Final appraisal determination

Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 Axitinib is not recommended within its marketing authorisation, that is, for the treatment of adults with advanced renal cell carcinoma after failure of prior treatment with sunitinib or a cytokine.

1.2 People currently receiving axitinib that is not recommended according to 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

2 The technology

2.1 Axitinib (Inlyta, Pfizer) is an oral multi-targeted kinase inhibitor with anti-tumour activity. Axitinib selectively inhibits vascular endothelial growth factor receptors 1, 2 and 3, platelet-derived growth factor receptor, and c-kit, which may inhibit angiogenesis in tumours. Axitinib has a marketing authorisation for ‘the treatment of adult patients with advanced renal cell carcinoma, after failure of prior treatment with sunitinib or a cytokine’.

2.2 The summary of product characteristics lists the following adverse reactions for axitinib: diarrhoea, hypertension, fatigue, dysphonia,
nausea, decreased appetite, palmar–plantar erythrodysaesthesia (hand–foot syndrome), hypothyroidism, headache, dysgeusia, haemorrhage, vomiting, stomatitis, constipation, rash, dry skin, proteinuria, asthaenia and mucosal inflammation. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Axitinib is available in 1-mg and 5-mg film-coated tablets at net prices of £703.40 and £3517 per 56-tablet pack respectively (excluding VAT). Axitinib is administered orally at a recommended starting dose of 5 mg twice daily. This dose may be increased to 7 mg and then up to 10 mg, or decreased to 3 mg and then down to 2 mg, depending on individual safety and tolerability. The manufacturer has agreed a patient access scheme with the Department of Health. The size of the discount is commercial in confidence. 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 (appendix A) considered evidence submitted by the manufacturer of axitinib and a review of this submission by the Evidence Review Group (ERG; appendix B).

Clinical-effectiveness evidence

3.1 The manufacturer conducted a systematic literature search and identified 1 randomised controlled trial (AXIS) that assessed axitinib for the second-line treatment of people with advanced renal cell carcinoma. AXIS was a phase III, international, multicentre, randomised, open-label, active-controlled trial comparing axitinib with sorafenib for treating advanced or metastatic renal cell
carcinoma after failure of prior first-line systemic therapy. The trial was undertaken in 175 centres in 22 countries and lasted for 3 years. The clinical-effectiveness evidence presented in the manufacturer’s submission was based mainly on this trial, but because it had no best supportive care comparator as defined in the scope, additional studies were used for an indirect comparison of axitinib with best supportive care.

3.2 Patients were eligible to enter the AXIS trial if they had measurable and progressive disease according to the Response Evaluation Criteria in Solid Tumours (RECIST) at least 2 weeks after 1 systemic first-line treatment with sunitinib, temsirolimus or cytokine(s), or at least 4 weeks or more treatment with bevacizumab plus interferon alfa-2a. The trial randomised 723 patients in a 1:1 ratio to receive either 5 mg axitinib twice daily or 400 mg sorafenib twice daily. The dose for axitinib was either maintained, or increased to 7 mg and then up to 10 mg twice daily, or reduced to 3 mg and then down to 2 mg twice daily, depending on individual safety and tolerability and at the discretion of the treating physician. If there were sorafenib-related adverse reactions, the dose could be reduced to 400 mg once daily and if necessary, further reduced to 400 mg on alternate days. No other chemotherapy or experimental anticancer medications were allowed in the trial period. Palliative care was allowed for pain control only of bone disease present at baseline and for disease-related symptoms. Baseline patient characteristics were balanced across the 2 treatment groups. The mean age was approximately 60 years (66% of the participants were less than 65 years), 72% were male and approximately 76% were white. The previous systemic therapies used were also similar across the 2 groups (in both groups, 54% of patients had received sunitinib, 35% had
received cytokines, 8% had received bevacizumab and 3% had received temsirolimus). There were no notable differences between the treatment groups in terms of disease history.

3.3 The primary outcome in the AXIS trial was progression-free survival as measured by an independent review committee (IRC), and this was defined as the time from randomisation to first disease progression or death from any cause (whichever occurred first). Secondary outcomes included progression-free survival as assessed by the investigator; overall survival, defined as the time from randomisation to the date of death from any cause; objective response rate, defined as the number of patients with complete or partial response according to RECIST criteria; duration of response, defined as the time of the first tumour response to the time of disease progression or death from any cause (whichever occurred first); and patient-reported outcomes (quality of life). Quality of life was assessed using the 15-item Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI-15), which measures symptoms and quality of life in people with advanced kidney disease; and the FKSI Disease-Related Symptoms subscale (FKSI-DRS), which measures symptoms related to advanced kidney cancer disease. Symptoms measured include lack of energy, pain, weight loss, bone pain, fatigue, shortness of breath, coughing, fevers and haematuria. The EQ-5D was also used to assess generic health status.

