The European Medicines Agency Review of Pazopanib for the Treatment of Advanced Renal Cell Carcinoma: Summary of the Scientific Assessment of the Committee for Medicinal Products for Human Use

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Abstract

On June 14, 2010, the European Commission issued a conditional marketing authorization valid throughout the European Union for pazopanib for the treatment of advanced renal cell carcinoma. Pazopanib is an antineoplastic agent that inhibits multiple receptor tyrosine kinases. The recommended oral dose is 800 mg once daily. The benefit of pazopanib is an increased progression-free survival. In the pivotal trial VEG105192, the median progression-free survival was 9.2 months (95% confidence interval, 7.4–12.9) in the pazopanib arm compared with 4.2 months (95% confidence interval, 2.8–4.2) in the placebo arm. The most common side effects include diarrhea, hair color change, hypertension, nausea, fatigue, anorexia, vomiting, dysgeusia, elevated alanine aminotransferase, elevated aspartate aminotransferase, and abdominal pain. The objective of this article is to summarize the scientific review of the application that led to approval in the European Union.

Introduction

Systemic treatments for advanced renal cell carcinoma (RCC) have improved in recent years following a better understanding of the biology of RCC and the development of several targeted agents, including sunitinib, sorafenib, temsirolimus, everolimus, and bevacizumab (1–5). Overexpression of proteins that are targeted by these agents, including vascular endothelial growth factor receptors (VEGFR) and platelet-derived growth factor receptors (PDGFR), has been identified in the vast majority of subjects with clear-cell RCC. These features are associated with increased angiogenesis, advanced tumor stage, aggressive phenotype, and poor survival, and they are currently considered valid targets for the treatment of RCC (6–9).

Glaxo Group Ltd. applied for a marketing authorization in the European Union for Votrient (pazopanib). Pazopanib is an orally administered, multitarget tyrosine kinase inhibitor (TKI) of VEGFR-1, 2, and 3; PDGFR-α and β; and stem cell factor receptor (c-KIT), with IC50 values of 10, 30, 47, 71, 84, and 74 nmol/L, respectively. The chemical name of pazopanib is 5-[(4-[(2,3-Dimethyl-2H-indazol-6-yl)(methyl)amino]pyrimidin-2-yl]amino]-2-methylbenzenesulfonamide monohydrochloride. The recommended dose of pazopanib is 800 mg once daily.

A review of this marketing authorization application was conducted by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), which recommended the granting of a conditional marketing authorization (Box 1) for pazopanib based on a positive benefit–risk balance. Following this review, the European Commission issued a conditional marketing authorization for pazopanib on June 14, 2010. The approved therapeutic indication is for first-line treatment of advanced RCC and for patients who have received prior cytokine therapy for advanced disease.

This article is a summary of the European Public Assessment Report (EPAR). The full scientific assessment report and most current product information are available on the EMA website (10).

Nonclinical Aspects

In repeat dose studies in rodents, effects in a variety of tissues (bone, teeth, nail beds, reproductive organs, hematologic tissues, kidney, and pancreas) were observed, with most effects occurring at plasma exposure levels below those observed in the clinic. Other observed effects...
Box 1. European Union Conditional Approval

Conditional approval is reserved for drugs that are used to treat, prevent, or diagnose seriously debilitating diseases or life-threatening diseases, for rare diseases (orphan medicinal products), or for drugs that are meant to be used in emergency situations. Several criteria have to be fulfilled before a conditional marketing authorization is granted:

1. Positive benefit–risk balance and benefits to public health resulting from immediate availability of the product.
2. Likelihood that comprehensive data will be provided.
3. Fulfillment of an unmet medical need.

With conditional approval, the applicant company is obliged to complete ongoing clinical trials, conduct new trials, or collect additional pharmacovigilance data (specific obligations) with a view to confirming that the benefit–risk balance is positive. Financial penalties may be applied in the case of noncompliance with specific obligations.

A conditional approval is only valid for 1 year but can be renewed. The renewal is given on the basis of confirmation of the benefit–risk balance, taking into account the specific obligations and the timeframe for their fulfillment. Once it is judged that remaining data have been provided or are no longer required, the marketing authorization can be converted to a standard authorization.

