehog pathway inhibitor (Hh). Activation of this pathway, present in over 90% of cases of basal cell carcinoma, causes cell proliferation. It represents a backup treatment for patients suffering from locally advanced or metastatic BCC where surgery or radiotherapy is inappropriate. Implementing this treatment should be decided in the SPC.
The main benefit of drug therapy at the locally advanced stage of BCC is to reduce the tumour volume so as to allow the patient access to surgery as that alone can have a curative objective. This aspect has not been evaluated in the vismodegib pivotal study.

[8] ANAES (Agence Nationale d'Accréditation et d'Évaluation en Santé [National Health Accreditation and Assessment Agency]). Prise en charge diagnostique et thérapeutique du carcinome basocellulaire de l'adulte. Recommandations pour la pratique clinique. Argumentaire. March 2004.
[9] EPAR ERIVEDGE 2013

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

◗ Metastatic basal cell carcinoma (mBCC) and locally advanced basal cell carcinoma (laBCC), where surgery or radiotherapy is inappropriate, are serious diseases and can result in severe, disfiguring lesions and be life-threatening.

◗ ERIVEDGE is a specific, curative therapy for basal cell carcinoma.

◗ The efficacy/adverse effects ratio is high.

◗ There is no alternative drug therapy at this stage of treatment.

◗ This medicinal product is intended as a backup therapy.

◗ Public health benefit:

Basal cell carcinoma is a common cancer (projections of cancer incidence in France between 45,000 and 85,000 cases a year) generally of good prognosis as it is easily treated with surgery (+/- radiotherapy). Locally advanced or metastatic forms are rare. Thus, the public health burden of locally advanced or metastatic basal cell carcinoma is low because of the restricted number of patients concerned (estimated to be about 400 to 800 new cases a year).
The improvement in the treatment of this cancer is a public health need falling within the scope of established priorities [Public Health Law 2004, Cancer Plan, Plan for the improvement of the quality of life of chronic sufferers].
In light of the available clinical trial data (objective response to the treatment in a non-comparative, phase II study), an impact in terms of morbidity or quality of life is not expected.
This proprietary medicinal product could be an interesting alternative to the extent that a reduction in the size of the tumour could allow recourse to surgery (this point has not as yet been demonstrated). Moreover, the transferability of these results to clinical practice cannot be guaranteed because of existing uncertainties in terms of safety (specifically infectious, cardiovascular, neurological, teratogenic).
No impact on the organisation of healthcare is expected.
Consequently, it is not expected that the proprietary medicinal product ERIVEDGE will benefit public health in this indication.

Taking account of these points, the Committee considers that the actual benefit of ERIVEDGE is substantial in the indications and at the dosage in the Marketing Authorisation.

010.2 Improvement in actual benefit (IAB)

Taking into account both the demonstration level (efficacy data limited to one non-comparative phase II study) and the absence of a valid alternative in the treatment of metastatic basal cell carcinoma and locally advanced basal cell carcinoma where surgery or radiotherapy is inappropriate, the Committee considers that ERIVEDGE provides a minor improvement in actual benefit (level IV) in the treatment strategy of these cancers.

010.3 Target population

The target population of ERIVEDGE is made up of patients suffering from metastatic basal cell carcinoma (mBCC) or locally advanced basal cell carcinoma (laBCC) where surgery or radiotherapy is inappropriate.

The incidence of BCC in France is unknown as most cases of BCC are treated with surgery or do not require particular follow-up.

Only a few registries have specifically studied this type of cancer (cancer registries in the departments of Doubs[10] and Haut-Rhin[11] in France, registry of cancer in the Canton of Vaud[12] in Switzerland).

Based on incidence data from these three registries (standardised incidences compared with the worldwide population), it is possible to calculate the average annual increase in the incidence of BCC in each of these departments:

- Doubs: +3.24 cases/100,000 men/year and +2.46 cases/100,000 women/year;
- Vaud: +1.33 cases/100,000 men/year and +1.76 cases/100,000 women/year;
- Haut-Rhin: +0.48 cases/100,000 men/year and -0.26 cases/100,000 women/year.

