Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House (8th floor) 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman Professor Kenneth R Paterson
NHS SCOTLAND

pazopanib 200mg, 400mg film-coated tablets (Votrient®) SMC No.(676/11)

GlaxoSmithKline UK

04 February 2011

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

pazopanib (Votrient®) is accepted for restricted use within NHS Scotland.

Indication under review: First-line treatment of advanced renal cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.

SMC restriction: use is restricted to the first-line treatment of advanced RCC.

Pazopanib was superior to placebo for the primary endpoint, progression free survival, in the whole population and the treatment naïve and cytokine pre-treated sub-groups. An indirect comparison demonstrated that pazopanib had similar efficacy to the main comparator.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of pazopanib. This SMC advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

First-line treatment of advanced renal cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.

Dosing Information

Pazopanib 800mg orally once daily. Dose modification should be in 200mg increments in a stepwise fashion based on individual tolerability in order to manage adverse reactions. The dose of pazopanib should not exceed 800mg. Pazopanib should be taken without food, at least one hour before or two hours after a meal and should be taken whole with water and not broken or crushed.

Pazopanib treatment should only be initiated by a physician experienced in the administration of anti-cancer agents.

Product availability date

1 July 2010

Summary of evidence on comparative efficacy

Pazopanib is an oral, selective tyrosine kinase inhibitor (TKI) that targets vascular endothelial growth factor receptor, platelet-derived growth factor receptor and c-Kit. It has a marketing authorisation for the first-line treatment of advanced renal cell carcinoma and for patients who have received prior cytokine therapy for advanced disease. The submitting company has requested that the Scottish Medicines Consortium (SMC) considers the use of this product when positioned in the first-line treatment of advanced RCC only, on the basis that in current practice the population eligible for second-line treatment after cytokine-based therapy is expected to be extremely small.

One double-blind placebo-controlled multi-centre parallel group study has been conducted to evaluate the efficacy and safety of pazopanib monotherapy in 435 treatment-naïve or cytokine pre-treated patients with advanced RCC. Patients were required to have a diagnosis of clear-cell or predominantly clear-cell histology, measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria, aged 18 years or over, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 and adequate renal, hepatic, and haematologic function. Patients with central nervous system (CNS) metastases were excluded. Patients were randomised 2:1 to pazopanib 800mg orally once daily or matching placebo, taken one hour before or two hours after meals. Patients received treatment continuously until disease progression, death or unacceptable toxicity or withdrawal of consent for any reason. There was pre-specified dose modification guidance for adverse events.

The primary endpoint was progression free survival (PFS), defined as the time between randomisation and progression or death. An independent imaging-review committee (IRC), who were blinded to study treatment, evaluated all scans based on RECIST criteria. Stratification factors of baseline ECOG PS, prior nephrectomy status and prior systemic treatment were incorporated according to the analysis plan. Significance tests were conducted for the intent-to-treat population and also for the treatment-naïve and cytokine pre-treated subgroups.The Pike

estimator of the treatment hazard ratio (HR) was calculated, together with a 95% confidence interval (CI).

In the overall study population the median PFS was significantly longer for pazopanib treated patients than placebo treated patients (9.2 months versus 4.2 months; HR 0.46, 95% CI 0.34 to 0.62). In the treatment naïve population (n=233), that represents the positioning proposed by the submitting company,, the median PFS was also significantly longer for with pazopanib than placebo (11.1 months versus 2.8 months; HR 0.40, 95% CI 0.27 to 0.60). In the cytokine pre-treated population (n=202) the median PFS was significantly longer for pazopanib treated patients than placebo treated patients (7.4 months versus 4.2 months; HR 0.54, 95% CI 0.35 to 0.84).

Secondary endpoints included: overall survival (OS; time from randomisation to death); confirmed objective response rate (RR; complete response plus partial response); duration of response; health related quality of life (HRQoL). Interim OS data were reported in the European Medicines Agency's (EMA) European Public Assessment Report and had a cut-off of May 2008. Median OS in the overall study population was prolonged in the pazopanib versus placebo treated patients (21.1 months versus 18.7 months; HR 0.73; 95% CI 0.53 to 1.00; one sided p=0.020). In the treatment naïve population median OS was 19.8 months versus 20.0 months (HR 0.74; 95% CI 0.47 to 1.15; p=0.079). Updated OS data with a March 2010 cut-off were included in the company's submission to SMC and presented for the treatment naïve group only and showed no significant difference between the two groups; 22.9 months versus 23.5 months respectively (HR 1.01, 95% CI 0.72 to 1.42). However, interpretation of OS data is limited due to the high level of crossover of patients on placebo to pazopanib following progression.

