HAUTE AUTORITÉ DE SANTÉ

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# TRANSPARENCY COMMITTEE

## Opinion

## 20 March 2013

## VOTUBIA 2.5 mg, tablet

**B/30 (CIP: 219 475-8)**

## VOTUBIA 5 mg, tablet

**B/30 (CIP: 219 476-4)**

Applicant: NOVARTIS PHARMA SAS

| | |
|---|---|
| INN | everolimus |
| ATC Code (2011) | L01XE10 (antineoplastic, mTOR inhibitor) |
| Reason for the review | **Extension of the indication** |
| List(s) concerned | **National Health Insurance** (French Social Security Code L.162-17)<br>**Hospital use** (French Public Health Code L.5123-2) |
| Indication(s) concerned | **"VOTUBIA is indicated for the treatment of adult patients with renal angiomyolipoma (AML) associated with tuberous sclerosis complex (TSC) who are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but who do not require immediate surgery."** |

| | |
|---|---|
| **Actual Benefit (AB)** | **Substantial AB** |
| **Improvement in Actual Benefit (IAB)** | **Given the efficacy of VOTUBIA (everolimus) in reducing renal angiomyolipoma volume associated with tuberous sclerosis complex in adult patients, VOTUBIA provides a substantial improvement in actual benefit (IAB III) in the treatment of patients not requiring immediate surgery (nephrectomy or embolisation).** |
| **Therapeutic use** | |
| **Recommendations** | **Inclusion on the list of medicines in the extension of indication** |

# 01 ADMINISTRATIVE AND REGULATORY INFORMATION

| | |
|---|---|
| Marketing Authorisation (procedure) | Date of initial Marketing Authorisation: 2/09/2011 (Centralised "conditional" Marketing Authorisation, rapporteur = Germany)<br>Date of the extension of the indication: 05/11/2012<br><br>The initial Marketing Authorisation awarded was conditional; the collection and transmission of long-term survival data based on the duration of response and the time before progression for studies C2845 and M2301 (studies for SEGA) were requested from the applicant by EMA.<br><br>This extension of the indication is accompanied by obligations and requirements relating to, in particular, kinetic and genotoxic potential information and long-term data from the pivotal study M2302 (see section 8.4 of the Opinion).<br><br>This proprietary medicinal product had a Risk Management Plan, in particular, including monitoring the following "significant" risks:<br>- Identified risks: Non-infectious pneumonitis, severe infections, anaphylactic reactions, stomatitis, wound healing complications, elevation of serum creatinine, proteinuria, renal failure, hyperglycaemia, diabetes de novo, dyslipidaemia, hypophosphataemia, heart failure, Cytopenia, haemorrhage, thromboembolic risk, secondary amenorrhoea, reactivation or exacerbation of pre-existing infections and safety of hepatically compromised patients.<br>- Potential risk: reprotoxicity, teratogenicity, developmental delay, infertility, pancreatitis and cholelithiasis. |
| Prescribing and dispensing conditions / special status | List I<br>Medicine for hospital prescription only.<br>Medicine requiring special monitoring during treatment.<br><br>Orphan medicinal product. |
| ATC Classification | 2011<br>L Antineoplastic and immunomodulating agents<br>L01 Antineoplastic agents<br>L01X Other antineoplastic agents<br>L01XE protein tyrosine kinase inhibitors<br>L01XE10 Everolimus |

# 02 BACKGROUND

On 4 January 2012, the Transparency Committee recommended that VOTUBIA 2.5 and 5 mg was included on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the " treatment of patients aged 3 years and older with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery" (substantial AB, IAB II).

This request for inclusion concerns an extension of the indication to patients with renal angiomyolipoma (AML) associated with tuberous sclerosis complex (TSC) who are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but who do not require immediate surgery.

## 03 THERAPEUTIC INDICATIONS

"**Renal angiomyolipoma associated with tuberous sclerosis complex (TSC)**
**VOTUBIA is indicated for the treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) who are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but who do not require immediate surgery.**
**The efficacy was demonstrated on analysis of the variation in sum of angiomyolipoma volumes.**

Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC)
VOTUBIA is indicated for the treatment of patients aged 3 years and older with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC), who require therapeutic intervention but are not amenable to surgery.
The efficacy is demonstrated on analysis of variation in SEGA volume. Further clinical benefits, such as improvement in disease-related symptoms, have not been demonstrated."

