**TRANSPARENCY COMMITTEE**  
**Opinion**  
**26 June 2013**

**VOTRIENT 200 mg, film-coated tablets**  
B/30 (CIP: 491 313 4)  
**VOTRIENT 400 mg, film-coated tablets**  
B/30 (CIP: 491 315 7)  
B/60 (CIP: 491 316 3)  

Applicant: GlaxoSmithKline  

<table>
<thead>
<tr>
<th>INN</th>
<th>pazopanib</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC code (year)</td>
<td>L01XE (protein kinase inhibitors)</td>
<td></td>
</tr>
<tr>
<td>Reason for the request</td>
<td>Inclusion</td>
<td></td>
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</tbody>
</table>
| List(s) concerned | National Health Insurance (French Social Security Code L.162-17)  
Hospital use (French Public Health Code L.5123-2) |  |
| Indication(s) concerned | “VOTRIENT is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.” |  |
### Actual Benefit

- **First-line treatment of advanced renal cell carcinoma**
  The actual benefit of VOTRIENT is low in the first-line treatment of advanced renal cell carcinoma.
  
- **Patients who have received prior cytokine therapy for advanced disease**
  Taking account of the clinical data from a placebo-controlled pivotal study previously assessed by the Committee, the lack of any direct comparison with a tyrosine kinase inhibitor (TKI) already available as second-line therapy, particularly sorafenib, and the absence of any new data in patients who have received prior cytokine therapy, the Committee considers that the actual benefit remains insufficient to justify reimbursement by National Health Insurance in the second-line treatment of metastatic renal cell carcinoma.

### IAB

- VOTRIENT does not provide an improvement in actual benefit (IAB V, non-existent) in the first-line treatment of advanced renal cell carcinoma.
  Second-line treatment: not applicable

### Therapeutic use

- VOTRIENT is a first-line treatment for advanced renal cell carcinoma.
## 01 ADMINISTRATIVE AND REGULATORY INFORMATION

<table>
<thead>
<tr>
<th>Marketing Authorisation</th>
<th>14 June 2010 (centralised procedure)</th>
</tr>
</thead>
</table>
| Prescribing and dispensing conditions / special status | List I  
Medicine for hospital prescription only. Prescription restricted to oncologists or doctors with cancer training. Medicine requiring special monitoring during treatment. |
| ATC Classification | 2012  
L : Antineoplastic and immunomodulating agents  
L01 : Antineoplastic agents  
L01X : Other antineoplastic agents  
L01XE : Protein kinase inhibitors  
L01XE11 : Pazopanib |
02 BACKGROUND

VOTRIENT obtained centralised conditional marketing authorisation for the treatment of advanced renal cell carcinoma in June 2010. On 1 July 2013, the European Commission lifted the conditional status of the marketing authorisation.

In its opinion of 2 February 2011, the Transparency Committee did not recommend inclusion of VOTRIENT on the list of medicines refundable by National Health Insurance or on the list of medicines approved for use by hospitals and various public services. In this opinion, the Committee took account of the following points:

"In view of the available clinical data based on a pivotal placebo-controlled study and in the absence of any direct comparison with the drugs already available, the Transparency Committee considers that the level of evidence of the results observed is inadequate for evaluating the level of effect of VOTRIENT or its role in the treatment of renal cell carcinoma. In the absence of a direct comparison with the tyrosine kinase inhibitors (TKI) already available, notably sunitinib in first-line therapy and sorafenib in second-line therapy, it is not possible to eliminate loss of opportunity for patients with regard to these drugs.

In the current state of the dossier and while awaiting the results of the non-inferiority study VEG108844 comparing VOTRIENT with sunitinib, the Transparency Committee considers that the actual benefit is insufficient to justify reimbursement by National Insurance."

The company has submitted a new application for the inclusion of its VOTRIENT products under the indication of advanced renal cell carcinoma, on the basis of new data, in particular a non-inferiority study versus sunitinib, which is discussed in detail in this document.

