TRANSPARENCY COMMITTEE

OPINION

2 February 2011

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

Applicant: GLAXOSMITHKLINE

pazopanib

ATC Code: L01XE11

List I
Medicine restricted to hospital use. Prescription restricted to specialists in oncology or to physicians with competence in oncology. Medicine requiring special monitoring during treatment.

Orphan drug status (29 June 2006)

Date of “conditional” (centralised) Marketing Authorisation: 14 June 2010

A “conditional” Marketing Authorisation was granted for this medicinal product. This means that additional evidence is awaited for this medicinal product. The European Medicines Agency will reassess all new information about this medicinal product every year, and if necessary, the Summary of Product Characteristics will be updated.

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

Medical, Economic and Public Health Assessment Division
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
pazopanib

1.2. Background
Pazopanib is a multi-target tyrosine kinase inhibitor of Vascular Endothelial Growth Factor Receptors (VEGFR)-1, -2, and -3, and platelet-derived growth factor (PDGFR)-α and -β.

1.3. Indication
"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."

1.4. 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."
2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

L : Antineoplastic and immunomodulating agents
L01 : Antineoplastic agents
L01X : Other antineoplastic agents
L01XE : Protein kinase Inhibitors
L01XE11 : Pazopanib

2.2. Medicines in the same therapeutic category

Tyrosine kinase inhibitors:
- SUTENT (sunitinib) is indicated for the treatment of advanced/metastatic renal cell carcinoma (MRCC).
- NEXAVAR (sorafenib) is indicated for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or patients who are considered unsuitable for such therapy.

2.3. Medicines with a similar therapeutic aim

Tyrosine kinase inhibitors (whose indication is not identical to that of VOTRIENT):

- TORISEL (temsirolimus) is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC) who have at least three of six prognostic risk factors.
- AFINITOR (everolimus) is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

Monoclonal antibodies:
- AVASTIN (bevacizumab) in combination with interferon alpha-2a is indicated for first line treatment of patients with advanced and/or metastatic renal cell cancer.

Cytokines:
- ROFERON-A (interferon alpha-2a) is indicated for the treatment of advanced renal cell carcinoma.
3. ANALYSIS OF AVAILABLE DATA

The submitted dossier contains one non-comparative phase II study (VEG102616) and one comparative phase III study (VEG105192, the pivotal study). 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 stopping the intergroup comparison (study VEG107769). In view of the methodology, these data are not likely to offer any reliable information on the efficacy and safety of the medicinal product.

3.1. Efficacy

The VEG102616 Study

This was a non-comparative phase II study conducted between October 2005 and September 2006 on a population of 225 patients with metastatic or locally recurrent renal cell carcinoma. The other inclusion criteria were an ECOG PS of 0 or 1 and normal organ function. Patients with brain or leptomeningeal metastases could not be included. VOTRIENT was given orally as a singly daily dose of 800 mg until disease progression, unacceptable toxicity, death, or decision of the patient or investigator.

The response rate (primary endpoint) after 12 weeks of treatment was 38% in the 60 analysed patients. The median duration of response was 68 weeks. The stabilisation rate was 47.1%.

The VEG105192 Study

This was a randomised double-blind phase III study comparing VOTRIENT with placebo in 435 patients with locally advanced or metastatic renal cell carcinoma.

The main eligibility criteria were:
- being over 18 years of age
- having locally advanced or metastatic renal cell carcinoma with clear cell or predominantly clear cell histology, measurable according to the Response Evaluation Criteria in Solid Tumours (RECIST)
- having an initial ECOG PS of 0 or 1 and acceptable organ function.

Exclusion criteria included:
- patients presenting with brain or leptomeningeal metastases.

Patients were randomised according to 2:1 ratio to receive VOTRIENT (orally as a single daily dose of 800 mg) or placebo until disease progression, death, unacceptable toxicity or withdrawal of consent.

NB: The original protocol, finalised in November 2005, planned to include patients previously treated with cytokines (interleukin-2 or interferon α). Following the US approval of sorafenib in December 2005 and of sunitinib in January 2006 as second-line therapies, the inclusion population was extended to treatment-naïve patients (amendment of 9 May 2006) with no change in the comparator. Patients in the pivotal study were enrolled between April 2006 and April 2007.
In Europe, sunitinib (SUTENT) and sorafenib (NEXAVAR) each have had a marketing authorisation for the treatment of renal cell carcinoma (advanced stage disease, after interferon alpha or interleukin 2 failure) since 19 July 2006.