## 04 DOSAGE

"Treatment with VOTUBIA should be initiated by a physician experienced in the treatment of patients with TSC and therapeutic drug monitoring.

Dosage
*Renal angiomyolipoma associated with TSC*
The recommended dose of VOTUBIA is 10 mg once daily.

Management of severe or intolerable suspected adverse reactions may require temporary dose reduction and/or interruption of VOTUBIA therapy. If dose reduction is required, the suggested dose is approximately 50% lower than the daily dose previously administered (see also section 4.4).

Table 1 summarises recommendations for dose reduction, interruption or discontinuation of VOTUBIA in the management of adverse reactions. General management recommendations are also provided as applicable. The clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment."

*Table 1 VOTUBIA dose adjustment and management recommendations in the event of adverse reactions*

| **Adverse effect** | **Severity**[1] | **VOTUBIA dose adjustment**[2] **and management recommendations** |
|---|---|---|
| Non-infectious pneumonitis | Grade 1<br>Asymptomatic, radiographic findings only | No dose adjustment required.<br>Initiate appropriate monitoring. |
| | Grade 2<br>Symptomatic, not interfering with ADL[3] | Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to ≤ grade 1.<br>Re-initiate VOTUBIA at a lower dose.<br>Discontinue treatment if failure to recover within 4 weeks. |
| | Grade 3<br>Symptomatic, interfering with ADL,[3] oxygen indicated | Interrupt VOTUBIA until symptoms resolve to ≤ grade 1.<br>Rule out infection, and consider treatment with corticosteroids.<br>Consider re-initiating VOTUBIA at a lower dose. If toxicity recurs at grade 3, consider discontinuation. |
| | Grade 4<br>Life-threatening, ventilatory support indicated | Discontinue VOTUBIA, rule out infection, and consider treatment with corticosteroids. |
| Stomatitis | Grade 1<br>Minimal symptoms, normal diet | No dose adjustment required.<br>Manage with non-alcoholic or salt water (0.9%) mouth wash several times a day. |
| | Grade 2<br>Symptomatic but can eat and swallow a modified diet | Temporary dose interruption until recovery to ≤ grade 1.<br>Re-initiate VOTUBIA at same dose.<br>If stomatitis recurs at grade 2, interrupt dose until recovery to ≤ grade 1. Re-initiate VOTUBIA at lower dose.<br>Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol) with or without topical corticosteroids(i.e. triamcinolone oral paste).[4] |
| | Grade 3<br>Symptomatic and unable to eat and swallow | Temporary dose interruption until recovery to ≤ grade 1.<br>Re-initiate VOTUBIA at a lower dose.<br>Manage with topical analgesic mouth treatments (i.e. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[4] |
| | Grade 4<br>Symptoms associated with life-threatening consequences | Discontinue VOTUBIA and treat with appropriate medical therapy. |
| Other non-haematological toxicities (excluding metabolic events) | Grade 1 | If toxicity is tolerable, no dose adjustment required.<br>Initiate appropriate medical therapy and monitor. |
| | Grade 2 | If toxicity is tolerable, no dose adjustment required.<br>Initiate appropriate medical therapy and monitor.<br>If toxicity becomes intolerable, temporary dose interruption until recovery to ≤ grade 1. Re-initiate VOTUBIA at same dose.<br>If toxicity recurs at grade 2, interrupt VOTUBIA until recovery to ≤ grade 1. Re-initiate VOTUBIA at lower dose. |
| | Grade 3 | Temporary dose interruption until recovery to ≤ grade 1.<br>Initiate appropriate medical therapy and monitor.<br>Consider re-initiating VOTUBIA at a lower dose. If toxicity recurs at grade 3, consider discontinuation. |
| | Grade 4 | Discontinue VOTUBIA and treat with appropriate medical therapy. |
| Metabolic events (e.g. hyperglycaemia, dyslipidaemia) | Grade 1 | No dose adjustment required.<br>Initiate appropriate medical therapy and monitor. |
| | Grade 2 | No dose adjustment required.<br>Manage with appropriate medical therapy and monitor. |
| | Grade 3 | Temporary dose interruption.<br>Re-initiate VOTUBIA at a lower dose.<br>Manage with appropriate medical therapy and monitor. |
| | Grade 4 | Discontinue VOTUBIA and treat with appropriate medical therapy. |

[1] Severity grade description: 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening

symptoms.