03 THERAPEUTIC INDICATION

"Advanced renal cell carcinoma (RCC)

VOTRIENT is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.

Soft tissue sarcoma (STS)

VOTRIENT is indicated for the treatment of adult patients with selective subtypes of advanced soft tissue sarcoma (STS) who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy.

The efficacy and safety of pazopanib have only been established in certain STS histological tumour subtypes (see section 5.1 of the SPC)."

See the Transparency Committee opinion of 9 January 2013 for this indication.

04 DOSAGE

"The recommended dose of pazopanib is 800 mg once daily.

Dose modifications:

Dose modification should be in 200 mg increments in a stepwise fashion based on individual tolerability in order to manage adverse reactions. The dose of pazopanib should not exceed 800 mg."
**05 THERAPEUTIC NEED**

Renal cell carcinomas account for 2% to 3% of cancers in adults. Histologically, 70% to 75% of these are clear cell tumours. Since the advent of targeted therapies, the median survival time for metastatic renal cell carcinoma is estimated to be 40 months.

The aim when treating advanced renal cell carcinoma is to improve overall survival and quality of life.

The treatment of advanced renal cell carcinoma depends on the prognostic criteria defined by the Memorial Sloan Kettering Cancer Center (MSKCC) classification, which takes into account general condition (Karnofsky index), the time between the initial diagnosis and first-line treatment, the LDH and haemoglobin levels and the corrected serum calcium level.

Until 2006, the treatment options essentially consisted of immunotherapy (interleukin-2 and interferon-alpha).

### First-line treatments

In patients with a good or intermediate prognosis, the first-line treatments are sunitinib (SUTENT), used in about 2/3 of patients, or the combination bevacizumab (AVASTIN)/interferon-alpha (ROFERON-A).

In patients with a good prognosis, such as patients with one metastatic site and a Karnofsky index > 80%, the cytokines (aldesleukin [PROLEUKIN] or interferon alpha [ROFERON-A]) are alternatives. In patients with a poor prognosis, the recommended treatment is temsirolimus (TORISEL), an mTOR inhibitor.

### Second-line treatments

If cytokines fail (aldesleukin [PROLEUKIN] or interferon-alpha [ROFERON-A]), tyrosine kinase inhibitors may be offered: sorafenib (NEXAVAR), axitinib (INLYTA) or sunitinib (SUTENT).

If VEGFR-TKIs fail (sunitinib, sorafenib and bevacizumab), everolimus (AFINITOR), a selective mTOR inhibitor, is available as second- or third-line treatment. Axitinib (INLYTA) is an option for the second-line treatment of advanced renal cell carcinoma after sunitinib fails.

**06 CLINICALLY RELEVANT COMPARATORS**

**06.1 Medicinal products**

### First-line treatment of advanced renal cell carcinoma:

Tyrosine kinase inhibitors:
- SUTENT (sunitinib), indicated for the treatment of advanced and/or metastatic renal cell carcinoma (mRCC)
- TORISEL (temsirolimus), indicated for the first-line treatment of patients with advanced renal cell carcinoma who have at least three of six MSKCC prognostic risk factors

Monoclonal antibodies:

- AVASTIN (bevacizumab) in combination with interferon alpha-2a, indicated for the first-line treatment of patients with advanced and/or metastatic renal cell carcinoma

Cytokines:
- ROFERON-A (interferon alpha-2a), indicated for the treatment of advanced renal cell carcinoma
- PROLEUKIN (aldesleukin), indicated for the treatment of metastatic renal cell carcinoma

Second-line treatment of advanced renal cell carcinoma:
Tyrosine kinase inhibitors:
- AFINITOR (everolimus), indicated for the treatment of patients with advanced renal cell carcinoma whose disease has progressed on or after treatment with VEGF-targeted therapy
- NEXAVAR (sorafenib), indicated for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy
- INLYTA (axitinib), indicated for the treatment of adult patients with advanced renal cell carcinoma after failure of prior treatment with sunitinib or a cytokine