The primary endpoint was progression-free survival, defined as the time from randomisation to documentation of disease progression, or death due to any cause. An independent committee performed the double-blind reading of follow-up scans.

The secondary endpoints were:
- global survival, defined as the time from randomisation to death due to any cause
- the response rate, defined as the percentage of patients with a complete response (CR) or partial response (PR) according to the Response Evaluation Criteria in Solid Tumours (RECIST)
- the duration of response, defined as the time between the first documented evidence of CR or PR and the first documented disease progression or death due to any cause (depending on the first event to occur)
- the time to response, defined as the time from randomisation to the first documented evidence of CR or PR (depending on the status recorded first)
- the patients’ quality of life, assessed upon study admission, and then at weeks 6, 12, 18, 24 and 48, using version 3 of the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) and the EuroQol-5D (EQ-5D) group questionnaire. The analysis was based on questionnaires completed by patients in both groups who were continuing their treatment prior to progression.

Results:
Overall, 223 (54%) of the 435 patients in the study were treatment-naive and 202 (46%) were second-line patients who had previously been treated with interleukin-2 or interferon alpha. The median patient age was 59 years. In 93% of the cases, the prognosis according to the MSKCC classification was good or intermediate. All patients had renal cell cancer with clear cell or predominantly clear cell histology. Three or more organs were affected in about half the patients (53%) and the majority of patients had lung (74%) and/or lymph node (54%) metastases at inclusion. The proportion of patients who had previously undergone nephrectomy was similar in both groups (89% in the VOTRIENT group and 88% in the placebo group).

The median progression-free survival (primary endpoint) in the overall population was 9.2 months in the VOTRIENT group versus 4.2 months in the placebo group, i.e. an absolute gain of five months (HR= 0.46 [0.34 – 0.62]). There was no difference between the two groups in median overall survival, i.e., 21.1 months for the VOTRIENT group versus 18.7 months for the placebo group, NS. The response rate was 30% in the VOTRIENT group and 3% in the placebo group, p<0.001.

1 The three risk factors correlated with survival are:
- Karnofsky score < 80%
- below normal serum haemoglobin levels
- corrected calcium level > 10 mg /dL
Good risk profile (no risk factors)
Intermediate risk profile (1-2 risk factors)
Poor risk profile (3 risk factors)
The median duration of response in the VOTRIENT group was 58.7 weeks, with a median time to response of 11.9 weeks. The quality of life data showed no differences between the two groups.

Table 1: Subgroup results for the primary endpoint

<table>
<thead>
<tr>
<th></th>
<th>VOTRIENT</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>Unilateral p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population</td>
<td></td>
<td></td>
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<tr>
<td>median (months) b</td>
<td>9.2</td>
<td>4.2</td>
<td>0.46 (0.34; 0.62)</td>
<td>&lt;0.0000001</td>
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<tr>
<td>Treatment-naive</td>
<td></td>
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<tr>
<td>median (months) c</td>
<td>11.1</td>
<td>2.8</td>
<td>0.40 (0.27; 0.60)</td>
<td>&lt;0.0000001</td>
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<tr>
<td>Previous cytokine</td>
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<tr>
<td>treatment median (months) d</td>
<td>7.4</td>
<td>4.2</td>
<td>0.54 (0.35; 0.84)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

b Pike estimator adjusted for ECOG status and previous treatment at inclusion
c Pike estimator not adjusted

d In the subgroup of patients receiving first-line treatment, progression-free survival was 11.1 months versus 2.8 months, i.e., an absolute gain of 8.3 months for those taking VOTRIENT. In the subgroup of patients in failure following cytokine treatment, progression-free survival was 7.4 months versus 4.2 months, i.e., an absolute gain of 3.2 months in those taking VOTRIENT.

Other data:
In the absence of any direct comparison, the dossier cites the results of an indirect comparison carried out by the applicant against the available drugs. In this regard, the Committee would like to point out that:
- the indirect comparison network is very poor
- the heterogeneity cannot really be evaluated,
- certain levels of effect correspond to results from intermediate analyses, and are therefore potentially biased (overestimation of treatment effect).
Overall, the results are uninformative, with very wide confidence intervals; they are therefore exploratory, and it is not possible to draw any conclusions from them.

