NICE National Institute for Health and Care Excellence

NICE guidance

Pazopanib for the first-line treatment of advanced renal cell carcinoma

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

This guidance was re-issued after a change to the patient access scheme (August 2013). Part B of the patient access scheme will not be activated. Reference to part B of the patient access scheme has been removed from the recommendations. Reference to it elsewhere in the document should be considered obsolete.

1.1 Pazopanib is recommended as a first-line treatment option for people with advanced renal cell carcinoma:

- who have not received prior cytokine therapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 **and**
- if the manufacturer provides pazopanib with a 12.5% discount on the list price as agreed in the patient access scheme.

1.2 When using ECOG performance status, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.

1.3 People who are currently being treated with pazopanib for advanced metastatic renal cell carcinoma but who do not meet the criteria in section 1.1 should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.

2 The technology

2.1 Pazopanib (Votrient, GlaxoSmithKline) is an orally administered tyrosine kinase inhibitor. It inhibits vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors on cancer cells, vascular endothelial cells and pericytes, stopping the proliferation of tumour cells and the development of tumour blood vessels. Pazopanib has a conditional 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 conditional marketing authorisation is linked to the provision of further data including the outcome of the ongoing head-to-head non-inferiority trial of pazopanib versus sunitinib in patients with advanced renal cell carcinoma (COMPARZ). Only the indication for pazopanib for the first-line treatment of advanced renal cell carcinoma is within the remit of the appraisal.

2.2 Pazopanib is contraindicated in people who have hypersensitivity to the active substance or to any of the excipients, and people with severe hepatic impairment. The summary of product characteristics lists the adverse events that may be associated with pazopanib treatment, the most common being diarrhoea, hair colour changes, hypertension, nausea, anorexia, vomiting, fatigue, taste disturbance or loss of taste, and abnormal liver function. For full details of side effects and contraindications, see the summary of product characteristics.

2.3 Pazopanib is administered orally. The recommended dosage is 800 mg once daily. The dose may be adjusted in steps of 200 mg according to tolerability in order to manage adverse reactions but should not exceed 800 mg. The price for a pack of 400 mg tablets (30 tablets per pack) is £1,121.00 (MIMS, November 2010). The daily cost of pazopanib is £74.73 as stated by the manufacturer. The manufacturer of pazopanib has agreed a 2-part patient access scheme with the Department of Health. Part A of the patient access scheme provides a 12.5% discount from the list price. Therefore, the daily acquisition cost of pazopanib is £65.39. Part B of the patient access scheme, the details of which are 'commercial in confidence', offers a future rebate linked to the outcome of the head-to-head COMPARZ trial. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The manufacturer's submission

The Appraisal Committee considered evidence submitted by the manufacturer of pazopanib and a review of this submission by the Evidence Review Group (ERG).

3.1 The manufacturer presented evidence on the clinical effectiveness of pazopanib used in line with the conditional marketing authorisation and the appraisal scope. The main clinical-effectiveness evidence came from patients in the treatment-naive subgroup of a phase 3 randomised controlled trial (RCT). The RCT, VEG105192, compared the effect of a once-daily dose of pazopanib plus best supportive care (155 patients) with placebo plus best supportive care (78 patients). Best supportive care was defined as the monitoring of progression, symptom control and palliative care without active treatment. The trial was conducted in patients with advanced renal cell carcinoma with predominantly clear cell histology. All patients had a good performance status (ECOG performance status 0 or 1) at the start of the trial. Baseline characteristics of the patients in the 2 treatment arms were equally balanced.

3.2 The primary outcome in the study was progression-free survival, which was defined as time from randomisation to disease progression or death. Tumour assessments were performed using RECIST (Response Evaluation Criteria in Solid Tumours) and were confirmed by an independent review committee. Once disease progression was confirmed, patients who previously received placebo plus best supportive care could be offered open-label pazopanib plus best supportive care in the open-label extension study (VEG107769) if the treating clinician thought this was in the best interests of the patient. At disease progression, only patients with an ECOG performance status of less than or equal to 2 were permitted to cross over to receive pazopanib. The median progression-free survival was statistically significantly longer in patients receiving pazopanib ($p<0.001$). The median progression-free survival was 11.1 months (95% confidence interval [CI] 7.4 to 14.8) for patients receiving pazopanib plus best supportive care and 2.8 months (95% CI 1.9 to 5.6) for patients receiving placebo plus best supportive care (hazard ratio [HR] 0.40, 95% CI 0.27 to 0.60) based on blinded imaging assessment by the Independent Review Committee. This meant there was a 60% reduction in risk of disease progression for patients receiving pazopanib plus best supportive care compared with those receiving placebo plus

best supportive care at the final analysis. The manufacturer performed sensitivity analyses of progression-free survival based on actual scan dates and investigators' assessment to confirm the robustness of the findings. The median progression-free survival based on actual scan dates was 10.8 months (95% CI 7.4 to 14.8) for patients receiving pazopanib plus best supportive care and 2.9 months (95% CI 1.9 to 5.4) for patients receiving placebo plus best supportive care (HR 0.36, 95% CI 0.24 to 0.55). These latter estimates were used in the indirect comparison.