3.4 Subgroup analyses of the primary and secondary end points were performed for the stratification factors based on Eastern Cooperative Oncology Group (ECOG) performance score (0 and 1) and prior treatment regimen (sunitinib, a cytokine, bevacizumab or temsirolimus). The evidence in the manufacturer’s submission was based on the subgroups of patients who were previously treated
with sunitinib or a cytokine (such as interferon alfa or interleukin 2), in line with the marketing authorisation for axitinib. These subgroups are referred to as the prior-sunitinib group and the prior-cytokine group in this document. Subgroups were also predefined for the secondary end points based on baseline patient characteristics of age (less than 65 years or 65 years or more); sex (male or female); ethnic origin (white or non-white); geographical region (Asia, Europe, North America or other); and Memorial Sloan-Kettering Cancer Centre (MSKCC) risk groups (favourable, intermediate or poor).

3.5 In the main trial population, there was a statistically significant difference of 2 months in the IRC-assessed median progression-free survival, which was 6.7 months in the axitinib group compared with 4.7 months in the sorafenib group. The hazard ratio (HR) for progression was 0.67 (95% confidence interval [CI] 0.54 to 0.81, p<0.0001), adjusted for the stratification factors (ECOG performance score and prior systemic therapy). However, the improvement in overall survival (20.1 months in the axitinib group compared with 19.2 months in the sorafenib group) was not statistically significant (HR 0.97, 95% CI 0.80 to 1.17, p=0.37).

3.6 FKSI-15, FKSI-DRS and EQ-5D quality-of-life data were collected at day 1, every 4 weeks thereafter, at the end of trial treatment or withdrawal, and on day 28 of the follow-up period. Higher FKSI-15, FKSI-DRS and EQ-5D scores indicate better quality of life. A repeated measures mixed-effects model was used to compare differences in quality of life between the 2 treatment groups. There were no statistically significant differences at follow-up between axitinib and sorafenib using the 3 health measures. For FKSI-15, there was no significant difference between axitinib and sorafenib after treatment (p=0.4833) and no significant interaction between
treatment and time (p=0.3943), and quality of life was maintained while patients remained on axitinib and sorafenib treatment. The axitinib group had mean FKSI-DRS scores 0.12 higher than the sorafenib group, measured using the FKSI-DRS measure for the main trial population (95% CI −0.45 to 0.69, p=0.67). For EQ-5D, the overall between-treatment comparison for axitinib compared with sorafenib was not statistically significant (no p value given); however, quality of life was maintained while patients remained on treatment and declined when patients stopped trial medication. The quality of life differences for the prior-cytokine group and the prior-sunitinib group are academic in confidence, and therefore cannot be shown here.

3.7 The safety analysis was performed for all patients who received at least 1 dose of axitinib or sorafenib in the AXIS trial (n=714). Diarrhoea was the most common treatment-emergent adverse event, occurring proportionately in both treatment groups (54.9% in the axitinib group and 53.2% in the sorafenib group). The most common additional adverse events in the axitinib group were hypertension, dysphonia, nausea and hypothyroidism. Hand–foot syndrome, rash and alopecia were more common in the sorafenib group than in the axitinib group. The sorafenib group had a higher occurrence of grade 3 (51.3% versus 50.4%) and grade 4 (10.1% versus 5.8%) adverse events compared with axitinib. Serious adverse events resulting in death, hospitalisation, significant disability and congenital abnormalities and/or birth defects in children of trial participants occurred equally in both treatment groups in the full trial population. The sorafenib group was associated with higher proportions of adverse events leading to dose reductions or interruptions (62% versus 55.4%) and permanent discontinuation of trial medication (13% versus 9.2%)
compared with axitinib. The adverse event data for the prior-cytokine and the prior-sunitinib groups are academic-in-confidence.

Prior-cytokine group

3.8 For the prior-cytokine group in the AXIS trial, the axitinib group had a statistically significant IRC-assessed median progression-free survival of 12.1 months compared with 6.5 months in the sorafenib group (HR 0.46, 95% CI 0.32 to 0.68, p<0.0001). There was also a statistically significant 3.7-month higher investigator-assessed progression-free survival in the axitinib group (HR 0.64, 95% CI 0.45 to 0.90, p=0.0049). However, there was no statistically significant improvement in overall survival, which was 29.4 months in the axitinib group and 27.8 months in the sorafenib group (HR 0.81, 95% CI 0.56 to 1.19, p=0.14).

Indirect treatment comparison

3.9 In a systematic review of the literature, the manufacturer identified 1 relevant trial, known as TARGET (treatment approaches in renal cancer global evaluation trial), that was considered suitable for an indirect comparison of axitinib compared with best supportive care. For the purpose of this appraisal, the manufacturer used placebo from the TARGET and RECORD-1 trials (see section 3.14) as a proxy for best supportive care. TARGET was a phase III, multicentre, randomised, double-blind, placebo-controlled trial comparing sorafenib with placebo for people with metastatic renal cell carcinoma who had received 1 prior systemic therapy. However, TARGET was made up mostly of patients who had received first-line cytokine therapy only (interferon alfa or interleukin 2), and also did not have a prior-sunitinib subgroup. Therefore, an indirect comparison of axitinib with best supportive care was possible only for the cytokine-refractory subgroup. The
patients in TARGET were similar to the patients in the AXIS trial in terms of age, sex and nephrectomy status. However, only 2 metastatic sites (lung and liver) were reported in TARGET, whereas AXIS reported more than 8 sites. MSKCC risk scores and prior treatments also differed between the 2 trials. Median progression-free survival was 5.5 months for sorafenib compared with 2.8 months for placebo using the intention-to-treat (ITT) population, and mean overall survival was 17.8 months for sorafenib compared with 14.3 months for placebo in the ITT population censored for crossover.