2 If dose reduction is required, the suggested dose is approximately 50% lower than the dose previously administered.

3 Activities of daily living (ADL)

4 Avoid using agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

## 05 THERAPEUTIC NEED[1,2,3,4]

Tuberous sclerosis complex (TSC) is a multi-system autosomal dominant condition, characterised by the occurrence of benign tumours (hamartoma), as the result of abnormalities to certain embryonic cells in various organs. It can have an impact on several sites, mainly affecting the central nervous system, skin, the kidneys, the heart and the lungs. Neurological signs, such as seizures, mental issues and developmental delay dominate the clinical outlook.

Occurrence in the kidneys is through the appearance of renal angiomyolipoma, which are generally bilateral. These angiomyolipoma are benign tumours, with the main complication being the risk of haemorrhage.
Angiomyolipoma larger than 4 cm are more at risk of complications. As a preventive measure, it is recommended that they are treated with embolisation or surgery.

Haemorrhagic AMLs are an emergency clinical situation, requiring immediate surgery. In this context, in the presence of haemorrhagic AMLs, embolisation is proposed as a first-line treatment. If embolisation is not possible or in the presence of AML > 5 cm a partial nephrectomy may be proposed.

A kidney transplant may also be suggested in cases of renal impairment.

As preventive treatment for complications of AML, VOTUBIA (everolimus) is the first palliative medicinal product enabling angiomyolipoma volume to be reduced; however it does enable them to be reduced completely (unlike curative surgery).

[1]Dr Wolkenstein "Tuberous sclerosis complex", Orphanet, February 2008.
[2]Pfister et al. Stratégie diagnostique et thérapeutique des angiomyolipomes [Diagnostic and therapeutic approach of angiomyolipoma]. Progrès thérapeutique 2002,12 :108-13.
[3]Rouvières et al. Atteintes de la sclérose tubéreuse de Bourneville : recommandations de prise en charge [The impact of tuberous sclerosis complex: treatment recommendations] Progrès en urologie 2012: 367-79.
[4]Lymphangioleiomyomatosis LTC guide. HAS March 2012.

# 06 CLINICALLY RELEVANT COMPARATORS

## 06.1 Medicinal products

VOTUBIA is the first treatment available in the specific indication "renal angiomyolipoma (AML) associated with tuberous sclerosis complex (TSC) that are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but which do not require immediate surgery."

## 06.2 Other health technologies

Arterial embolisation can also be used if there are AML at risk of complications.
A partial nephrectomy may be proposed in cases of failed embolisation or when this treatment is not possible.
VOTUBIA is used in cases where these procedures are not possible or are not relevant.

### ◗ Conclusion

**There are no relevant comparators.**

# 07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

| Country | Reimbursement | | |
|---|---|---|---|
| | Indication<br><br>Reimbursed Yes/No/Assessment in progress | | Scope (indications) and condition(s) |
| Germany | Reimbursed since September 2011 in the indication for SEGA and since November 2012 in the indication for AML. | | NA |
| United Kingdom | Reimbursed since October 2011 in the indication for SEGA | Assessment in progress in the indication for AML. | NA |
| Italy | Assessment in progress in both SEGA and AML indications. | | |
| Spain | Assessment in progress in both SEGA and AML indications. | | |

# 08 ANALYSIS OF THE AVAILABLE DATA

The assessment of the efficacy and safety of VOTUBIA (everolimus) for angiomyolipoma is based on:

- a phase III (pivotal), randomised, double-blind study (M2302-EXIST-2), that compared the efficacy of everolimus versus placebo in terms of the reduction in angiomyolipoma volume in 118 patients with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis,
- a sub-group analysis of patients with angiomyolipoma defined *a posteriori,* from the M2301 study (pivotal study of the first indication for SEGA), means that the results are only exploratory; therefore they will not be presented in this opinion.

## 08.1 Efficacy: study M2302- EXIST-2

Method: randomised, double-blind, phase III study, comparing everolimus (VOTUBIA) with placebo, carried out on 118 patients with angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis; patients were monitored up to progression of the angiomyolipoma, unacceptable toxicity or treatment discontinuation from any cause observed. The final analysis was performed 6 months after the last patient had been randomised.