3.3 At the time of the interim overall survival analysis (23 May 2008), 31 of 78 (40%) treatment-naive patients randomised to receive placebo in the VEG105192 trial had crossed over to receive pazopanib. At the final analysis (15 March 2010), a total of 40 (51%) treatment-naive patients randomised to placebo had crossed over to receive pazopanib. Overall survival for the treatment-naive, intention-to-treat population, unadjusted for crossover, was 22.9 months (95% CI 17.6 to 25.4 months) for patients randomised to pazopanib plus best supportive care and 23.5 months (95% CI 12.0 to 34.3 months) for patients randomised to placebo plus best supportive care. The hazard ratio for overall survival was 1.01 (95% CI 0.72 to 1.42, p=0.525). The manufacturer presented a variety of methods to adjust for crossover when estimating median overall survival, including the inverse probability censoring weighted (IPCW) and rank preserved structural failure time (RPSFT) methods. The manufacturer considered the RPSFT weighted method to be the most appropriate because it was considered an acceptable approach for NICE's technology appraisal guidance on sunitinib for the treatment of gastrointestinal stromal tumours and everolimus for advanced renal cell carcinoma after previous treatment. The RPSFT weighted method estimated the overall survival of patients randomised to receive placebo assuming that they had not crossed over, that is, as if they had remained on placebo for the duration of the trial. The method proportionally 'shrunk' the estimated amount of additional survival given to patients who crossed over to receive pazopanib. The RPSFT analysis suggested that treatment with pazopanib was consistently associated with survival benefit compared with placebo (HR 0.501, 95% CI 0.136 to 2.348). The manufacturer also noted that the 0.501 hazard ratio lies within the range of estimates obtained from the different methods used to adjust for crossover. This hazard ratio was subsequently used for the indirect comparison.

3.4 No head-to-head trials analysing the efficacy of pazopanib compared with other

active treatment options were available. Therefore, the manufacturer undertook a search for trials of comparator interventions and carried out an indirect comparison to estimate the relative effect of pazopanib versus the comparators (sunitinib, interferon-alpha and best supportive care). Seven studies were included in the indirect comparison, including 1 study of pazopanib compared with placebo (VEG105192), 1 study of sunitinib compared with interferon-alpha (Motzer et al. 2009) and 5 studies that directly compared interferon-alpha with a non-interferon control therapy (medroxyprogesterone acetate and vinblastine). The populations in the pazopanib (VEG105192) and sunitinib (Motzer et al. 2009) studies were comparable, but with the exception that a higher proportion of patients with a baseline ECOG performance status of 0 were recruited to the sunitinib study than to the VEG105192 trial (approximately 60% versus 40%). Both studies restricted entry to patients with renal cell carcinoma with either clear cell or predominantly clear cell histology. The average age of patients in both studies was 60 years and 83% to 91% of patients had prior nephrectomy. The patient populations in the 5 interferon-alpha studies were generally similar. All patients had renal cell carcinoma, the age range was 60 to 66 years and 57% to 100% of patients had prior nephrectomy. Three of the interferon-alpha studies included some patients with a baseline ECOG performance status of 2.

3.5 Hazard ratios for progression free survival and overall survival from all 7 studies were used in the indirect comparison to obtain hazard ratios for pazopanib versus interferon-alpha and pazopanib versus sunitinib. The hazard ratios for progression-free survival used in the indirect comparison for pazopanib versus placebo plus best supportive care, sunitinib versus interferon-alpha and interferon-alpha versus best supportive care were 0.36 (95% CI 0.24 to 0.55), 0.539 (95% CI 0.451 to 0.643) and 0.704 (95% CI 0.0.580 to 0.854). Median progression-free survival estimates derived from the indirect comparison for pazopanib, sunitinib, interferon-alpha and placebo plus best supportive care were 11.3 months (95% CI 5.1 to 17.5), 10.7 months (95% CI 7.9 to 13.4), 5.4 months (95% CI 5.4 to 5.4) and 5.6 months (95% CI 4.0 to 7.3) respectively.