Conclusion

The comparators listed are all clinically relevant with the exception of:
- TORISEL, as it is only indicated in patients with at least three of six prognostic risk factors
- the cytokines, because of their limited therapeutic use (patients with a low prognostic risk)

### INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

<table>
<thead>
<tr>
<th>Country</th>
<th>REFUNDED</th>
<th>Population(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES/NO</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>Yes</td>
<td>Marketing authorisation population</td>
</tr>
<tr>
<td>20 EU countries including Germany, Ireland, Sweden, Finland, Belgium, Netherlands, Norway</td>
<td>Yes</td>
<td>Marketing authorisation population</td>
</tr>
</tbody>
</table>

### SUMMARY OF PREVIOUS ASSESSMENTS

<table>
<thead>
<tr>
<th>Date of opinion (reason for request)</th>
<th>CT opinion of 2 February 2011 following application for inclusion on the list of medicines refundable by National Health Insurance and the list of medicines approved for hospital use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>“VOTRIENT is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.”</td>
</tr>
<tr>
<td>Actual Benefit (wording)</td>
<td>Insufficient (see Background section)</td>
</tr>
<tr>
<td>Improvement in Actual Benefit (wording)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Studies requested</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
The application includes the results of a non-comparative phase II study, a comparative pivotal study (VEG105192) and its open-label follow-up phase (VEG107769; patients who were on placebo receiving pazopanib), which have already been examined by the Committee (TC opinion of 02/02/2011).

Follow-up data from the pivotal study were collected from a small number of patients originally randomised to the placebo group (n=71) and then treated with open-label VOTRIENT after the between-group comparison had finished (study named VEG107769). In view of the methodology, these data are unlikely to offer a sufficient level of evidence for the efficacy and safety of the medicinal product.

New data were provided for first-line treatment in support of this application for inclusion:
- the non-inferiority study VEG108844 versus sunitinib
- the VEG113046 (PISCES) study, which aimed to evaluate patient preference between pazopanib and sunitinib as a first-line treatment for metastatic kidney cancer

The application cites the results of an indirect comparison, performed by the company, versus the available medicinal products. It should be noted that in the original application assessed in 2011, the company had attempted to perform an indirect comparison, but the methodological deficiencies observed (namely a poor network and very wide confidence intervals) meant that no reliable conclusions could be drawn from these data.

The new analysis excludes treatments with marketing authorisation for the treatment of metastatic renal cell carcinoma, particularly bevacizumab and sorafenib, and the indirect comparison is based on a subgroup from the pazopanib pivotal study (first line) and on data from a study of sunitinib. Given the methodology used, this new approach cannot identify the contribution of pazopanib to the first-line treatment of metastatic renal cell carcinoma.

No new data have been provided for second-line treatment.

### 09.1 Efficacy

#### (A) Reminder of data already examined by the Committee

**VEG102616 study**
A non-comparative phase II study undertaken between October 2005 and September 2006 in a population of 225 patients with metastatic or locally recurrent renal cell carcinoma. The other inclusion criteria were ECOG PS score of 0 or 1, and normal organ function. Patients with brain or leptomeningeal metastases could not be included.

VOTRIENT was administered orally as a single daily dose of 800 mg until disease progression, unacceptable toxicity, death, or patient’s or investigator’s decision.

After 12 weeks of treatment, the response rate (primary endpoint) was 34.7%. The median duration of response was 68 weeks. The stabilisation rate was 47.1%.

**VEG105192 study**
A randomised, placebo-controlled, double-blind study in patients with locally advanced and/or metastatic renal cell carcinoma, which evaluated the efficacy and safety of VOTRIENT (800 mg daily) versus placebo. The primary endpoint was progression-free survival and the main secondary endpoint was overall survival.

Out of the 435 patients enrolled, 233 were first-line patients who were treatment-naïve, and 202 were second-line patients who had previously been treated with interleukin-2 or interferon alpha. The median age of the patients was 59 years. In 93% of cases the prognosis was good or intermediate according to the MSKCC classification.