3.10 The indirect comparison was performed using Bayesian Markov-chain Monte Carlo sampling to determine the relative efficacy of the treatments. Sampling was performed using WinBugs. The hazard ratios from AXIS (median progression-free survival [HR 0.46, 95% CI 0.32 to 0.68, p<0.0001] and overall survival median [HR 0.81, 95% CI 0.56 to 1.19, p=0.14]) and TARGET (median progression-free survival [HR 0.54, 95% CI 0.45 to 0.64, p<0.001], and median overall survival censored for crossover [HR 0.78, 95% CI 0.62 to 0.97, p=0.029]) were used in a fixed-effects model with an assumption of proportional hazards. Point estimates of the hazard ratio for each pair of treatments and 95% credible intervals (CrI) were calculated. The result of the indirect comparison showed a 75% reduction in disease progression for axitinib compared with placebo (assumed here to be equivalent to best supportive care) (progression-free survival of 11 months for the axitinib group compared with 3.5 months for the best supportive care group [median HR 0.25, 95% CrI 0.17 to 0.38]). For overall survival (33.5 months for the axitinib group compared with 23.5 months for the best supportive care group), the median hazard ratio for death censored for crossover was 0.63 (95% CrI 0.41 to 0.99).
3.11 The manufacturer identified some limitations in the evidence networks from the AXIS and TARGET trials that had an impact on the indirect comparison. The manufacturer stated that in the AXIS trial, the relative efficacy as measured by overall survival (which was not statistically significant) may have been diluted because an active comparator (sorafenib) was used in the trial. The overall survival results may also have been confounded because of the subsequent treatments received after progression. In the prior-cytokine subgroup, 46.4% of patients in both the axitinib and sorafenib groups received subsequent treatments after progression. In the prior-sunitinib subgroup, 60% of patients in the axitinib group and 65.2% of patients in the sorafenib group received subsequent treatments. The manufacturer also stated that the overall survival analysis may have been affected by the relatively long survival after progression because of the patient heterogeneity usually seen in advanced renal cell carcinoma, the likelihood of receiving subsequent therapy, and the variability in treatment decisions made after progression.

3.12 The manufacturer stated that in the TARGET trial, the overall survival result may have been confounded by crossover from the placebo arm to the sorafenib treatment arm. It said that the method of adjusting for crossover (censoring of the patients) was not appropriate because it could lead to selection bias. The manufacturer stated that the rank-preserving structural failure time (RPSFT) method used in previous NICE technology appraisals of everolimus and sunitinib would have been more appropriate, and that the method usually improves the hazard ratio in favour of the active treatment. Another limitation with the evidence from TARGET was the absence of a prior-sunitinib group. The manufacturer stated that the prior-cytokine group (patients who
have never received a tyrosine kinase inhibitor such as sunitinib) and the prior-sunitinib group were considered to be clinically different populations that were not interchangeable. First-line therapy was considered to have failed more rapidly in the prior-cytokine group than in the prior-sunitinib group. Therefore, the prior-cytokine group may benefit more from second-line treatment, as shown by the higher median progression-free survival. Because of this, separate evidence was presented for the prior-sunitinib subgroup.

**Prior-sunitinib group**

3.13 For the subgroup of patients who were previously treated with sunitinib in the AXIS trial, there was a statistically significant difference in the IRC-assessed median progression-free survival of 1.4 months (4.8 months in the axitinib group compared with 3.4 months in the sorafenib group, HR 0.74, 95% CI 0.57 to 0.96, p=0.0107), adjusted for performance status. The axitinib group also had a 2-month longer investigator-assessed progression-free survival than the sorafenib group (HR 0.64, 95% CI 0.49 to 0.82, p=0.0002). The hazard ratio for median overall survival was 0.997 (95% CI 0.78 to 1.27, p=0.49), based on 15.2 months median overall survival in the axitinib group and 16.5 months in the sorafenib group.