For the whole study population the RR for pazopanib-treated patients was 30% (95% CI 25.1 to 35.6) and the median duration of response was 58.7 weeks (95% CI 52.1 to 68.1). For treatment naïve patients the RR was 32% (95% CI 24.3 to 38.9) and for cytokine pre-treated patients was 29% (95% CI 21.2 to 36.5). For the whole pazopanib treated population the numbers of complete and partial responses were 1 and 87 respectively.

Patient reported quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 version 3), and the EuroQoL (EQ-5D) and were used at baseline and every six weeks to week 24 and also at week 48. Key endpoints were summary scores from the EORTC QLQ-global health status/QoL score, EQ-5D index and EQ-5D VAS, and there were no statistically significant differences between pazopanib- and placebo-treated patients for these endpoints in a mixed-model repeated-measures analyses.

An open-label extension to the pivotal study recruited 70 patients with advanced RCC who had progressed on placebo (and one pazopanib treated patient) in order to evaluate the safety and efficacy of pazopanib 800mg orally once daily. The study had similar eligibility criteria as the pivotal study except patients with an ECOG PS 0 to 2 were included. The median PFS (investigator assessment) was 8.3 months (95% CI 6.1 to 11.4), median OS was 16.8 months (95% CI 16.3 to [not reported]) and RR was 32%.

Summary of evidence on comparative safety

The most common adverse events (AE) of any grade reported in pazopanib treated patients were diarrhoea (52% versus 9% in placebo treated patients), hypertension (40% versus 10%), hair colour changes (38% versus 3%), nausea (26% versus 9%), anorexia (22% versus 10%), vomiting (21% versus 8%) and fatigue (19% versus 8%). The most common AE of grade 3/4 severity were hypertension (4% versus <1%) and diarrhoea (4% versus <1%). Alanine aminotransferase (ALT) (53% versus 22%) and aspartate transaminase (AST) (53% versus 19%) elevations were the most common clinical laboratory abnormalities (any grade) and grade 3/4 abnormalities were relatively rare. ALT elevations at least three times upper limit of normal occurred in 52 (18%) patients on pazopanib and recovered on dose modification, interruption or discontinuation in 45 patients. Haematological abnormalities (any grade) included leucopenia, neutropenia, thrombocytopenia and lymphocytopenia and grade 3/4 haematological AE were rare. Certain other adverse events previously observed with TKIs including proteinuria, hypothyroidism, hand-foot syndrome or palmar-plantar erythrodyaesthesia, mucositis and stomatitis each occurred with an incidence of less than 10% in patients receiving pazopanib in the first-line study sub-population.

There were four fatal AEs in the pazopanib group that were considered attributable to study treatment (ischaemic stroke, abnormal hepatic function and rectal haemorrhage, peritonitis/bowel perforation and abnormal hepatic function).

Summary of clinical effectiveness issues

The EMA granted conditional approval for pazopanib, noting that the addition of a safe treatment option that is associated with clear clinical benefits and with a distinct pharmacodynamic profile is considered to offer a major advantage in the context of therapies for this disease.

The submitting company has requested that SMC consider the use of pazopanib in the first-line treatment of advanced RCC only. Sub-group analysis of the primary endpoint, progression free survival, in treatment naïve and cytokine pre-treated patients was pre-specified and the primary endpoint was met for the whole study population as well as these sub-groups. However, the generalisability of the study results is limited. Efficacy in patients with an ECOG PS of 2 or greater and those with CNS metastases is not known. In addition, the efficacy of pazopanib in patients with advanced renal cell carcinoma other than clear-cell or predominantly clear-cell histology is not known, although other histologies account for only about 20% of RCC.