Inclusion criteria: patients 18 years and older with:

- tuberous sclerosis complex defined according to Gomez criteria (see Appendix) by two major signs or one major sign + 2 minor signs, or sporadic lymphangioleiomyomatosis,
- a diagnosis of renal angiomyolipoma,
- at least one angiomyolipoma lesion ≥ 3 cm confirmed by two successive radiological assessments.

Treatments:

- Everolimus 10 mg/m$^2$/day, n=79,
- Placebo, n=39.

Primary efficacy endpoint: response rate (percentage of responder patients), defined as:

- a volume reduction of angiomyolipoma ≥ 50%; the angiomyolipoma volume being equivalent to the sum of the volumes of all identified lesions,
- absence of new angiomyolipoma developing that are above 1 cm diameter in size,
- absence of an increase in renal volume ≥ 20% of NADIR,
- absence of grade ≥ 2 haemorrhagic angiomyolipoma.

MRI investigations were performed at 3 months and at 6 months, then every 6 months.

RESULTS:

The median age of patients included was 32 years in the everolimus group and 29 years in the placebo group. Tuberous sclerosis complex had been identified in 97.5% of patients in the everolimus group and 92.3% in the placebo group.

The proportion of lesion volumes was slightly different at inclusion: 84.8% of patients in the everolimus group versus 79.5% of patients in the placebo group presented with lesions larger than 4 cm in diameter.

*Table 1: Response rate (analysis on ITT basis)*

| | Everolimus n=78 | Placebo n=39 |
|---|---|---|
| **Responder patients** | N=33/78 | N=0/39 |
| Percentage [95% CI] | 41.8% [30.8; 53.4] | 0% [0.0; 9.0] |
| Difference vs. placebo [95% CI] | **41.8 [23.5; 58.4]** | |
| p versus placebo | **<0.0001** | |
| Non-responder patients | | |
| - No clinical progress | 32 (40.5%) | 31 (79.5%) |
| - Progression of angiomyolipoma | 1 (1.3%) | 2 (5.1%) |
| - Not recorded | 13 (16.5%) | 6 (15.4%) |

A significant reduction in responder rate was observed with everolimus versus placebo: 41.8% versus 0, difference 41.8 [23.5; 58.4], p<0.0001.
No clinically relevant progress (>50%) was observed in 40.5% of patients in the everolimus group and 79.5% in the placebo group (statistical test not available).

## 08.2 Adverse effects

In the phase III Exist-2 study, adverse effects were observed in 76/79 patients in the everolimus group (96.2%) and 25/39 patients in the placebo group (64.1%). Serious adverse effects (grade 3-4) were observed in 29.1% of patients in the everolimus group versus 7.7% of patients in the placebo group respectively.
The most common (>11%) adverse effects were:

- stomatitis: 48.1% vs. 2.6%,
- hypercholesterolaemia: 20.3% vs. 2.6%,
- mouth ulcers: 16.5% vs. 25.1%,
- acne: 15.2% vs. 5.1%,
- asthenia: 12.7% vs. 7.7%,
- anaemia: 11.4% vs. 2.6%.

## 08.3 Summary & discussion

The efficacy and safety of everolimus (VOTUBIA) in angiomyolipoma (AML) were evaluated in a placebo-controlled study (Exist-2), in patients with angiomyolipoma associated with tuberous sclerosis complex. The response rate was defined as the reduction ≥ 50% in AML volume; the absence of new AML > 1 cm, an increase in renal volume ≥ 20% and grade ≥ 2 haemorrhagic AML.

**Efficacy**
The response rate was higher with everolimus than with placebo: 41.8% versus 0, difference 41.8 [23.5; 58.4], p<0.0001.
No clinically relevant progress (reduction ≥ 50% in AML volume) was observed in 40.5% of patients in the everolimus group and 79.5% in the placebo group (statistical test not available).

**Safety**
The most commonly observed adverse events in these studies were: stomatitis, hypercholesterolaemia, mouth ulcers, acne, asthenia and anaemia.

**Discussion**

The efficacy of everolimus was demonstrated in the variation in angiomyolipoma volume but not for clinical endpoints such as the improvement in disease-related symptoms: haemorrhage or renal impairment.
However, when everolimus does reduce the angiomyolipoma volume, it does not enable it to be reduced totally. Also, treatment discontinuation is likely to result in the restart of tumour growth. Chronic treatment with everolimus is thus potentially required while the safety of an elevated cumulative dosage is unknown.
Finally, unlike with cerebral lesions (SEGA) where the size of the tumour is proportional to the seriousness and requires emergency treatment, this is not the case for renal lesions (AML).