3.6 The pazopanib overall survival value was estimated using the RPSFT weighted method. The manufacturer used hazard ratios derived from all 7 studies in a Weibull survival model to estimate the median overall survival values for pazopanib versus interferon-alpha and pazopanib versus sunitinib. In the base-case scenario, derived using the RPSFT weighted method, the median overall

survival estimates for pazopanib, sunitinib, interferon-alpha and placebo plus best supportive care were 27.8, 26.8, 15.8 and 12.1 months, respectively. These results indicated that pazopanib was associated with a decreased risk of death (37% reduction) compared with interferon-alpha, and that pazopanib appeared to have comparable efficacy with sunitinib in terms of overall survival. The manufacturer highlighted that the 95% confidence intervals around the hazard ratios were wide, indicating a level of uncertainty with the estimates. Sensitivity analyses were performed that included varying the hazard ratio for overall survival in the VEG105192 trial by using different methods for adjusting for crossover and varying the interferon-alpha studies included. The manufacturer concluded that the results of these sensitivity analyses of the indirect comparison were similar to those of the base-case analysis.

3.7 Only the VEG105192 trial, which compared pazopanib and placebo, and the study by Motzer et al. (2009), which compared sunitinib with interferon-alpha, reported health-related quality of life data. For the VEG105192 trial, there were no statistically significant differences between pazopanib and placebo for any of the instruments used (European Organisation for Research and Treatment of Cancer [EORTC] quality of life questionnaire – Core 30, EQ-5D, EQ-5D-VAS). For the comparison of sunitinib with interferon-alpha, patients receiving sunitinib had a statistically significantly better quality of life than patients receiving interferon-alpha, as measured by the EQ-5D, EQ-5D-VAS and the Functional Assessment of Cancer Therapy (FACT) Kidney Symptom Index Disease-related Symptom (FKSI-DRS) Index, FACT-Kidney Symptom Index – 15-item scale (FKSI-15 Index) and the FACT-General Scale (FACT-G). No indirect comparison was made for this outcome.

3.8 In the VEG105192 trial, 91% of patients receiving pazopanib experienced an adverse event. In 87% of patients the adverse events were related to study medication. In the placebo group 74% of patients experienced an adverse event and in 37% of patients these were related to study medication. The most frequent adverse events related to pazopanib treatment were diarrhoea, hair colour change, hypertension, nausea, anorexia and increased liver enzymes. The manufacturer conducted an indirect comparison using 1 of the interferon-alpha studies to estimate the adverse event rates of pazopanib compared with sunitinib. The adverse event rates for pazopanib were generally lower than for sunitinib, in particular for dyspepsia, mucositis or stomatitis, fatigue, hand-foot

syndrome, skin discolouration, hypophosphataemia, anaemia and altered taste. However, only the difference in fatigue was statistically significant (HR 0.21, 95% CI 0.06 to 0.77).

3.9 The manufacturer submitted an economic model to assess the cost effectiveness of pazopanib in treatment-naive patients. The model compared pazopanib with interferon-alpha, sunitinib and best supportive care. The manufacturer described the model as a 'partitioned survival' model, characterised by 3 mutually exclusive health states: alive pre-progression, alive post-progression and dead. Unlike a Markov model, which models transitions between health states explicitly using transition probabilities, the partitioned survival model calculated the proportion of patients in each treatment arm at any time after starting treatment, using parametric survival curves fitted to empirical data on overall survival and progression-free survival over time. The proportion of patients in the 'alive post-progression' health state at any given time was calculated as the difference between overall survival and progression-free survival. In the model, pazopanib was assumed to be given until disease progression or death (if occurring before progression). After starting treatment, patients were assumed to be in an 'alive pre-progression' health state, and to be at risk of disease progression and/or death over time. Patients who experienced disease progression were assumed to discontinue treatment with pazopanib (and receive only best supportive care) and to transition to an 'alive post-progression' health state and to stay in that state until death.

3.10 For the model, a utility value of 0.70 was assumed for patients who had no disease progression and no adverse events, based on the mean EQ-5D utility value among patients without adverse events in the VEG105192 trial. Disease progression was assumed to be associated with a decrement in utility of 15% (that is, a post-progression utility value of 0.59). These values were used for all the interventions in the model. Utility decrements for adverse events were also obtained from the VEG105192 trial. As a result of the lack of published utility data in this patient population, the manufacturer commissioned a health state preference study to generate utility values for progression-free survival and post-progression survival and disutilities for treatment-related adverse events such as anaemia, diarrhoea, fatigue, hand-foot syndrome, nausea, mucositis and hypertension. The utility decrements for adverse events were used in a sensitivity analysis.