In the pivotal study further anti-cancer therapy post-discontinuation was received by 28% (81/290) versus 61% (89/145) of patients in the pazopanib and placebo arms respectively. Of the patients assigned to placebo, 48% (70/145) enrolled in the open-label pazopanib study making interpretation of OS data from the pivotal study problematic. The submitting company presented a variety of methods for adjusting for cross-over and favoured the rank preserved structural failure time (RPSFT) analysis. In the treatment-naïve population the weighted HR for OS using the RPSFT approach was 0.501 (95% CI 0.136 to 2.348). The HR obtained from the RPSFT analysis has been used in the indirect comparison and in the economic analysis in the company's submission. This method was considered satisfactory by the statistician consulted

by SMC. It should be noted that there was no significant difference in overall survival for pazopanib versus placebo, even when the analysis was adjusted for crossover.

There are no direct comparative data for pazopanib for the treatment of metastatic RCC. The company is currently undertaking a non-inferiority study of pazopanib versus sunitinib. As part of the conditional approval from the EMA a pooled analysis of this study and a study to evaluate efficacy and safety of pazopanib versus sunitinib for the treatment of Asian patients with locally advanced and/or metastatic renal cell carcinoma is to be undertaken to provide robust clinical data to characterise the comparable efficacy and safety of pazopanib versus sunitinib. The company has also committed to provide final OS data for the comparative study as well as the pivotal placebo-controlled study to the EMA.

The company provided an adjusted (Bucher method) indirect comparison of pazopanib versus sunitinib to provide some comparative efficacy and safety data, and to support the economic analysis. The indirect comparison indicated that pazopanib has comparable efficacy to sunitinib; HR for PFS 0.949 (95% CI 0.575 to 1.568) and HR for OS 0.969 (95% CI 0.359 to 2.608). The company commented that the wide confidence intervals for OS, was due to the RPSFT derived approach for OS for pazopanib. SMC statistical advice indicated that, although there are limitations with the Bucher indirect comparison method and a mixed treatment comparison may be preferable, a number of sensitivity analyses were performed which gives some confidence in the results. Therefore the indirect comparison provides some evidence that pazopanib has comparable efficacy and safety to sunitinib.

SMC clinical experts noted that pazopanib would be a useful alternative treatment option as it appears to offer similar clinical benefits to sunitinib and has a different tolerability profile in the context of currently available anti-VEGF treatments.

Summary of comparative health economic evidence

The manufacturer presented a lifetime cost-utility analysis comparing pazopanib with either sunitinib, interferon (IFN) or best supportive care (BSC) for the treatment of patients with advanced RCC. The economic analysis focused on the use of pazopanib as a first-line treatment option and expert responses indicated that sunitinib is the main comparator.

Estimated hazard ratios for progression free survival (PFS) and overall survival (OS) for pazopanib versus BSC were taken from the pivotal study. Clinical data for pazopanib compared with IFN and sunitinib were obtained via an adjusted indirect comparison using the Bucher method. Estimates of PFS and OS for the IFN arm of the model were obtained by fitting Weibull functions to the Kaplan-Meier data from the IFN arm of the sunitinib trial. These curves were used as the reference curves which allowed hazard ratios for PFS and OS to be applied for each of the other comparators using the indirect comparison results.

The model used was similar to a Markov cohort model with three mutually exclusive health states: alive pre-progression, alive post-progression and dead. The utility value applied to the progression free health state was 0.7 based on the mean EQ-5D utility value in the pivotal trial. Utility decrements associated with adverse events were also obtained from the trial. For the post- progression health state a value of 0.59 was chosen from published estimates. Monitoring and supportive care costs for pre- and post-progression were based on costs used in the NICE technology assessment of sunitinib. The cost of sunitinib used in the economic analysis

incorporated the sunitinib Patient Access Scheme (PAS), which offers the first cycle of treatment free.