**Simulated treatment comparison**

3.14 The manufacturer identified 1 trial (RECORD-1 [renal cell cancer treatment with oral RAD001 given daily]) in an additional systematic review of the literature in which sunitinib-refractory patients received best supportive care after disease progression. This was used to provide a link between axitinib and best supportive care in a prior-sunitinib population. The RECORD-1 trial compared
everolimus plus best supportive care with placebo plus best supportive care, in patients with metastatic renal cell carcinoma that progressed after treatment with a tyrosine kinase inhibitor. As there was no direct link between the treatments used in the AXIS trial and those used in RECORD-1, the manufacturer performed a simulated treatment comparison to create an adjusted indirect comparison between the axitinib prior-sunitinib group from AXIS and the best supportive care prior-sunitinib group from RECORD-1. The aim of the comparison was to estimate how the prior-sunitinib group from the AXIS trial would have performed if they had been treated with placebo, using data from RECORD-1. Patients in RECORD-1 were allowed to cross over to the everolimus arm, although the impact of the crossover was adjusted for using the RPSFT method, which the manufacturer considered to be valid. The manufacturer stated that 2 different figures for median progression-free survival for the everolimus arm of the prior-sunitinib group were published by 2 different authors (5.6 months and 3.9 months). The manufacturer chose the 3.9-month figure and this resulted in a hazard ratio of 0.34 (95% CI 0.23 to 0.51) when compared with 1.8 months for placebo in the prior-sunitinib group. The median overall survival was 14.8 months for everolimus in the prior-sunitinib group compared with 10.0 months for placebo in the ITT population (HR 0.53, confidence intervals not reported).

3.15 There were several differences highlighted between the AXIS and RECORD-1 trials. Firstly, 14% of patients in RECORD-1 had stopped prior treatment because of intolerance, rather than progressing from the prior treatment as in the AXIS trial. Secondly, only 43 patients in the everolimus arm of RECORD-1 had received prior sunitinib only, in contrast to the 194 prior-sunitinib patients in the axitinib arm of the AXIS trial. The manufacturer noted that some...
of the 43 patients in RECORD-1 may have had sunitinib intolerance rather than sunitinib-refractory disease, which may have led to potential bias because sunitinib-intolerant patients would be expected to respond better to subsequent treatment than patients with sunitinib-refractory disease. Thirdly, patients in RECORD-1 had received 1 or more prior treatments, whereas patients in AXIS had received only 1 first-line treatment. In RECORD-1, median progression-free survival was assessed in a prior-sunitinib-only subgroup (n=56). However, the overall survival and patient characteristics for this subgroup were not assessed. As a result, 2 approaches were taken in the simulated treatment comparison to compare axitinib with best supportive care in a prior-sunitinib population. The first compared the axitinib prior-sunitinib group in AXIS with the best supportive care ITT group in RECORD-1, and assumed that the ITT group would have the same overall survival and patient characteristics as the prior-sunitinib group in RECORD-1. The second approach compared the axitinib prior-sunitinib group with the everolimus prior-sunitinib group, and then applied the RPSFT-adjusted hazard ratio for everolimus to best supportive care to create a modelled prior-sunitinib group.

3.16 The simulated treatment comparison was performed by analysing patient-level data from the axitinib arm of the AXIS trial to derive parametric failure-time (survival) equations incorporating baseline predictors of the end points (progression-free survival and overall survival). Five distributions were examined, but only the 2 best fitting (log-normal and Weibull) were used in the comparison, and an assumption of proportional hazards was applied. The results of the comparison suggested a progression-free survival and overall survival benefit from axitinib treatment compared with best supportive care and everolimus treatment when the log-normal and
Weibull distributions were used. The estimated increase in mean progression-free survival and overall survival for the best supportive care ITT and everolimus prior-sunitinib simulated treatment comparison curves are commercial-in-confidence. The progression-free survival hazard ratio (0.34) for the prior-sunitinib group and adjusted overall survival hazard ratio (0.53) for the ITT group of RECORD-1 were applied to the everolimus simulated treatment comparison curves to generate modelled AXIS-like, prior-sunitinib progression-free survival and overall survival curves for best supportive care. This resulted in an estimated median progression-free survival of 1.7 months for the group of patients referred to in the manufacturer’s submission as ‘axitinib-like patients’ if they had received placebo, compared with 5.8 months if they had received axitinib (HR not reported), a difference of 4.6 months. The median overall survival estimated for these patients was 8.3 months for placebo compared with 15.2 months for axitinib (HR not reported).

*Indirect treatment comparison (RENCOMP)*

3.17 The manufacturer also provided an additional analysis, using retrospective observational data from a Swedish database (Renal Comparison; RENCOMP) to estimate the overall survival hazard ratio for people who received sorafenib or best supportive care after first-line treatment with sunitinib. Patient characteristics such as age, sex and nephrectomy status were similar across the 2 treatment groups (sorafenib and best supportive care). However, the sorafenib and best supportive care groups differed in terms of year of diagnosis, lead time between metastatic disease and first prescription of sunitinib, diagnosis of primary metastatic disease and place of treatment. A multivariate Cox proportional regression analysis was performed using variables with significance at the 5%
level to adjust for uncertainty resulting from confounding, and an assumption of proportional hazards was applied. This resulted in a median overall survival hazard ratio of 0.62 (95% CI 0.41 to 0.94, p=0.023). The results from RENCOMP were used in an indirect comparison with the results from the prior-sunitinib group in the AXIS trial (median progression-free survival HR 0.74 [95% CI 0.57 to 0.96] and median overall survival HR 0.997 [95% CI 0.78 to 1.27]), to generate indirect hazard ratios for axitinib and best supportive care in the prior-sunitinib group. The results showed that axitinib was associated with an improvement in overall survival compared with best supportive care in a sunitinib-refractory population (HR 0.62, 95% CrI 0.38 to 0.997).