3.11 The manufacturer agreed a 2-part patient access scheme with the Department of Health. Part A of the patient access scheme provides a 12.5% discount to the list price of pazopanib. Part B of the patient access scheme, the details of which are 'commercial-in-confidence', offers a future rebate linked to the outcome of the head-to-head COMPARZ trial. The manufacturer assumed that there would be no additional costs to the NHS associated with administering the patient access scheme. The costs considered in the economic model included acquisition costs for study medications, drug administration costs for infusions, costs of treating grade 3 or higher adverse events, routine follow-up costs, costs of progression and supportive care costs. In order to account for dose reductions and dose interruptions, the manufacturer adjusted the cost of study medication by using relative dose intensities reported in RCTs of the study treatments. In the model, the manufacturer used a dose intensity for pazopanib of 86%, equivalent to 688 mg per patient per day. Similar dose intensities were used for sunitinib (86%) and interferon-alpha (84%). Only the costs of treating adverse events that were grade 3 or higher with an incidence of at least 5% were considered for any treatment based on the indirect comparison. The cost per event was assumed to be independent of treatment.

3.12 For part A of the patient access scheme, which provides a 12.5% discount to the pazopanib list price, sunitinib was extendedly dominated by a combination of pazopanib and interferon-alpha. An option is 'extendedly dominated' when its ICER is higher than that of the next, more effective, option when compared with a common baseline (that is, it is dominated by a combination of 2 other alternatives). As a result, using the RPSFT weighted method of adjusting for crossover, the ICERs for pazopanib versus sunitinib, interferon-alpha and best supportive care were £1,790, £38,925 and £32,898 per QALY gained respectively. These ICERs were derived from incremental costs of £122, £27,921 and £32,216, and incremental QALYs of 0.068, 0.717 and 0.979 respectively. The manufacturer provided additional cost-effectiveness analyses using alternative methods of adjusting for crossover. The ICERs for pazopanib versus sunitinib, interferon-alpha and best supportive care ranged from £1,790 to £5,327, £21,625 to £72,274 and £20,824 to £48,877 per QALY gained respectively. One-way sensitivity analyses showed that the ICER was most sensitive to the efficacy estimates for pazopanib versus interferon-alpha, which contribute to the relative efficacy of pazopanib and sunitinib. Specifically, the model is sensitive to the method used for adjusting for crossover for overall survival data from the

VEG105192 trial. The manufacturer also provided cost-effectiveness estimates based on part B of the patient access scheme. However, these data are 'commercial-in-confidence' and therefore no details can be reported.

3.13 The ERG stated that the evidence base was not ideal for this appraisal as there were no data available from head-to-head comparisons of pazopanib with sunitinib or interferon-alpha. However, the ERG commented on the substantial amount of evidence on the efficacy and safety of pazopanib and on the considerable effort that had gone into providing these data, and the methods were generally well reported.

3.14 The ERG commented that the choice of model appeared to be appropriate given the decision problem and the data available. The time horizon appeared to be appropriate, although there were concerns that it may overestimate survival because the median age of diagnosis is 60 to 65 years and constant all-cause mortality was assumed, rather than taking data from life tables, which would have the impact of mortality increasing over time. The ERG stated that the results appeared valid with the methods used. Most of the model analyses performed could be replicated, although this was not true for all sensitivity analyses.

3.15 The ERG noted that in the manufacturer's original submission the base-case analysis was based on estimates from the model using the unweighted unadjusted RPSFT method to adjust for crossover and pooled interferon-alpha studies. In the updated analysis, provided as an addendum to the original submission, the method used for adjusting for crossover was the RPSFT weighted method, unadjusted. The ERG acknowledged that the manufacturer had presented a set of analyses that comprehensively covered the range of methods available for crossover. The ERG stated that the RPSFT weighted method advocated by the manufacturer was weakened by the lack of an adequately developed method to analyse relatively immature data robustly. The RPSFT weighted method provided a higher hazard ratio than the unweighted method, and although this did affect the results, the change in method had not necessarily been favourable to pazopanib.