In the overall population, median progression-free survival (the primary endpoint) was longer with VOTRIENT than with placebo (9.2 versus 4.2 months, i.e. an absolute gain of 5 months (HR= 0.46
[0.34 – 0.62]). There was no difference between the two groups in median overall survival (21.1 months on VOTRIENT versus 18.7 months on placebo, NS).

In the subgroup of patients on first-line treatment, there was an absolute gain in median progression-free survival of 8.3 months in favour of VOTRIENT (11.1 months versus 2.8 months). For second-line treatment, this gain was 3.2 months.

The quality-of-life data did not reveal any difference between the two groups.

Treatment discontinuation due to adverse events was twice as common in the VOTRIENT group as in the placebo group (15% versus 6%). Liver function abnormalities were reported in 3.8% of patients. Diarrhoea was the most common serious adverse event in the VOTRIENT group (2.1%). Overall, VOTRIENT demonstrated its efficacy in renal cell carcinoma compared with placebo in terms of progression-free survival, with no established impact on either overall survival or quality of life.

(B) New data for first-line treatment

VEG108844 study

An open-label, phase III, randomised study comparing pazopanib with sunitinib in patients with locally advanced or metastatic renal cell carcinoma who had received no prior systemic therapy.

Methodology:

The primary analysis in the study was a non-inferiority analysis of progression-free survival. The statistical analysis was based on the following hypothesis: non-inferiority would be established if the upper limit of the 95% confidence interval for relative risk was below 1.25. This margin corresponded to a maximum acceptable reduction of efficacy between the two treatment groups of 2.2 months less progression-free survival on pazopanib.

The primary efficacy endpoint was progression-free survival, defined as the time from randomisation to documentation of disease progression, or death from any cause. Blind reading of follow-up scans was performed by an independent committee.

The secondary endpoints were:
- overall survival, defined as the time from randomisation to death due to any cause
- response rate, defined as the percentage of patients with complete response (CR) or partial response (PR) according to the Response Evaluation Criteria for Solid Tumours (RECIST)
- response duration, defined as the time between the first documented evidence of CR or PR and the first documentation of disease progression or death due to any cause (whichever occurred first)
- quality of life evaluated using three questionnaires: FKSI-19, FACIT-F and the Cancer Treatment Satisfaction Questionnaire (CTSQ)

Patients were 1:1 randomised to receive either:
- pazopanib 800 mg, administered orally once daily
- sunitinib 50 mg daily for 4 weeks followed by 2 weeks with no treatment, and then resumed in the next cycle

Each of these treatments was continued until disease progression, death, toxicity judged as unacceptable or withdrawal of consent.

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6 The FKSI (Functional Assessment of Cancer Therapy-Kidney Symptom Index) is a scale for evaluating the symptoms related to kidney cancer and its treatments, consisting of 15 items (maximum score = 60). The FKSI-DRS subscale, consisting of 9 items (maximum score = 36), more specifically evaluates the impact of treatment on symptoms related to the disease.

7 A scale consisting of 13 items with 4 levels (4 = no fatigue; 0 = exhaustion)
Results:

A total of 1,110 patients were randomised (557 in the pazopanib group and 553 in the sunitinib group).

The median age of the patients was 61 years. The disease was metastatic in 98% of cases. In 83% of cases, patients had a good or intermediate prognosis according to the MSKCC classification. About three quarters of patients were in good general health (Karnofsky score: 90-100). Almost all patients (94%) had an LDH level ≤ 1.5 times the normal value.

A similar percentage of patients in each treatment group had previously undergone nephrectomy (82% in the pazopanib group and 84% in the sunitinib group).

The results presented are those that have been analysed by an independent committee.

Results for the primary efficacy endpoint:

The study’s main analysis was performed only in the ITT population. The hazard ratio (HR) for the primary endpoint was 1.0466 with a 95% confidence interval upper limit of 1.22, which was therefore below the limit of 1.25 set in the protocol (see Table 1).