## 08.4 Study programmes

Within the framework of its Marketing Authorisation, this extension of the indication comes with obligations and requirements dictated by the Marketing Authorisation, including, in particular:

- adequate documentation of the pharmacokinetics of everolimus in children (CL/F, volume apparent, Cmax, Cmin, ASC, etc.), including (but not limited to) the impact of age, weight, body surface area and the joint administration with enzyme inducers, in order to increase the still limited understanding of the properties of everolimus in this group of patients,
- a re-assessment of the genotoxic potential of the impurities of everolimus,
- the submission of the clinical study report including the extension phase of study M2302 (study of angiomyolipoma).

# 09 THERAPEUTIC USE[1,3, 4,5]

Tuberous sclerosis complex (TSC) is a multi-system autosomal dominant condition, characterised by the occurrence of benign tumours (hamartoma), as the result of abnormalities to certain embryonic cells, in various organs. It has an impact on several sites, mainly affecting the central nervous system, skin, the kidneys, the heart and the lungs. Neurological signs, such as seizures, mental issues and developmental delay dominate the clinical outlook.

Occurrence in the kidneys is through the appearance of renal angiomyolipoma, which are generally bilateral. The main problem caused by these angiomyolipoma, which are benign tumours, is the risk of haemorrhage. This is particularly significant when they are larger than 4 cm in diameter.
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Renal asymptomatic angiomyolipoma < 4 cm in diameter do not justify systematic treatment, as long as symptoms do not occur. They must be monitored annually via ultrasound. Angiomyolipoma that are > 4 cm in diameter or with an intratumoural aneurysm > 5 mm pose an increased risk of haemorrhage. They should be monitored twice yearly via ultrasound in order to assess their growth. When a preventive treatment for asymptomatic AML is selected, embolisation should be proposed as a first-line treatment; surgery may be suggested in cases of failure of embolisation or in certain specific cases (isolated AML, extrarenal location etc.).

Haemorrhagic AML are an emergency clinical situation requiring immediate surgery. In this context, arterial embolisation is proposed as a first-line treatment. If embolisation is not possible or when the size of the angiomyolipoma is greater than 5 cm, a partial nephrectomy may be proposed and should be as conservative as possible.

A kidney transplant may also be suggested in cases of renal impairment.

<u>The therapeutic use of VOTUBIA</u>:
As preventive treatment for extensive angiomyolipoma with a risk of complications, in a non-haemorrhagic context, VOTUBIA (everolimus) is the first palliative treatment that enables angiomyolipoma volume to be reduced; however it does not enable them to be reduced completely, unlike curative surgery.
However, treatment discontinuation leads to the re-start of tumour growth, making the treatment chronic while the safety of an elevated cumulative dosage is still unknown. As a result, according to experts, everolimus should only be for patients with extensive angiomyolipoma at risk of complications, in a non-haemorrhagic context not able to undergo immediate surgery (embolisation or nephrectomy**)**.
Being treated with everolimus should not mean that the patient misses the opportunity for surgery; it is not an alternative to surgery, but a temporary treatment, potentially in preparation for surgery itself.

[5] Pfister et al. Stratégie diagnostique et thérapeutique des angiomyolipomes [Diagnostic and therapeutic approach of angiomyolipoma]. Progrès thérapeutique 2002,12 :108-13.

# 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

◗ Renal angiomyolipoma (AML) are one of the manifestations of tuberous sclerosis complex. They are benign renal tumours with the primary complication being spontaneous haemorrhagic rupture, which in rare cases, may lead to chronic renal impairment and may possibly even be fatal.

◗ Everolimus (VOTUBIA) reduces AML volume, but without actually reducing them completely, and is a palliative treatment,

◗ These medicinal products are first-line therapies in patients with extensive AML at risk of complications, in a non-haemorrhagic context and not able to undergo immediate surgery (embolisation or nephrectomy**)**.

◗ At the present time, there are no treatment alternatives.

The efficacy/adverse effects ratio for this medicinal product is high.