3.16 The ERG also highlighted a concern about the manufacturer's assumption that as soon as a patient's disease progressed, they stopped treatment. The ERG considered that, in practice, it is unlikely this will happen immediately because

patients will only know the status of their disease when they have their next review, which may not be at the exact time the disease progresses. This assumption may create a small bias in favour of the more costly treatments such as pazopanib.

3.17 The ERG also stated that there was some uncertainty around the utility value estimate used. The manufacturer used an estimate that was based on the EQ-5D utility value among all patients without adverse events in the VEG105192 trial. The manufacturer also assumed this value to be similar for all interventions. The ERG noted, however, that given the minimal impact adverse events had on the model (in terms of QALYs and costs) this was not likely to be a major issue.

3.18 The ERG conducted an exploratory analysis to address concerns about the weighted unadjusted RPSFT results for overall survival being used for the base-case analysis. It assessed the potential impact of a robust weighted analysis on the results, particularly with a model adjusted for baseline covariates, for which methods are still in development. The ERG considered the impact of weighting by comparing the unweighted analyses with the weighted analyses when the models were unadjusted for baseline. The ERG concluded that, overall, weighting does have an impact on the hazard ratio, but it is difficult to establish the direction and magnitude of this effect. The ERG performed multivariate sensitivity analyses around utility value estimates for progression-free survival, utility decrement for progression and duration of utility with adverse events. The results of these analyses indicated that they are sensitive to some combinations of changes and that the ICER associated with pazopanib could increase to more than £50,000 per QALY gained. However, the confidence interval around the hazard ratio for overall survival was very wide. The ERG noted that the manufacturer only reported pair-wise probabilistic sensitivity analysis, therefore the ERG used the base case to compare all 4 treatment options. The ERG concluded that pazopanib is most likely to be the most cost-effective option at willingness to pay thresholds between £35,000 and £50,000. However, the ERG stated that such analyses take the base case at face value and that it was not possible to explore the uncertainty of the various methods used to adjust for crossover or the point estimates used in the economic model due to limited data available for some parameters.

3.19 Full details of all the evidence are in the manufacturer's submission and the ERG

report.

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of pazopanib, having considered evidence on the nature of advanced renal cell carcinoma and the value placed on the benefits of pazopanib by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.2 The Committee heard from the patient experts and clinical specialists that advanced renal cell carcinoma is a relatively rare cancer and noted the views of patient experts and clinical specialists on the severity of the disease. The Committee noted that there are limited treatment options for patients with advanced renal cell carcinoma and that currently sunitinib is the only first-line treatment recommended by NICE (see NICE's technology appraisal guidance on sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma). The Committee heard from the patient experts that, while sunitinib is considered an effective treatment, it is associated with a number of side effects as a result of its toxicity. These include hypertension, fatigue, diarrhoea and hand-foot syndrome. The patient experts highlighted that hand-foot syndrome is frequently intolerable. The clinical specialists stated that patients receiving treatment with sunitinib require a 2-week rest period as part of the treatment cycle, because patients are not able to tolerate sunitinib after 4 weeks. In addition, for a number of patients the dose of sunitinib has to be adjusted to maintain tolerability. The clinical specialists considered that the 2-week rest period and dose adjustment may reduce the benefits gained from sunitinib. The clinical specialists and patient experts were of the opinion that pazopanib is a useful option because it has a more favourable toxicity profile than sunitinib.

4.3 The Committee considered the evidence on the clinical effectiveness of pazopanib presented in the manufacturer's submission and the ERG report. The Committee noted that the VEG105192 trial compared pazopanib with placebo and the trial was generally of acceptable quality. It was aware of the ERG's concerns

that the trial included only a small number of patients from the UK. The Committee accepted advice from clinical specialists that the data were relevant to clinical practice in England and Wales. The Committee considered the evidence from the VEG105192 trial. It noted that pazopanib, when compared with placebo, produced a statistically significant improvement in median progression-free survival of approximately 8 months (10.8 versus 2.9 months [Independent Review Committee assessment, HR 0.36, 95% CI 0.24 to 0.55]).

4.4 The Committee then discussed the estimates of overall survival gain obtained from the VEG105192 trial. The Committee acknowledged that the estimates of overall survival for pazopanib versus placebo according to the intention-to-treat analysis (22.9 versus 23.5 months; HR 1.01, 95% CI 0.72 to 1.42) had been confounded by crossover and that 51% of patients who had received placebo crossed over to receive pazopanib after disease progression. The Committee heard from the clinical specialists that an increase in progression-free survival would be expected to result in an increase in overall survival, and agreed that it was appropriate to adjust the results to control for the crossover using statistical modelling techniques.