If at any time the benefit–risk balance is considered to be negative, the marketing authorization can be suspended or revoked.

Clinical Pharmacology

Pharmacokinetics

Administration of pazopanib with food resulted in a ~2-fold increase in mean pazopanib Cmax and AUC values compared with administration under fasting conditions. Based on these findings, it is recommended to administer pazopanib at least 1 hour before or 2 hours after a meal.

No dose adjustment is required in patients with creatinine clearance >30 mL/min. Caution is advised, however, in patients with creatinine clearance <30 mL/min, because there is no experience with pazopanib in this patient population. As appropriate, dose modification based on individual tolerability should be considered.

Pazopanib is contraindicated in patients with severe hepatic impairment. The recommended dosage of pazopanib in people with moderate hepatic impairment [defined as an elevation of bilirubin >1.5× to 3× upper limit of normal (ULN) regardless of the alanine aminotransferase (ALT) values] is 200 mg once daily. It is recommended that patients with mild abnormalities in liver parameters [defined as either normal bilirubin and any degree of ALT elevation or an elevation of bilirubin (>35% direct) up to 1.5× ULN regardless of the ALT value] are treated initially with the standard dose of 800 mg pazopanib once daily (recommendations on hepatic impairment were updated after the initial marketing authorization following an assessment of the interim results of the phase I pharmacokinetic study Phl-60, National Cancer Institute protocol 8063).

Results of in vitro studies indicate that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Concomitant treatment with strong inhibitors of CYP3A4 should be avoided due to the risk of increased exposure to pazopanib.

Concomitant administration of pazopanib with uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) substrates (e.g., irinotecan) should also be undertaken with caution because pazopanib is an inhibitor of UGT1A1 (as appropriate, dose modification based on individual tolerability should be considered).

Inhibition of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) by pazopanib in the gastrointestinal tract could not be excluded. Care should be taken when pazopanib is coadministered with other oral P-gp or BCRP substrates (for instance, separation of time of intake or dose reduction should be considered, as appropriate, for drug substrates of BCRP or P-gp when coadministered with pazopanib if alternative noninteracting treatment options are not preferred).

In vitro, pazopanib inhibited human organic anion transporting polypeptide (OATP1B1). The possibility that pazopanib will affect the pharmacokinetics of substrates of OATP1B1 (e.g., rosuvastatin) could not be excluded.

Included body weight loss, diarrhea, or morbidity that was either secondary to local gastrointestinal effects caused by high local mucosal exposure (monkeys) or pharmacologic effects (rodents). Proliferative hepatic lesions (eosinophilic foci and adenoma) were seen in female mice at exposures 2.5 times the human exposure (based on the AUC).

Pazopanib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits at exposures >300-fold lower than the human exposure (based on the AUC). Therefore, if pazopanib is used during pregnancy or if the patient becomes pregnant while receiving pazopanib, the potential hazard to the fetus should be explained to the patient. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with pazopanib.

No animal or human data were available regarding the excretion of pazopanib in milk; therefore, a risk to the breastfeeding child could not be excluded.
Dose-finding study

VEG10003 was a multicenter, phase I, open-label, non-randomized, multiple-dose–finding study of pazopanib in adult subjects with solid tumors who were refractory to standard therapy or for whom no standard therapy existed (10). The maximum tolerated dose (MTD) was not reached in this study. The 800 mg once daily dose of pazopanib was selected for evaluation in phase II/III studies, including the RCC studies, based on a manageable safety profile and the fact that increasing the pazopanib dose above 800 mg once daily did not result in a consistent increase in systemic exposure at steady state, so no further benefit was expected with higher doses of pazopanib.

Clinical Efficacy

Phase III study (VEG105192)

VEG105192 was a randomized, double-blind, placebo-controlled, multicenter phase III study to evaluate the efficacy and safety of pazopanib compared with placebo (11). The study was initially designed to enroll subjects with locally advanced or metastatic RCC who had progressed from one prior cytokine-based therapy, but it was expanded to include treatment-naive advanced RCC subjects shortly after the first subject was enrolled. The main eligibility criteria included adult patients with measurable disease [i.e., presenting with at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST)], clear-cell or predominantly clear-cell histology, and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Subjects were randomly assigned 2:1 to receive oral pazopanib 800 mg daily or a matching placebo. Stratification factors included prior systemic therapy, ECOG performance status, and prior nephrectomy status. Subjects continued on the investigational product until disease progression, death, unacceptable toxicity, or withdrawal of consent occurred.