3.2. Adverse effects
The rate of treatment discontinuation due to adverse events was 15% in the VOTRIENT group versus 6% in the placebo group. These events mainly involved liver function abnormalities (3.8%) and diarrhoea (2%).
Serious adverse events were reported in 24% of patients in the VOTRIENT group and 19% of patients in the placebo group. Diarrhoea was the most common serious adverse event in the VOTRIENT group (2.1%).
3.3. Conclusion

The efficacy and safety of VOTRIENT (800 mg daily) were evaluated in a randomised placebo-controlled double-blind study of patients with locally advanced and/or metastatic renal cell cancer. The primary endpoint was progression-free survival and the major secondary endpoint was global survival.

Out of the 435 patients enrolled, 233 were first-line patients who were treatment-naive and 202 were second-line patients who had previously been treated with interleukin-2 or interferon alpha.
Median patient age 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 (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, i.e. 21.1 months under VOTRIENT versus 18.7 months under 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.
Quality of life data showed no differences 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 when compared with placebo in terms of progression-free survival, with no established impact on either overall survival or quality of life.
It is not possible to draw reliable conclusions about the therapeutic benefit of VOTRIENT in the treatment of advanced stage renal cell carcinoma from the results suggested by an indirect comparison (the confidence intervals are too wide). So in the absence of any direct comparison, it is not possible to rule out a loss of opportunity with regard to the tyrosine kinase inhibitors (TKIs) already available, notably sunitinib in first-line therapy and sorafenib in second-line therapy.

A “conditional” marketing authorisation was granted for VOTRIENT in the absence of data against an active comparator. In February 2012, the applicant is due to submit the results of the VEG108844 non-inferiority study comparing VOTRIENT with sunitinib in the treatment of patients with locally advanced and/or metastatic renal cell carcinoma.
4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit
Renal cancer is a serious and life-threatening disease. These proprietary medicinal products are intended as curative therapy. The efficacy/adverse effects ratio is low.

Public health benefit:
In France, the public health burden represented by renal cell carcinoma may be regarded as moderate (approximately 8,000 new cases in 2005). In terms of mortality, it accounts for 2.5% of all cancer deaths. The public health burden for the subpopulation of patients with advanced renal cell carcinoma is considered to be moderate.
Improving the treatment of cancer patients and their quality of life is a public health need, which is an established priority (French law of 9 August 2004 on public health policy: the Cancer Plan and the Plan for improving quality of life for patients with chronic diseases).
In view of the results available from the single placebo-controlled phase III study and in the absence of data versus an active comparator, pazopanib cannot be expected to further reduce morbidity.
In addition, there has been no observed improvement in overall survival.
Moreover, the pivotal study did not demonstrate any improvement in quality of life. It is not certain that the results of the pivotal study can be transposed to clinical practice.
No impact on the healthcare system is anticipated.
Therefore, the proprietary medicinal product VOTRIENT is not likely to fulfil an identified public health need.
Consequently, there is no anticipated public health benefit from the proprietary medicinal product VOTRIENT in this indication.

VOTRIENT is a first-line or second-line treatment for patients in therapeutic failure following treatment with cytokines.
Alternative medicinal products exist.

In view of the available clinical data based on a pivotal placebo-controlled study and in the absence of any direct comparison against the already-available medicinal products, the Transparency Committee considers that the level of evidence of the observed results is inadequate for evaluating the level of effect of VOTRIENT and its role in the treatment of renal cell carcinoma. In the absence of a direct comparison against the already-available tyrosine kinase inhibitors (TKIs), notably sunitinib in first-line therapy and sorafenib in second-line therapy, it is not possible to eliminate a loss of opportunity for patients with regard to these medicinal products.
In the current state of the dossier and while awaiting the results of the VEG 108844 non-inferiority study comparing VOTRIENT with sunitinib, the Transparency Committee considers that the actual benefit is insufficient to justify reimbursement by National Health Insurance.

4.2. Improvement in actual benefit (IAB)
Not applicable

4.3. Transparency Committee recommendations
The Transparency Committee does not recommend inclusion on the list of medicines reimbursed by National Health Insurance or on the list of medicines approved for hospital use and various public services.

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