In the base case, the manufacturer estimated the following results:

Pazopanib vs	Incremental cost	Incremental QALYs	ICER (cost per QALY)
Sunitinib	£4,263	0.068	£62,414
Interferon	£32,062	0.717	£44,697
BSC	£36,356	0.979	£37,126

A PAS was submitted by the manufacturer and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The PAS is a two part scheme with part A involving a discount on the list price and part B involving a one-off financial rebate if pazopanib does not meet the non-inferiority conditions in the comparative study with sunitinib that is required as part of the EMA conditional marketing authorisation. Incorporating part A of the PAS, the following results were estimated:

Pazopanib vs	Incremental cost	Incremental QALYs	ICER (cost per QALY)
Sunitinib	£122	0.068	£1,790
Interferon	£27,921	0.717	£38,925
BSC	£32,216	0.979	£32,898

A weakness in the analysis related to the proportion of patient crossover in the placebo arm of the pivotal trial which made interpretation of the OS data from the pivotal study problematic. The manufacturer made a good attempt at adjusting for this crossover and presented the results using a range of different methods. In the base case the manufacturer favoured the RPSFT method which resulted in a hazard ratio for OS of 0.501. However, the sensitivity analysis showed that the magnitude of OS benefit associated with pazopanib ranged from 0.300 to 0.797 when different methods were used. The economic results were particularly sensitive to the survival estimates used in the model, which relates to the small differences in effect between treatments.

The following limitations were also noted:

- SMC statistical advice indicated that a mixed treatment comparison may have been preferable, but the results of the adjusted indirect comparison indicate that it is reasonable to conclude that pazopanib and sunitinib have comparable efficacy. However, the base case analysis assumed an advantage in terms of PFS and OS with pazopanib which may not be appropriate.
- When the differences in PFS and OS between pazopanib and sunitinib were removed the cost per quality adjusted life year (QALY) was £174k (without PAS) and dominant (with PAS). However, it should be noted that this sensitivity analysis still includes differences in adverse event rates.
- No goodness-of-fit statistics were provided to show that the Weibull function was the best fit to the data. The manufacturer justified the choice of the Weibull function in order to be consistent with the approach used by NICE. No sensitivity analysis was provided to show the effect of using alternative parametric functions.

Despite these limitations, the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Interest Group submission was not made.

Additional information: guidelines and protocols

The National Institute of Health and Clinical Excellence (NICE) published; Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma (multiple technology appraisal guidance 169) in March 2009. Sunitinib is recommended as a first-line treatment option for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

NICE published; Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma (multiple technology appraisal guidance 178) in August 2009. Bevacizumab, sorafenib and temsirolimus are not recommended as first-line treatment options for people with advanced and/or metastatic renal cell carcinoma. Sorafenib and sunitinib are not recommended as second-line treatment options for people with advanced and/or metastatic renal cell carcinoma.

The European Association of Urology (EAU) published EAU Guidelines on Renal Cell Carcinoma: 2010 Update in July 2010. A general recommendation for therapy with targeting agents in patients with metastatic RCC is given. For the first-line treatment of low or intermediate risk metastatic RCC the following treatments are specifically recommended: sunitinib, bevacizumab plus interferon-alpha or pazopanib.

Additional information: comparators

Sunitinib is the main comparator and is indicated for the treatment of advanced/metastatic renal cell carcinoma. Other treatments are indicated for the treatment of advanced RCC but are not used widely in NHS Scotland and are not approved by SMC/NICE.

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)	Cost for 30 weeks (£)
pazopanib	**800mg orally once daily**	**N/A**	**15,694**
sunitinib	50mg orally once daily for 4 weeks, followed by 2-week rest period	3,139	15,694

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMs (October 2010). Median exposure in pazopanib study was 7.4 months; therefore costs for 30 weeks treatment for pazopanib and five (6-week) cycles of sunitinib are included in the table. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The manufacturer estimated the net drug budget impact without the PAS would be £240k in year 1 rising to £347k in year 5. It was assumed that around 200 patients would be eligible for treatment and the market share was estimated at 28% in year 1 (56 patients) and 40% in year 5 (81 patients). With the PAS, the net drug budget impact was estimated at £7k in year 1 rising to £11k in year 5.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomised phase III trial. J Clin Oncol 2010; 28; 1061-68

GlaxoSmithKline. Clinical Study Report VEG105192 (table 7.28). Cut-off 15 March 2010.

European Medicines Agency. European Public Assessment Report for pazopanib (Votrient). EMEA/H/C/001141. 14 June 2010. www.ema.europa.eu

This assessment is based on data submitted by the applicant company up to and including 10 December 2010.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards together with the SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.