The primary endpoint of this study was progression-free survival (PFS), defined as the time between the date of randomization and the earliest date of disease progression (RECIST) or death due to any cause, based on the evaluation of a blinded independent review committee (IRC).

Patients from 80 centers in 23 countries, including Latin American, Asian, Australian, eastern and western European, and African countries, participated in the study. Enrollment was open from April 2006 to April 2007. The intention-to-treat (ITT) population was the primary population used for the analysis of efficacy data and consisted of 433 randomized patients (290 and 145 patients allocated to pazopanib and placebo, respectively). Demographics and disease characteristics were generally similar between the treatment-naive and cytokine-pretreated subjects (Table 1).

In the ITT population, a statistically significant improvement in PFS was observed in the pazopanib arm compared with the placebo arm based on IRC evaluation, with an HR of 0.46 [95% confidence interval (CI), 0.34–0.62; log-rank \( P < 0.0001 \)]. The median PFS was 9.2 months (95% CI, 7.4–12.9) in the pazopanib arm compared with 4.2 months (95% CI, 2.8–4.2) in the placebo arm (Fig. 1). Results based on the investigator’s evaluation were consistent with those based on the IRC evaluation (HR = 0.44; 95% CI, 0.34–0.57). The effect of pazopanib on PFS observed in all subgroups analyzed was consistent with the results of the primary efficacy analysis (Fig. 2).

A planned interim analysis of overall survival was used for the initial marketing authorization application. It was performed when 176 events had occurred (HR = 0.73; 95% CI, 0.53–1.00; cutoff date of May 23, 2008), with similar results in the treatment-naive (HR = 0.74; 95% CI, 0.47–1.15) and cytokine-pretreated subgroups (HR = 0.72; 95% CI, 0.46–1.14). Response rates were higher in the pazopanib arm compared with the placebo arm (30% and 3%, respectively). The median duration of response in the pazopanib group was 58.7 weeks (95% CI, 52.1–68.1 weeks) as per IRC review. The median time to response with pazopanib treatment was 11.9 weeks.

Clinical Safety

The safety population comprised 586 subjects with RCC who had received at least 1 dose of investigational product (study VEG105192, N = 290; extension study VEG107769, N = 71; supportive phase II study VEG102616, N = 225). Overall, the median duration of exposure was ~7.4 months (including dose interruptions). The most common adverse reactions (treatment-related adverse events) of any grade were diarrhea (49%), hair color change (39%), hypertension (38%), nausea (27%), fatigue (24%), anorexia (21%), vomiting (15%), dysgeusia (16%), elevated ALT and aspartate aminotransferase (14% and 12%, respectively), and abdominal pain (10%).

Serious adverse events (SAE) were reported for 24% of subjects in the pazopanib arm and 19% of subjects in the placebo arm during the study. Treatment-related SAEs reported in 2 or more subjects in the pazopanib arm included diarrhea (2%), anemia (1%), abnormal hepatic function (≤1%), hepatotoxicity (1%), hypertension (<1%), and vomiting (<1%). The most important treatment-related SAEs were transient ischemic attack; ischemic stroke; myocardiomalacia; cardiac dysfunction; gastrointestinal perforation and fistula; QT prolongation; and pulmonary, gastrointestinal, and cerebral hemorrhage. Individually, these treatment-related SAEs were reported in ≤1% of treated patients.