**Cost-effectiveness evidence**

3.18 The manufacturer conducted a systematic review of the literature and identified 3 studies on the cost effectiveness of active treatments compared with best supportive care for advanced and metastatic renal cell carcinoma after failure of a systemic therapy. None of the studies identified included axitinib, so the manufacturer carried out a de novo analysis on the cost effectiveness of axitinib compared with best supportive care for treating advanced renal cell carcinoma after failure of prior treatment with sunitinib or a cytokine. The economic evaluation was based on the 2 separate populations specified in the marketing authorisation for axitinib (the groups of people in whom prior treatment with sunitinib or cytokines has failed, also referred to as the prior-sunitinib and the prior-cytokine groups).

3.19 A 3-state Markov cohort model was developed, based on previous modelling of metastatic cancer using Microsoft Excel. All patients entered the model in the ‘progression-free’ health state and in each
cycle could progress to the ‘progressed disease’ health state, progress from either of these health states to ‘death’, or remain in their current health state. The model had a lifetime horizon of 10 years consisting of 4-weekly cycles, included a half-cycle correction, and both costs and benefits were discounted at 3.5%. The analysis was performed from the perspective of the NHS and personal social services.

3.20 The proportion of patients in each health state at each point in time was calculated directly from parametric survival function equations. For the axitinib prior-cytokine group, the Weibull distribution was used to extrapolate the overall survival and progression-free survival data because it was considered to provide the best model fit. Survival models based on log-logistic and Gompertz parametric distributions were used in a sensitivity analysis for overall survival because, of the 5 parametric distributions tested by the manufacturer, they provided the next-best model fit. However, the log-normal and Gompertz distributions were used in the sensitivity analysis to extrapolate progression-free survival. For the best supportive care group, parametric survival curves were generated by applying the hazard ratios from the indirect comparison (see section 3.10) to the parametric survival functions used to model the axitinib treatment group.

3.21 For the axitinib prior-sunitinib group, the log-normal distribution was used in the base case to extrapolate overall survival data because it provided the best model fit. The Weibull and Gompertz distributions provided the next-best fits, so these were explored in a sensitivity analysis. The Weibull distribution was used for progression-free survival data in the base-case analysis, whereas the log-normal and Gompertz distributions were explored in the sensitivity analysis. For the best supportive care group, the prior-
sunitinib progression-free survival and the ITT population-adjusted hazard ratios (see section 3.16) were applied to the everolimus simulated treatment comparison curves to generate a modelled AXIS-like, prior-sunitinib progression-free survival and overall curves. Only the Weibull option was used in the economic model for the survival curves, because the log-normal distribution did not support the use of hazard ratios. In a sensitivity analysis, the overall survival hazard ratio generated from the indirect comparison of the RENCOMP analysis and the prior-sunitinib overall survival analysis from the AXIS trial was applied to the axitinib parametric survival functions to generate parametric survival curves for the best supportive care group.

3.22 The utility values used in the model were derived from the AXIS trial using the EQ-5D questionnaire. The analysis was based on the full AXIS population because the p values indicated no statistically significant difference between the prior-sunitinib and prior-cytokine subgroups. The mean utility value for the progression-free health state was 0.69, based on the average of the EQ-5D index value at each time point in the AXIS trial and weighted by the number of patients still on treatment at that time point. The utility value for the progressed disease health state was 0.61, based on the weighted average of the mean utility at the end of treatment. The utility values used in the model were assumed to reflect the adverse event profile of the treatment from the AXIS trial. In a systematic review of the literature, the manufacturer did not identify any sources reporting utility values for people with advanced renal cell carcinoma receiving best supportive care after sunitinib treatment has failed. Therefore, the manufacturer assumed that people receiving best supportive care would have the same utility value as people receiving axitinib in the model. Utility values from previous
NICE technology appraisals, derived from a phase II study of sunitinib in a cytokine-refractory population, were explored in a sensitivity analysis. Quality of life was assumed to remain constant for each health state in the post-trial period.

3.23 The average cycle (4 weeks/28 days) costs of axitinib were estimated by applying the proposed patient access scheme, which is commercial in confidence and so cannot be shown here. This was based on the recommended dosing schedule of 5 mg twice daily until disease progression. The cost was adjusted for the relative dosing intensity observed in the AXIS trial, which was 102%. A dosing intensity of 80% was assumed in a scenario analysis to reflect the lower intensities observed in clinical practice and previous NICE technology appraisals. Drug discontinuation occurred because of disease progression or adverse events. The probabilities of discontinuation per cycle applied in the model were 0.80% and 1.26% for the prior-cytokine and prior-sunitinib groups respectively, although the discontinuation rates from adverse events alone were assumed to be the same. No administration cost was included in the manufacturer’s model because axitinib is taken orally and the patient access scheme is a simple discount applied at the point of invoice. No drug costs were assumed for best supportive care.