4.5 The Committee discussed the manufacturer's approach to estimating overall survival, adjusting for crossover. It acknowledged that the manufacturer had presented a set of analyses that comprehensively covered the range of methods available to adjust for crossover, including an analysis of survival in patients who did not receive post-study cancer therapy. The Committee noted the hazard ratios for overall survival varied from 0.30, based on patients who did not receive post-study cancer therapy, to 0.642, based on the IPCW method, and that these had wide confidence intervals. The Committee acknowledged that the hazard ratio chosen by the manufacturer for the indirect comparison (HR 0.501, 95% CI 0.136 to 2.348) was estimated by the RPSFT weighted method. Although subject to uncertainty, the hazard ratio was in the middle of the range of estimates generated by the manufacturer. The Committee noted the ERG's comments suggesting that this approach was reasonable and it accepted the use of this hazard ratio in the indirect comparison. The Committee concluded that there was sufficient evidence that pazopanib increased progression-free and overall survival compared with placebo, although there was uncertainty about the precise magnitude of the overall survival gain. The Committee noted that the pazopanib trial was only conducted with patients who had a good ECOG

performance status of 0 or 1. Therefore the Committee concluded that pazopanib is a clinically effective first-line treatment for advanced renal cell carcinoma for patients with an ECOG performance status of 0 or 1 when compared with placebo or best supportive care.

4.6 The Committee then discussed the manufacturer's indirect comparison, used to estimate progression-free survival and overall survival for pazopanib compared with sunitinib, interferon-alpha and best supportive care. It noted that the results of the indirect comparison for median progression-free survival for pazopanib versus interferon-alpha (11.3 versus 5.4 months; HR 0.512, 95% CI 0.326 to 0.802) were comparable with the corresponding results from the sunitinib study by Motzer et al. (2009; 11.0 versus 5.1 months; HR 0.539, 95% CI 0.451 to 0.643). The Committee noted the results of the indirect comparison that suggested pazopanib was associated with considerably improved overall survival compared with either interferon-alpha or best supportive care, and was comparable with sunitinib, although the confidence intervals around the hazard ratios were wide. The Committee heard from the clinical specialists that, in their opinion, the estimates obtained for progression-free survival (with no need for adjustment for crossover) supported the overall survival estimates. The Committee noted that the results of a direct comparison would be available in 2012 when an ongoing head-to-head study of pazopanib versus sunitinib (the COMPARZ trial) was complete, but until then it was reasonable to consider that pazopanib was as clinically effective as sunitinib. The Committee concluded that pazopanib is likely to be more clinically effective than interferon-alpha and is probably comparable in its effectiveness to sunitinib.

4.7 The Committee heard from the clinical specialists that the evidence presented by the manufacturer suggested that pazopanib has a more favourable toxicity profile than sunitinib, especially in relation to hand-foot syndrome. It noted that in the VEG105192 trial, 1.9% of patients receiving pazopanib had hand-foot syndrome (all grades) compared with 0% receiving placebo, while in the study by Motzer et al. (2009), 29% of patients receiving sunitinib) experienced hand-foot syndrome (all grades) compared with 3% of patients receiving interferon-alpha. The Committee noted that grade 3 or 4 hand-foot syndrome occurred in 0% of patients receiving either pazopanib or placebo in the VEG105192 study, while 9% of patients receiving sunitinib in the study by Motzer et al. (2009) had grade 3 or 4 hand-foot syndrome compared with 1% of patients receiving interferon-alpha.

The Committee discussed the evidence provided by the manufacturer on the adverse events associated with pazopanib. The Committee noted that the numbers of grade 3 and 4 adverse events were similar between the pazopanib and placebo groups in the VEG105192 trial. The Committee noted that the evidence from the indirect comparison indicated that the number of adverse events was generally lower for pazopanib than for sunitinib, although only statistically significant for fatigue. The Committee noted that the results of the indirect comparison were not presented for hand-foot syndrome. The Committee was aware of the evidence from the patient experts about the debilitating adverse effects of treatment with sunitinib and the importance of an alternative treatment being available for patients experiencing such adverse effects. The Committee agreed that pazopanib would be a useful treatment option for patients with advanced renal cell carcinoma.

Cost effectiveness

4.8 The Committee considered the manufacturer's economic model and the critique and exploratory sensitivity analyses performed by the ERG. It broadly accepted the model structure, but was aware of the points raised by the ERG about the uncertainties around the parameter values used in the economic model.