The incidence of fatal SAEs was similar in the pazopanib group (4%) and the placebo group (3%). Fatal SAEs were considered by the investigator to be related to the investigational product for 4 of 9 subjects in the pazopanib arm, and none of 3 subjects in the placebo arm. The events that were considered treatment-related included abnormal hepatic function, rectal hemorrhage, peritonitis, and ischemic stroke. Overall, for the RCC studies, the incidence of fatal SAEs was 3% for pazopanib-treated subjects as of the clinical cutoff date. Seven patients died due to SAEs that were considered related to pazopanib treatment.
Other events of special interest were hepatic toxicity (i.e., cases of hepatic failure, including fatalities that had been reported during pazopanib treatment); hypertension (in the pivotal study, subjects in the pazopanib arm had a 40% incidence of adverse events of hypertension or worsening of hypertension compared with 10% in the placebo group); QTc prolongation (across all RCC studies, 10 out of 558 subjects with post-baseline evaluation developed QTc prolongations >500 msec; Torsade de Pointes and 1 case of sudden death occurred in the group of pazopanib-treated subjects); increased risk of vascular events (specifically arterial thromboembolic events, such as myocardial infarction, ischemic stroke, and transient ischemic attack; the exposure-adjusted incidence rate of arterial thromboembolic events per 100 patient years was 3.85%, CI, 1.33–6.37 vs. 0, for pazopanib and placebo, respectively); hemorrhagic events (3 patients experienced serious hemorrhagic events related to pazopanib, namely, retroperitoneal bleeding, hematuria, and bleeding esophageal varices); gastrointestinal perforations or fistulae (5 subjects suffered SAEs related to gastrointestinal perforations or fistulae; 2 of which were fatal; 1 nonfatal case was considered related to pazopanib); hypothyroidism; and proteinuria. For all of these events, detailed recommendations are included in the summary of product characteristics.

### Table 1. Summary of selected baseline disease characteristics in treatment-naïve and cytokine-pretreated subgroups (VEG105192: ITT population)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Treatment-naïve</th>
<th>Cytokine-pretreated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Pazopanib</td>
</tr>
<tr>
<td></td>
<td>(N = 78)</td>
<td>(N = 155)</td>
</tr>
<tr>
<td>Stage of disease at initial diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>8 (10)</td>
<td>15 (10)</td>
</tr>
<tr>
<td>II</td>
<td>14 (18)</td>
<td>22 (14)</td>
</tr>
<tr>
<td>III</td>
<td>24 (31)</td>
<td>49 (32)</td>
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<tr>
<td>IV</td>
<td>32 (41)</td>
<td>67 (43)</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Time since initial diagnosis (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>8.5</td>
<td>7.9</td>
</tr>
<tr>
<td>Range</td>
<td>1–152</td>
<td>1–176</td>
</tr>
<tr>
<td>Time since diagnosis of stage IV disease (months)</td>
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<td></td>
</tr>
<tr>
<td>Median</td>
<td>3.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Range</td>
<td>0–89</td>
<td>0–149</td>
</tr>
<tr>
<td>Most frequent locations of disease at baseline*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>55 (71)</td>
<td>114 (74)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>48 (62)</td>
<td>89 (57)</td>
</tr>
<tr>
<td>Bone</td>
<td>22 (28)</td>
<td>49 (32)</td>
</tr>
<tr>
<td>Liver</td>
<td>17 (22)</td>
<td>41 (26)</td>
</tr>
<tr>
<td>Kidney</td>
<td>22 (28)</td>
<td>40 (26)</td>
</tr>
<tr>
<td>Number of organs involved*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10 (13)</td>
<td>23 (15)</td>
</tr>
<tr>
<td>2</td>
<td>25 (32)</td>
<td>46 (30)</td>
</tr>
<tr>
<td>3</td>
<td>43 (55)</td>
<td>86 (55)</td>
</tr>
<tr>
<td>ECOG performance status</td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>33 (42)</td>
<td>63 (41)</td>
</tr>
<tr>
<td>1</td>
<td>45 (58)</td>
<td>92 (59)</td>
</tr>
<tr>
<td>MSKCC risk category*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable risk</td>
<td>31 (40)</td>
<td>56 (38)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>40 (51)</td>
<td>87 (56)</td>
</tr>
<tr>
<td>Poor risk</td>
<td>5 (6)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (3)</td>
<td>6 (4)</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan-Kettering Cancer Center.

*As defined by the investigator.

Sixty-one of the assignments in the treatment-naïve subgroup and 47 in the cytokine-pretreated subgroup required the use of total calcium measurements because of missing baseline albumin levels for calculation of corrected calcium.