3.24 The manufacturer stated that the costs associated with routine medical monitoring were based on those used in 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 (NICE technology appraisal guidance 178) and Everolimus for the second-line treatment of advanced renal cell carcinoma (NICE technology appraisal guidance 219). The manufacturer also stated that this assumption
was validated with expert clinical opinion to ensure consistency with current clinical practice in the UK. These costs were applied equally to the axitinib and best supportive care groups in the manufacturer’s model because patients were assumed to receive the same management regardless of their treatment. For the progression-free state, the total cost per cycle (£109.69) was based on 1 GP visit per cycle, 1 tumour scan per 3 cycles and 1 blood test per cycle. The total cost per cycle for the progressed disease state was £319, and this included 1 GP visit per cycle, 3 visits by a specialist community nurse every 2 cycles, and 28 vials of pain medication per cycle. A scenario analysis was explored in which patients visited an oncologist rather than their GP. This resulted in a total management cost per cycle of £176.69 for the progression-free state and £386 for the progressed disease state. Costs associated with adverse events were included in the model for the progression-free state only, and were assumed by the manufacturer to be similar for the prior-sunitinib and prior-cytokine groups. Only the costs for grade 3 and 4 adverse events (which occurred in over 5% of the patient population) were included. For the axitinib group, the included adverse events were hypertension (£424 per episode) and diarrhoea (£544 per episode), and the cost of anaemia (£2068.47 per episode) was applied to the best supportive care group in a sensitivity analysis.

**Manufacturer’s additional evidence and results**

3.25 In response to the appraisal consultation document, the manufacturer presented evidence to support the robustness and reliability of the results for the prior-sunitinib group by developing the simulated treatment comparison analysis to include estimates of the standard errors and confidence intervals for the adjustment factors. Estimates of the standard error of the logarithm of the
median progression-free survival and crossover-adjusted overall survival were obtained from RECORD-1. The delta method was used to estimate the standard error for the adjustment factors to enable the calculation of a 95% confidence interval. The manufacturer also provided a second set of 95% confidence intervals that only considered uncertainty in the derived axitinib equation and not the uncertainty in the survival estimates for the best supportive care population in the RECORD-1 trial. The 2 sets of confidence intervals estimated for progression-free survival were similar, but the confidence interval that accounted for uncertainty in the overall survival estimate was wider than the one excluding the uncertainty. The manufacturer stated that this difference in the overall survival confidence intervals was a result of the wide 95% confidence intervals for the acceleration factor from the RPSFT analysis used to adjust for crossover in RECORD-1.

3.26 In response to the appraisal consultation document, the manufacturer also provided its reasoning for the plausibility of the survival gains of axitinib compared with best supportive care generated by its simulated treatment comparison in terms of the ratio of progression-free survival gain to overall survival gain. It stated that this relationship between the survival gains was also observed in some placebo-controlled trials for advanced renal cell carcinoma such as RECORD-1 (1 to 1.6 months, progression-free survival to overall survival gain) and TARGET (1 to 1.3 months, progression-free survival to overall survival gain considering the censoring method of adjusting for crossover). The manufacturer also presented the results in the context of a meta-analysis of 28 trials of advanced renal cell carcinoma that compared an active therapy with placebo or best supportive care. In this study, a subgroup of 24 studies without crossover resulted in a 1 to
1.61 months progression-free survival to overall survival gain, whereas another subgroup of 16 studies in which patients received prior therapy resulted in a 1 to 1.42 months progression-free survival to overall survival gain. The manufacturer also stated that, in a previous NICE technology appraisal (Everolimus for the second-line treatment of advanced renal cell carcinoma), the Committee had accepted a 1 to 1.4 months progression-free survival and overall survival gain relationship.

3.27 The manufacturer presented updated economic analyses that include a revised patient access scheme agreed with the Department of Health. The size of the discount is commercial in confidence. The manufacturer’s updated results, including the various sensitivity analyses, include the revised patient access scheme unless stated otherwise.

3.28 The updated economic analyses incorporated a 15-year time horizon to address the ERG’s concern that the 10 years used in the original model may not be in line with real-life expectancy. The manufacturer also applied prior-cytokine and prior-sunitinib subgroup specific utility values and relative dose intensity rates rather than the estimates for the ITT population used in the original model. In addition, a value of 0% for the percentage of people with hypertension, which was less than 1% in the TARGET trial, was applied to the revised model; this was assumed to be 2% in the original model. The probabilistic sensitivity analyses were also updated to include the use of standard errors rather than standard deviations for the progression-free health state utility (standard error \[SE\]=0.0035), progressed disease health state utility (SE=0.0175) and relative dosing intensity (SE=1.86%). The standard error of the cost of death was also applied in the revised analysis. Finally, the manufacturer identified and corrected a
transcript error that involved the timescale of the simulated treatment analysis. The correction reduced the estimated mean costs and quality-adjusted life years (QALYs) in all cases for both arms and this only had a marginal impact on the incremental cost effectiveness ratios (ICERs) for the 2 populations.

Prior-cytokine group

3.29 The results of the updated economic analysis showed that the additional QALY gains from axitinib treatment were observed in the progression-free state. The base-case assumptions resulted in an ICER of £55,284 per QALY gained (with the patient access scheme applied) for axitinib compared with best supportive care after failure of a prior cytokine. All the incremental costs and QALYs gained in the manufacturer’s submission are commercial in confidence.