4.9 The Committee discussed the cost-effectiveness data submitted by the manufacturer for pazopanib compared with sunitinib, interferon-alpha and best supportive care. The Committee discussed the key parameters used in the model. It agreed that the cost-effectiveness estimates derived from the hazard ratio estimate for overall survival for pazopanib versus placebo, obtained using the unadjusted weighted RPSFT analysis (hazard ratio 0.501), were reasonable (see section 4.6). The Committee then considered the utility values used in the model (0.70 for patients who had no disease progression and no adverse events and 0.59 for post progression). It was aware of the issues raised by the ERG about the methods used by the manufacturer to derive the values but also noted that these issues were not considered to be major. The Committee noted that these utility values were lower than those used in NICE's technology appraisal guidance on sunitinib but that the difference of 0.11 between these values was greater. The Committee agreed that this difference in utility values between the health states was reasonable and therefore accepted the utility values modelled

by the manufacturer.

4.10 The Committee was aware that a 2-part patient access scheme has been agreed by the Department of Health (see section 2.3). The Committee agreed that when considering the cost effectiveness of pazopanib it was appropriate to consider both parts of the patient access scheme. The Committee noted that when the manufacturer had presented cost-effectiveness estimates for part A of the patient access scheme, it had also provided additional cost-effectiveness results that used alternative methods of adjusting for crossover in the VEG105192 trial. It acknowledged that the ICERs were highly sensitive to the method used for adjusting for crossover, with ICERs ranging from £21,600 to £72,300 per QALY gained for pazopanib versus interferon-alpha, and from £1,790 to £5,330 per QALY gained for pazopanib versus sunitinib. Given that the Committee accepted the RPSFT-derived hazard ratio of 0.501 used for the indirect comparison, it agreed that the base-case ICERs for pazopanib compared with best supportive care, interferon-alpha and sunitinib of £33,000, £38,900 and £1,790 per QALY gained (based on incremental costs of £32,200, £27,900, £122 and incremental QALYs of 0.979, 0.717 and 0.068 respectively) were reasonable estimates.

4.11 The Committee then discussed how to apply these ICERs given that a treatment such as sunitinib, recommended using the supplementary advice on appraising life extending, end-of-life treatments, should not, in view of the same supplementary advice, automatically be considered a standard comparator when a new treatment for the same indication is appraised. The Committee agreed that for this reason, and because sunitinib and pazopanib were developed at the same time, it was appropriate that pazopanib also be considered against interferon-alpha when applying the supplementary advice on appraising life extending, end of life treatments. The Committee was aware that only the ICERs for pazopanib compared with best supportive care and interferon-alpha in relation to part A of the patient access scheme were higher than the range normally considered a cost-effective use of NHS resources.

4.12 The Committee next considered whether pazopanib fulfilled the criteria for an end of life treatment in the context of the supplementary advice from NICE that should be taken into account when appraising treatments which may extend the life of people with a short life expectancy and which are licensed for indications that affect small numbers of people with incurable illnesses. For this to be

applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

When taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.13 The Committee was aware from discussion with the clinical specialists that in England and Wales the total number of people that would be eligible for treatment with pazopanib was less than 4000. The Committee heard from the clinical specialist that the life expectancy for people with advanced renal cell carcinoma receiving best supportive care alone was unlikely to be greater than 24 months and was potentially as low as 5 months. The Committee also noted that the evidence from the RPSFT analysis suggested that pazopanib increased overall survival by more than 3 months compared with placebo, and from the indirect comparison by more than 3 months compared with interferon-alpha. In summary, the Committee was satisfied that pazopanib met the criteria for being a life-extending, end-of-life treatment, and that the evidence presented for this consideration was sufficiently robust.

4.14 The Committee considered the central estimate of the ICER (£38,900 per QALY gained) and the robustness and uncertainty of the ICER. The Committee was aware of exploratory net benefit analyses carried out by the ERG which indicated that pazopanib would be considered cost effective at willingness to pay thresholds between £35,000 and £50,000 per QALY gained. The Committee considered that the magnitude of additional weight that would need to be assigned to the original QALY benefits in this patient group was within the range considered acceptable for an end of life treatment. Therefore, the Committee

concluded that pazopanib should be recommended as a first-line treatment option for patients with advanced renal cell carcinoma who have not received prior cytokine therapy and have an ECOG performance status of 0 or 1, and if the manufacturer provides pazopanib with a 12.5% discount on the list price.