Subjects with an unknown MSKCC risk category were missing results for 1 or more of the 5 risk criteria.
Pharmacovigilance

The applicant company submitted a risk management plan, which included a risk minimization plan. Identified safety concerns included hepatic dysfunction, pulmonary hemorrhage, gastrointestinal bleeding, cerebral hemorrhage, gastrointestinal perforation and fistulae, cardiac arrhythmias, cardiac ischemia, cardiac dysfunction, QT effects (including Torsade de Pointes), cerebrovascular ischemic events, venous thromboembolic events, hypertension, hypothyroidism, diarrhea, fatigue/asthenia, hypoglycemia, impaired healing, proteinuria, thrombocytopenia, leukopenia, and neutropenia.
Pharmacovigilance activities will include the use of an oncology-specific electronic medical record epidemiology database to monitor the rates of liver test abnormalities in pazopanib users and epidemiologic health care insurance claims databases to monitor cardiac and cerebrovascular ischemic events and events of Torsade de Pointes. In addition, an ongoing study in patients with mild to severe hepatic dysfunction and a planned study on the effect on cardiac conduction will provide further evidence about these identified safety concerns.

Overall Conclusions, Benefit–Risk Assessment, and Recommendation

Pazopanib has been shown to be an effective drug for patients with advanced RCC. The difference in terms of PFS compared with placebo observed in the pivotal study was statistically significant and clinically relevant. The overall safety profile of pazopanib was comparable with that of other marketed TKIs and inhibitors of angiogenesis. On the basis of indirect comparisons, pazopanib was associated with a lower incidence of rash, mucositis, and hand and foot syndrome, but a higher incidence of high-grade ALT elevations, all-grade hypertension, and hair discoloration.

The choice of placebo as the comparator in the pivotal trial has been a concern. Indeed, in previous scientific advice given to the company, the CHMP recommended the use of an active comparator. Although the efficacy of pazopanib had been established, no data from trials using another TKI as an active comparator were available to clarify any important differences in efficacy and safety, inform treatment choice, or rule out loss of opportunity for the patients.

During the scientific review of pazopanib, the CHMP convened an oncology scientific advisory group (SAG) to discuss the benefits and risks of pazopanib from a clinical perspective, and whether it was possible to rule out the risk of a clinically relevant loss in terms of efficacy or safety compared with currently approved agents in this indication. The expert group agreed that a major loss in efficacy or safety was unlikely. However, in the absence of direct comparative data, it was not possible to draw any firm conclusions about possible important differences in efficacy and safety between the available treatment options.

The SAG also pointed out that there were no comprehensive data on the benefits and risks of pazopanib in patients who had previously received systemic treatments other than with cytokines. In the absence of relevant data, the SAG concluded that no benefit–risk assessment for pazopanib could be made for patients pretreated with other systemic treatments (including TKI inhibitors, mTOR inhibitors, or a combination of cytokines and anti-VEGF).

Conditional approval

The CHMP concluded that there was a need to gain more understanding about the benefit–risk balance of pazopanib compared with other available medicinal products for the same indication. The CHMP therefore required a postmarketing, noninferiority, randomized, controlled, phase III clinical study to evaluate the efficacy and safety of pazopanib versus the TKI sunitinib, and it stated that the results of this study would have to be submitted as a specific obligation for this conditional marketing authorization.

In conclusion, the benefit–risk assessment of pazopanib was considered positive for the first-line treatment of advanced RCC and for patients who have received prior cytokine therapy for advanced disease. Therefore, on June 14, 2010, the European Commission granted a conditional marketing authorization valid throughout the European Union for pazopanib. The EMA will review new information annually until all specific obligations for the pazopanib conditional approval are fulfilled. Detailed information on this medicinal product is available on the EMA website (10).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

This publication is a summary of the EPAR, which is available together with the summary of product characteristics and other product information on the EMA website (http://www.ema.europa.eu). The authors remain solely responsible for the opinions expressed in this publication.

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The scientific assessment as summarized in this report is based on the marketing authorization application submitted by the applicant company and on important contributions from, among others, the rapporteur and corapporteur assessment teams, CHMP members, and the oncology SAG.

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