3.30 The manufacturer performed a univariate deterministic sensitivity analysis by varying some of the model input parameters using the 95% confidence interval. The cost-effectiveness result for the prior-cytokine group was most sensitive to changes in the overall survival hazard ratio and the post-progression utilities for axitinib and best supportive care in the univariate deterministic sensitivity analysis. The ICERs ranged from approximately £40,000 to more than £100,000 per QALY gained for changes in the utilities and more than £350,000 per QALY gained for changes in overall survival (with the patient access scheme applied). The base-case ICER was also sensitive to changes in the values of the survival parameters for the axitinib group. Changes in the cost estimates (such as GP visits, specialist nurse visits and tumour scans), discontinuation because of adverse events, relative dose intensity of axitinib, changes in the progression-free utility for the best supportive care group, and changes in the IRC-assessed
progression-free survival hazard ratio from the AXIS trial had very little effect on the base-case results.

3.31 The probabilistic sensitivity analysis indicated that axitinib would have a 42% chance of being cost effective compared with best supportive care, if the maximum acceptable ICER was £50,000 per QALY gained with the patient access scheme applied to the prior-cytokine group. The manufacturer did not present the probability of axitinib being cost effective if the maximum acceptable ICERs were £20,000 per QALY gained or £30,000 per QALY gained.

3.32 The manufacturer also explored various scenario analyses to account for the uncertainties associated with some of the assumptions in the base-case model. All results include the patient access scheme. The scenario analyses explored the effect on the ICER of:

- using alternative parametric distributions (log-normal, log-logistic and Gompertz) to extrapolate survival
- using external data to estimate utility values
- reducing the dosing intensity of axitinib to 80%
- assuming an oncologist visit instead of a GP visit for estimating costs in the progression-free state.

The results showed that the base-case ICER, when applying the patient access scheme, was most sensitive to the method of extrapolation of overall survival (£21,959 per QALY gained for the log-logistic method and £72,537 per QALY gained for the Gompertz method); whereas other scenarios resulted in ICERs close to the revised base case.
Prior-sunitinib group

3.33 The results of the economic analysis showed that there were additional QALY gains with axitinib before and after progression, although most of the additional QALYs gained were observed before progression. The base-case analysis resulted in an ICER of £33,538 per QALY gained (with the patient access scheme applied) for axitinib compared with best supportive care for the prior-sunitinib group. All the incremental costs and QALYs gained are commercial in confidence.

3.34 The univariate sensitivity analysis performed for the prior-sunitinib group showed that the ICER was most sensitive to changes in the survival parameter values for the axitinib group, with ICERs ranging from approximately £25,000 to £48,000 per QALY gained (with the patient access scheme applied). The base-case ICER was also sensitive to changes in the progressed disease utility values for the axitinib and best supportive care groups and progression-free utility value for the axitinib group; the resulting ICERs ranging from approximately £29,000 to £40,000 per QALY gained (with the patient access scheme applied). Changes in the cost estimates (such as GP visits, specialist nurse visits and tumour scans), discontinuation because of adverse events, relative dose intensity of axitinib and changes in the progression-free utility for the best supportive care group had little impact on the base-case result.

3.35 The probabilistic sensitivity analysis showed that axitinib would have a 65% chance of being cost effective compared with best supportive care, if the maximum acceptable ICER was £50,000 per QALY gained and uncertainty around the median crossover-adjusted overall survival for best supportive care was considered (when applying the patient access scheme). However, when the
uncertainty was excluded from the second set of the confidence intervals used, the probability of axitinib being cost effective compared with best supportive care increased to 90% at a maximum acceptable ICER of £50,000 per QALY gained, applying the patient access scheme. The manufacturer did not present the probability of axitinib being cost effective if the maximum acceptable ICERs were £20,000 per QALY gained or £30,000 per QALY gained.

3.36 Several scenario analyses were also performed by the manufacturer to explore the effect on the ICER of:

- using alternative parametric distributions (Weibull, log-normal and Gompertz) to extrapolate survival
- using alternative methods of comparison with best supportive care
- using external data to estimate utility values
- reducing the dosing intensity of axitinib to 80%
- assuming an oncologist visit instead of a GP visit for estimating costs in the progression-free state.

The ICER was most sensitive to the use of the Weibull and Gompertz distributions to extrapolate overall survival using the RENCOMP method of comparison (£47,515 and £39,479 per QALY gained respectively, with the patient access scheme applied), and reducing the dosing intensity of axitinib (£27,324 per QALY gained, with the patient access scheme applied). It was least sensitive to the use of alternative distributions to extrapolate overall survival using the simulated treatment method of comparison and costing based on oncologist visit (ICERs ranged from £28,958 to £34,722 per QALY gained, with the patient access scheme applied). The manufacturer also applied the assumption of no QALY or survival gain post-progression used in the ERG’s
exploratory analysis to the updated analysis. The ICER estimated using this assumption and the updated analysis (including the patient access scheme) was £52,850 per QALY gained.