4.15 The Committee considered part B of the patient access scheme which linked a specific future rebate to the outcome of the COMPARZ trial. The Committee accepted that the approach taken in part B of the patient access scheme, the details of which are provided 'commercially in confidence', was reasonable and that the ICERs were acceptable. The Committee concluded that pazopanib should be recommended as indicated above (see section 4.14) and if the manufacturer provides a future rebate linked to the outcome of the COMPARZ trial, as agreed under the terms of the patient access scheme and to be confirmed when the COMPARZ trial data are made available.

4.16 The Committee considered whether its recommendation was associated with any potential issues related to equality. The Committee concluded that healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

5.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has advanced renal cell carcinoma and the healthcare professional responsible for their care thinks that pazopanib is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Recommendations for further research

6.1 An ongoing head-to-head study of pazopanib versus sunitinib (COMPARZ) is due to report in June 2012.

7 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Kathryn Abel
Reader and Consultant Psychiatrist and Director of Centre for Women's Mental Health, University of Manchester

Dr David Black
Director of Public Health, Derbyshire County Primary Care Trust

Dr Daniele Bryden
Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Trust

Dr Andrew Burnett
Director for Health Improvement and Medical Director, NHS Barnet

David Chandler

Lay Member

Dr Chris Cooper
General Practitioner, St John's Way Medical Centre, London

Dr Christine Davey
Research Adviser, North and East Yorkshire Alliance Research and Development Unit, York

Richard Devereaux-Phillips
Public Affairs and Reimbursement Manager UK and Ireland, Medtronic, Watford

Professor Rachel A Elliott
Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Wasim Hanif MD FRCP
Consultant Physician and Honorary Senior Lecturer, University Hospital Birmingham

Dr Alan Haycox
Reader in Health Economics, University of Liverpool Management School

Professor Cathy Jackson
Professor of Primary Care Medicine, University of St Andrews

Dr Peter Jackson
Clinical Pharmacologist, University of Sheffield

Henry Marsh
Consultant Neurosurgeon, St George's Hospital, London

Professor Gary McVeigh
Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr Eugene Milne
Deputy Regional Director of Public Health, North East Strategic Health Authority

Dr Neil Myers
General Practitioner, Glasgow

Dr Richard Nakielny
Consultant Radiologist, Sheffield Teaching Hospitals Foundation Trust

Professor Katherine Payne
Professor of Health Economics, University of Manchester

Dr Danielle Preedy
Lay Member

Ellen Rule
Programme Director, NHS Bristol

Miles Scott
Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Dr Peter Selby
Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Dr Matt Stevenson
Technical Director, School of Health and Related Research, University of Sheffield

Professor Paul Trueman
Professor of Health Economics, Brunel University, London

Dr Judith Wardle
Lay Member

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Christian Griffiths
Technical Lead

Nicola Hay
Technical Adviser

Lori Farrar
Project Manager

8 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by Aberdeen HTA Group:

- Kilonzo M, Hislop J, Elders A et al. Pazopanib for the first line treatment of patients with advanced and/or metastatic renal cell carcinoma (September 2010)

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope. Manufacturers or sponsors were also invited to make written submissions. Professional or specialist, and patient or carer groups gave their expert views on pazopanib by providing a written statement to the Committee. Manufacturers or sponsors, professional or specialist, patient or carer groups, and other consultees have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- GlaxoSmithKline

Professional or specialist and patient or carer groups:

- James Whale Fund for Kidney Cancer
- Kidney Cancer UK
- Macmillan Cancer Support
- Cancer Research UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- United Kingdom Oncology Nursing Society

Other consultees:

- Department of Health
- NHS Waltham Forest
- Welsh Assembly Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- Novartis
- Pfizer
- Aberdeen HTA
- National Institute for Health Research Health Technology Assessment Programme

The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer or sponsor consultees and commentators. They gave their expert personal view on pazopanib by providing oral evidence to the Committee.

- Dr Thomas Powles, Senior Lecturer and Consultant, nominated by GlaxoSmithKline and Pfizer Ltd – clinical specialist
- Dr David Chao, Consultant Medical Oncologist, nominated by Royal College of Physicians – clinical specialist
- Jacqueline Lowe, nominated by Kidney Cancer UK – patient expert
- Bill Savage, patient advocate, nominated by James Whale Fund for Kidney Cancer – patient expert

Representatives from the following manufacturer or sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific

issues and comment on factual accuracy.

- GlaxoSmithKline

Update information

August 2013: Part B of the patient access scheme was removed.

April 2017: The company changed from GlaxoSmithKline to Novartis. Contact details for the patient access scheme updated.

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