There was no analysis of the primary efficacy endpoint in the per-protocol population. However, a sensitivity analysis performed in the per-protocol population (pazopanib, n=501; sunitinib, n=494) showed a HR for median progression-free survival of 1.069 [0.910; 1.255]. Given the pre-set margin, this analysis cannot demonstrate non-inferiority between the two treatments.

Table 1: Results of the non-inferiority test for progression-free survival (ITT population)

<table>
<thead>
<tr>
<th>Numbers, n (%)</th>
<th>Pazopanib (N=557)</th>
<th>Sunitinib (N=553)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (event)</td>
<td>21 (4)</td>
<td>28 (5)</td>
</tr>
<tr>
<td>Disease progression (event)</td>
<td>315 (57)</td>
<td>295 (53)</td>
</tr>
<tr>
<td>Censored, follow-up complete</td>
<td>156 (28)</td>
<td>168 (30)</td>
</tr>
<tr>
<td>Censored, follow-up ongoing</td>
<td>65 (12)</td>
<td>62 (11)</td>
</tr>
</tbody>
</table>

**Adjusted hazard ratio**

Estimate (95% CI) 1.0466 (0.8982 – 1.2195)

**Estimated progression-free survival (months)**

<table>
<thead>
<tr>
<th>quartile (95% CI)</th>
<th>Pazopanib</th>
<th>Sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st quartile (95% CI)</td>
<td>4.2 (3.1 – 4.5)</td>
<td>4.0 (2.9 – 4.4)</td>
</tr>
<tr>
<td>2nd quartile (95% CI)</td>
<td>8.4 (8.3 -10.9)</td>
<td>9.5 (8.3 – 11.1)</td>
</tr>
<tr>
<td>3rd quartile (95% CI)</td>
<td>19.3 (16.6 – 22.1)</td>
<td>22.2 (19.3 – 26.3)</td>
</tr>
</tbody>
</table>

Secondary endpoint results:

There was no difference in overall survival between the two groups: 45% of patients (n=250) died in the pazopanib group versus 46% (n=252) in the sunitinib group.

There was no difference in overall response between the two groups: 33% in the pazopanib group versus 29% in the sunitinib group.

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*The three risk factors related to survival are:
- Karnofsky score < 80%
- Serum haemoglobin levels at the lower limit of normal
- Corrected serum calcium > 10 mg/dL
Good risk profile (no risk factors)
Intermediate risk profile (1-2 risk factors)
Poor risk profile (3 risk factors)*
The time to response was 3 months in the pazopanib group and 4.3 months in the comparator group. The duration of response was 13.8 months in the pazopanib group and 18 months in the comparator group.

The quality of life evaluation scores showed no difference on the FKSI-19 scale, and variable results on the two FACIT-F and CTSQ (Cancer Treatment Satisfaction Questionnaire) scales. A statistically significant difference could be noted in one measure, but this was sometimes below the recognised threshold of clinical relevance:
- In analysis of the total FACIT-F scores, the difference of 2.32 observed between pazopanib and sunitinib treatment in the general fatigue score was statistically significant, but the minimum clinically relevant difference for this score is 3.0.
- In the Cancer Treatment Satisfaction Questionnaire (CTSQ), a difference of 8.5 points was observed, but the minimum clinically relevant difference for this score is 10.3.
Consequently, no conclusions can be drawn from these results as to a difference between the two treatments in terms of quality of life.

**VEG113046 (PISCES) study**
A randomised, double-blind, cross-over study in patients with metastatic kidney cancer who had received no prior systemic therapy, with the primary objective of evaluating patient preference for treatment with pazopanib versus sunitinib.