Assuming this average annual increase is constant from year to year, it is possible to estimate the incidence of BCC per projection in 2012 in each of these departments:

- Doubs: 139.7 cases/100,000 men/year and 117.5 cases/100,000 women/year;
- Vaud: 95.8 cases/100,000 men/year and 97.3 cases/100,000 women/year;
- Haut-Rhin: 83.1 cases/100,000 men/year and 56.3 cases/100,000 women/year.

Considering the lowest projections of incidence (83.1 cases/100,000 men/year and 56.3 cases/100,000 women/year in Haut-Rhin) and the highest (139.7 cases/100,000 men/year and 117.5 cases/100,000 women/year in Doubs) and applying them to the French population for 2012[13] (31,769,000 men and 33,817,000 women), it is possible to estimate the number of new patients suffering from BCC in France in 2012:

- Low projection: 26,394 men/year and 19,052 women/year;
- High projection: 44,383 men/year and 39,732 women/year.

The incidence of mBCC would be less than 0.1% of all BCC.[8] The incidence of laBCC, where surgery or radiotherapy is inappropriate, is unknown, but it should be noted that the percentage of relapse per analysis of 5-year survival is about 1% with surgery[8] (conventional surgical excision and Mohs micrographic surgery).

Assuming that the incidence of mBCC and laBCC, where surgery or radiotherapy is inappropriate, is at most about 1% and applying it to the estimation of the number of new patients suffering from

[10] Grange F. Epidémiologie des cancers cutanés in B. Guillot. Dépistage et cancers cutanés. Collection Dépistage et cancer sous la direction de Daniel Serin. Springer-Verlag France, Paris, 2008. cited by l'INCA (Institut National du Cancer [National Cancer Institute]). Détection précoce des cancers de la peau. Mesure 17, action 17.2 du Plan Cancer. November 2011.]

[11] Halna J, et al. Etude épidémiologique des cancers cutanés basée sur la population d'un département français de 1988 à 1996. Résultats du registre des cancers du Haut-Rhin. Nouv Dermatol 2000; 19: 48-55. [cited by ANAES (Agence Nationale d'Accréditation et d'Évaluation en Santé [National Health Accreditation and Assessment Agency]). Prise en charge diagnostique et thérapeutique du carcinome basocellulaire de l'adulte. Recommandations pour la pratique clinique. Argumentaire. March 2004.]

[12] Levi F, et al. Trends of skin cancer in the canton de Vaud 1976-92. Br J Cancer 1995; 72: 1047-53. [cited by ANAES (Agence Nationale d'Accréditation et d'Évaluation en Santé [National Health Accreditation and Assessment Agency]). Prise en charge diagnostique et thérapeutique du carcinome basocellulaire de l'adulte. Recommandations pour la pratique clinique. Argumentaire. March 2004.]

[13] INSEE (Institut National de la Statistique et des Études Économiques [National Institute of Statistics and Economic Studies]). Evolution of the population up to 2013. Provisional data as at end 2012.

BCC in France in 2012, it is possible to estimate the maximum number of new patients suffering from mBCC or laBCC where surgery or radiotherapy is inappropriate in France in 2012:

- Low projection: 264 men/year and 191 women/year, i.e. about 400 new cases/year;
- High projection: 444 men/year and 397 women/year, i.e. about 800 new cases/year.

Overall, the target population of ERIVEDGE may be estimated at most between 400 and 800 new patients per year with mBCC and laBCC where surgery or radiotherapy is inappropriate.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion of ERIVEDGE 150 mg, capsule 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 dosage in the Marketing Authorisation.

◗ Packaging

It is not appropriate for the prescription conditions as regards indication, dosage and treatment duration. The Committee wishes to reiterate that, in accordance with its deliberations of 20 July 2005, standardisation of pack size to 30 days is recommended for treatments lasting one month.

◗ Proposed reimbursement rate: 100%