◗ Public health benefit:
Tuberous sclerosis complex (TSC) is a rare genetic condition. Renal angiomyolipoma (AML) are the most common renal manifestation of TSC and occur in 34% to 80% of patients. VOTUBIA is indicated in patients not requiring embolisation or immediate conservative surgery. Due to the small number of patients concerned, the public health burden of the population likely to be treated with VOTUBIA for AML associated with TSC is low.
The results from the placebo-controlled study have shown the short-term efficacy of VOTUBIA in the reduction in the size of AML (palliative treatment) (41.9% vs. 0% of responders). No improvement in short-term morbidity (in particular, in terms of an impact on haemorrhages and renal function) was highlighted in this study.
Only short-term data is available (70% of patients with follow-up < 1 year, median radiological follow-up < 6 months and median treatment duration = 38 weeks).
Available data, therefore, do not enable the impact of VOTUBIA to be quantified in terms of medium to long-term morbidity (renal function, haemorrhages, safety of treatment), mortality and quality of life compared with current treatments.
The transferability of study data into current clinical practice is acceptable.
Consequently, it is not expected that VOTUBIA will benefit public health in this new indication.

**As a result, the Committee considers that the actual benefit of VOTUBUIA is substantial in the extension of the indication in adult patients with renal angiomyolipoma (AML) associated with tuberous sclerosis complex (TSC) who are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but who do not require immediate surgery.**

**The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and/or on the list of medicines approved for hospital use in this extension of the indication and at the dosages in the Marketing Authorisation.**

**◗Proposed reimbursement rate: 65%**

## 010.2 Improvement in actual benefit (IAB)

Given the efficacy of VOTUBIA (everolimus) in reducing extensive renal angiomyolipoma volume associated with tuberous sclerosis complex, VOTUBIA provides a substantial improvement in actual benefit (IAB III) in the treatment of adult patients who are at risk of complications and are not able to undergo immediate surgery (nephrectomy or embolisation).

## 010.3 Target population[1,3]

The target population of VOTUBIA corresponds to patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC), who are not able to undergo immediate surgical resection.

This population can be estimated from the following data:

- according to Orphanet[1] data, the prevalence of TSC in the general population is estimated at 8.8/100,000 in Europe, which, when relating that value to the French population, corresponds to approximately 5,800 patients,
- renal angiomyolipoma affect 34% to 80% of patients, which is 1,900 to 4,600 patients,
- according to experts, only 50% of patients require treatment (950 to 2,300 patients) and approximately 1/3 of these patients are not able to undergo immediate surgery (nephrectomy or embolisation), which is 320 to 770 patients.

**Estimation**
The target population of VOTUBIA in this extension of the indication is between 320 and 770 patients.

# 011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗**Packaging:** appropriate for the prescription conditions.

The Transparency Committee would like to receive additional information, which will enable the therapeutic use of VOTUBIA in current clinical practice to be documented in the management of AML in patients with tuberous sclerosis complex (clinical characteristics of patients, progress under treatment).

## Appendix

**Table 5-1 Diagnostic criteria for Tuberous Sclerosis Complex**

| **Major Features** |
|---|
| 1. Facial angiofibromas or forehead plaque<br>2. Non-traumatic ungual or periungual fibroma<br>3. Hypomelanotic macules (three or more)<br>4. Shagreen patch (connective tissue nevus)<br>5. Multiple retinal nodular hamartomas<br>6. Cortical tuber[a]<br>7. Subependymal nodule<br>8. Subependymal giant cell astrocytoma<br>9. Cardiac rhabdomyoma, single or multiple<br>10. Lymphangioleiomyomatosis[b]<br>11. Renal angiomyolipoma[b] |
| **Minor Features** |
| 1. Multiple, randomly distributed pits in dental enamel<br>2. Hamartomatous rectal polyps[c]<br>3. Bone cysts[d]<br>4. Cerebral white matter radial migration lines[a,d]<br>5. Gingival fibromas<br>6. Non-renal hamartoma[c]<br>7. Retinal achromic patch<br>8. 'Confetti' skin lesions<br>9. Multiple renal cysts[c] |
| Definite Tuberous Sclerosis Complex:<br>Either two Major Features or one Major Feature plus two Minor Features. |
| a. The co-occurrence of cerebral cortical dysplasia and cerebral white matter radial migration lines should be considered as one major feature of TSC.<br>b. In patients with both lymphangioleiomyomatosis and renal angiomyolipoma, another feature of TSC must be identified before a definite diagnosis is assigned.<br>c. Histologic confirmation of these features is suggested.<br>d. Radiographic confirmation of these features is sufficient. |