Patients in the “PS” group received 800 mg pazopanib (4 x 200 mg) orally once daily for 10 weeks, followed by a 2-week washout period, then 50 mg sunitinib (4 x 12.5 mg) orally once daily for 4 weeks, then 2 weeks of placebo, then 50 mg sunitinib (4 x 12.5 mg) orally once daily for 4 weeks. The opposite sequence applied to patients in the “SP” group: 50 mg sunitinib (4 x 12.5 mg) orally once daily for 4 weeks, then 2 weeks of placebo, then 50 mg sunitinib (4 x 12.5 mg) orally once daily for 4 weeks, followed by a 2-week washout period, then 800 mg pazopanib (4 x 200 mg) orally once daily for 10 weeks.

The primary endpoint was patient preference as indicated by the answer to the following question: “Now that you have completed both treatments, which of the two drugs would you prefer to continue to take as the treatment for your cancer, assuming that both drugs will work equally well in treating your cancer?”

**Results:**
A total of 169 patients were randomised. One patient was randomised in error and was thus excluded from the analysis. Patient preference (the primary endpoint) was 22% for sunitinib and 70% for pazopanib. Given the objective chosen, no conclusions can be drawn from this study as to the efficacy and safety of pazopanib versus sunitinib.
09.2 Adverse effects

The safety data from the non-inferiority study versus sunitinib revealed the following points:
- The treatment withdrawal rate due to adverse events was 24% in the pazopanib group versus 19% in the sunitinib group. These events were primarily abnormal liver function tests (6%) in the pazopanib group and cytopenia (3%) in the sunitinib group.
- The most frequent adverse events (> 40% in both treatment groups) were diarrhoea, fatigue, nausea and hypertension, as well as palmar plantar erythrodysesthesia (hand-foot syndrome) only in the sunitinib group. Of these adverse events, fatigue (63% vs. 55%) and hand-foot syndrome (50% vs. 29%) were more common in the sunitinib group than in the pazopanib group. There was a higher incidence of diarrhoea (63% vs. 57%) and hypertension (46% vs. 41%) in the pazopanib group than in the sunitinib group.

09.3 Summary & discussion

In June 2010, VOTRIENT (pazopanib) obtained centralised conditional marketing authorisation, in the absence of any data versus an active comparator, for the treatment of advanced renal cell carcinoma (first-line and second-line). At the EMA's request, the company promised to submit the results of a non-inferiority study (VEG108844), comparing VOTRIENT with SUTENT (sunitinib) in the treatment of patients with locally advanced and/or metastatic renal cell carcinoma, in February 2012.

The Transparency Committee had considered that as the application stood on 2 February 2011, the actual benefit of pazopanib was insufficient for reimbursement by National Health Insurance for the treatment of advanced renal cell carcinoma.

First-line treatment of advanced renal cell carcinoma

In support of its new application for inclusion, the company submitted the results of a randomised open-label study (VEG108844) which had the primary objective of establishing the non-inferiority of pazopanib to sunitinib in patients with locally advanced or metastatic renal cell carcinoma who had received no prior systemic therapy.

A total of 1,110 patients were randomised (557 in the pazopanib group and 553 in the sunitinib group); the median age of the patients was 61 years.

The primary efficacy endpoint was progression-free survival, defined as the time from randomisation to the first documentation of disease progression, or death due to any cause.

In the main analysis (ITT population), the hazard ratio (HR) for the primary endpoint was 1.0466 with a 95% confidence interval upper limit of 1.22, which was therefore below the limit of 1.25 set in the protocol.

However, there was no per-protocol analysis, and this result was not corroborated by the sensitivity analysis in the per-protocol population (pazopanib, n=501; sunitinib, n=494), which showed a HR for median progression-free survival of 1.069 [0.910; 1.255]. The upper limit of the 95% confidence interval (1.255) was greater than the pre-set margin.

Overall survival and overall response did not differ between the two groups.

No reliable conclusions could be drawn from the quality of life evaluation scores as to any difference between the two treatments. In fact, these results varied depending on the scale used: there was no difference on one scale (FACIT-F), although there were differences on the FKSI-19 and CTSQ (Cancer Treatment Satisfaction Questionnaire) scales but with values below the threshold for clinical relevance, meaning no reliable conclusions can be drawn as to a difference between these two treatments.

The safety profile differed between the two groups, with notably a higher incidence of abnormal liver function tests (ALT) in the pazopanib group and a higher incidence of hand-foot syndrome in the sunitinib group.

Another randomised, double-blind, crossover study of pazopanib versus sunitinib (PISCES) had the primary objective of evaluating the preference of 169 patients. This showed a more common
preference for pazopanib than for sunitinib (70% vs. 22%) but no conclusions as to the efficacy and safety of pazopanib versus sunitinib can be drawn.

The Committee wishes to emphasise the following points:
- The result that pazopanib is non-inferior to sunitinib is the subject of serious doubt. In fact, the result found in the ITT population, which increases the chances of a non-inferiority conclusion, was not corroborated by the sensitivity analysis performed in the per-protocol population. The lack of confirmation in the per-protocol population cannot confirm the absence of non-inferiority with certainty, but there is legitimate doubt.
- The clinical significance of the non-inferiority threshold defined in the protocol corresponds to an acceptable reduction in efficacy of 2.2 months’ progression-free survival, which is too much from the patient’s point of view.
- The acceptable reduction in efficacy in this study is not counterbalanced by a gain, particularly not in terms of safety.
- Due to its methodology and objective, no conclusions as to the efficacy and safety of pazopanib in comparison with sunitinib can be drawn from the PISCES study, which had the main objective of evaluating patient preference for treatment with pazopanib versus sunitinib.

**Second-line treatment of advanced renal cell carcinoma: patients who have received prior cytokine therapy**

As no new data have been provided in patients who have received prior cytokine therapy, the Transparency Committee considers that the conclusions of its opinion dated 2 February 2011 do not need to be changed.

**010 THERAPEUTIC USE**

The treatment algorithm for metastatic renal cell carcinoma is based mainly on the identification of prognostic factors for the disease using the MSKCC\(^9\) classification, which was established in the era of immunotherapy but still remains the reference. This enables three prognostic groups (good, intermediate or poor) to be defined from clinical and laboratory criteria. As first-line therapy for locally advanced or metastatic disease, sunitinib (SUTENT) or a combination of bevacizumab (AVASTIN) and interferon alfa are the treatments recommended for patients with a good or intermediate prognosis. Temsirolimus (TORISEL) is reserved in the guidelines for patients with a poor prognosis. VOTRIENT is a first-line treatment for advanced renal cell carcinoma.

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\(^10\) Memorial Sloan-Kettering Cancer Center
TRANSPARENCY COMMITTEE CONCLUSIONS

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

011.1 Actual benefit

- **First-line treatment of advanced renal cell carcinoma**
  - Renal cell carcinoma is a serious and life-threatening disease.
  - These proprietary medicinal products are intended as specific curative cancer therapy.
  - The efficacy/adverse effects ratio is low.

  **Public health benefit:**
  In France, the incidence of renal cell carcinoma is estimated to be about 11,000 new cases per year (InVS projections, 2010\(^\text{11}\)). In 2005, it was the 12\(^\text{th}\) most common cause of death from cancer, accounting for 2.5% of all cancer deaths.\(^{12}\) The public health burden of renal cell carcinoma can be regarded as moderate. The public health burden for the subpopulation of patients with advanced renal cell carcinoma is considered to be moderate.

  Improving the management of cancer patients and their quality of life is a public health need which is an established priority (Law of 9 August 2004 on public health policy, Cancer Plan 2009-2013, Plan to improve the quality of life of patients with chronic diseases 2007-2011).

  In view of the results available from the phase III non-inferiority study versus sunitinib, pazopanib is not expected to have any additional impact, in comparison with sunitinib, in terms of reducing morbidity and mortality, especially as doubts remain as to the demonstration of non-inferiority due to the discordance in the progression-free survival results between the ITT analysis (non-inferiority demonstrated) and the sensitivity analysis in the PP population (non-inferiority not demonstrated).

  Furthermore, the differences in quality of life noted between patients treated with pazopanib and those treated with sunitinib in this study are not clinically relevant for any of the questionnaires used (below the established minimum clinically relevant difference). Therefore, no impact on quality of life is expected.

  The applicability of the results presented to clinical practice is acceptable.

  No impact on the provision of healthcare is expected.

  VOTRIENT is therefore unlikely to contribute any response to the identified public health need.

  - Alternative medicinal products exist.
  - This is a first-line therapy.

  Taking account of the level of evidence (see Conclusion section) for the efficacy of VOTRIENT in the first-line treatment of metastatic renal cell carcinoma, the Committee considers that its actual benefit is low.

- **Second-line treatment in patients who have received prior cytokine therapy for advanced disease**
  - Renal cell carcinoma is a serious and life-threatening disease.
  - These proprietary medicinal products are intended as specific curative cancer therapy.
  - The efficacy/adverse effects ratio is low.

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Public health benefit:
In France, the incidence of renal cell carcinoma is estimated to be about 11,000 new cases per year (InVS estimates, 2010). In 2005, it was the 12th most common cause of death from cancer, accounting for 2.5% of all cancer deaths. The public health burden of renal cell carcinoma can be regarded as moderate. The public health burden for the subpopulation of patients with advanced renal cell carcinoma is considered to be moderate.
Improving the management of cancer patients and their quality of life is a public health need which is an established priority (Law of 9 August 2004 on public health policy, Cancer Plan 2009-2013, Plan to improve the quality of life of patients with chronic diseases 2007-2011).
In view of the results of the placebo-controlled VEG105192 study previously examined by the Committee and in the absence of any new data, VOTRIENT is not expected to have any impact, as a second-line treatment for advanced renal cell carcinoma, on the morbidity, mortality and quality of life of patients treated. It is unclear whether the results presented are applicable to clinical practice. No impact on the provision of healthcare is expected. VOTRIENT is therefore unlikely to contribute any response to the identified public health need. Consequently, no public health benefit is expected from VOTRIENT in patients with advanced renal cell carcinoma who have received prior cytokine therapy.

Alternative medicinal products exist.
Its use as a second-line treatment after cytokines have failed has not been established.

In the absence of any new efficacy data for VOTRIENT as a second-line treatment for advanced renal cell carcinoma, the Committee considers that the actual benefit remains insufficient to justify reimbursement by National Health Insurance.

011.2 Improvement in actual benefit (IAB)
VOTRIENT does not provide an improvement in actual benefit (IAB V, non-existent) in the first-line treatment of advanced renal cell carcinoma.

011.3 Target population
The target population of VOTRIENT consists of patients with advanced (locally advanced and/or metastatic) renal cell carcinoma who have not previously been treated (first line). This population can be estimated from the following data:
- In 2011, a projection by the InVS estimates that there were 11,092 new cases of renal cell carcinoma in France.
- Clear-cell renal cell carcinoma accounts for 70% to 85% of renal cancers, i.e. between 7,764 and 9,428 patients.
- According to publications, the incidence of patients diagnosed with locally advanced and/or metastatic renal cell carcinoma from the outset ranges from 15% to 50%. The mean value of 30% cited in the EPAR for INLYTA will be used for the purposes of calculation.

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(between 2,329 and 2,828 patients). Approximately 30\%^{14} to 40\%^{18} of localised cases will progress to advanced or metastatic disease (between 1,630 and 2,640 patients). Therefore, the number of first-line patients with advanced disease is between 3,960 and 5,468 first-line patients per year.

The target population of VOTRIENT as a first-line treatment for advanced renal cell carcinoma is estimated to be 4,000 to 5,500 patients per year.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee:

- recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication: first-line treatment of advanced renal cell carcinoma

- **does not recommend** inclusion on the list of medicines refundable by National Health Insurance or on the list of medicines approved for hospital use in the second-line treatment of advanced renal cell carcinoma

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