**Evidence Review Group comments on the manufacturer’s clinical-effectiveness evidence**

3.37 The ERG stated that there were a few limitations with the literature search conducted by the manufacturer, some of which were addressed by the manufacturer after clarification. Despite these limitations, the ERG considered that the search was adequate and accurately reflected the research question. It stated that AXIS, TARGET and RECORD-1 were good-quality clinical trials with sound methodologies, except for the method used to adjust for crossover in TARGET (censoring of patients). The ERG considered that censoring often introduces bias and it agreed that the method used to account for the crossover which occurred in RECORD-1 (RPSFT) was more appropriate. The ERG noted that, although the outcomes reported in the AXIS trial corresponded with those in the final scope, only progression-free survival and overall survival outcomes were presented for the comparison of axitinib with best supportive care.

3.38 The ERG noted that baseline patient characteristics were not reported separately for the prior-cytokine groups in either the AXIS or the TARGET trial. Therefore, the indirect comparison of the trial populations was based on the ITT groups in the 2 trials. The ERG noted that the patient characteristics of the ITT groups in the AXIS and TARGET trials were reasonably similar, with slight differences observed only in the MSKCC scores and the number of metastatic sites. The ERG considered that the potential bias associated with
the hazard ratio for overall survival in TARGET may limit the robustness of the indirect comparison in the prior-cytokine group.

3.39 The ERG noted that the patient characteristics reported by the manufacturer for the AXIS and RECORD-1 trials were based on the prior-sunitinib group of the axitinib and everolimus arms and the ITT group of the sorafenib and placebo arms. The ERG also noted the differences between the AXIS and RECORD-1 trials that were highlighted by the manufacturer (see section 3.15), which could limit the evidence available for comparing axitinib with best supportive care in a prior-sunitinib group. The ERG was uncertain whether a simulated treatment comparison presents a valid and reliable estimate of the clinical effectiveness of axitinib compared with best supportive care in this group of patients. The ERG considered that there could be potential bias associated with the simulated treatment comparison because it involves a comparison of 2 single treatment arms and not a comparison of randomised treatment allocation. The ERG also stated that the results of the comparison could not be verified because individual patient data from the AXIS trial were used and were not provided by the manufacturer. However, the ERG indicated that the analysis seemed to have been performed correctly and the reporting of methods, results and limitations was clear despite the issues identified. The ERG agreed with the manufacturer that combining observational data (a lower level of evidence) from the RENCOMP database with the data from the AXIS trial was a potential source of uncertainty because patients were not randomly allocated to receive the second-line treatments and the reasons for discontinuing first-line treatments were not known.
Evidence Review Group comments on the manufacturer’s cost-effectiveness evidence

3.40 The ERG was satisfied with the manufacturer’s modelling approach, which was consistent with other published economic studies of advanced renal cell carcinoma and used a population that reflected the actual clinical population. It re-emphasised that approximately 94% of the renal cell carcinoma population will receive sunitinib for first-line treatment and 6% will receive cytokines. The ERG was satisfied that the best supportive care comparator used in the model reflected recommended UK clinical practice and was in line with the final scope for this appraisal.

3.41 The ERG accepted the manufacturer’s choice of the distributions used in the base-case and scenario analyses. The ERG noted the manufacturer’s clarification that patients who withdrew from treatment prematurely because of adverse events were still followed up in the trial, and were included in the estimation of progression-free survival and overall survival curves for the axitinib arm rather than the best supportive care arm. The ERG stated that this approach would only be valid if the patients were followed up for progression as well, and not for survival only. The ERG considered that the estimate of the QALYs in the axitinib group may have been affected if they were not followed up for progression, because disease is expected to progress earlier once patients stop treatment. It also noted that, because of earlier progression to the progressed disease state, the overall costs would be higher for the axitinib group compared with the cost in the model, which was set at ‘zero’ for the patients. The ERG indicated that making this adjustment in the model would increase the base-case ICERs, although the impact would be limited by the relatively small group of patients withdrawing from the treatment prematurely.
3.42 The ERG was satisfied with the manufacturer’s assumption that the utility value was the same for people receiving axitinib and people receiving best supportive care. It agreed that, although people on axitinib may experience utility decreases from adverse events, people receiving best supportive care would experience utility decreases from actively progressing uncontrolled disease. The ERG was concerned that the utility value applied in the progressed disease state remained constant after entry into that state, when it should actually decline as patients near the end of life. It noted that applying declining utility values would increase the ICER slightly if axitinib patients stayed in the progressed disease state for longer than best supportive care patients (prior-sunitinib group), but no impact would be observed if the time spent in the progressed disease state was the same for both treatment arms (prior-cytokine group). The ERG noted from the AXIS clinical trial report that health states were based on the US valuation. It stated that the utilities used in the model appear to be high because studies have shown that US valuations are consistently higher than UK valuations. The ERG stated that it could not reproduce the original utility for the progression-free state; a higher utility value of 0.73 was produced instead using the method described in the manufacturer’s submission.

Evidence Review Group comments on the manufacturer’s additional evidence

3.43 The ERG stated that the additional details of the simulated treatment comparison provided by the manufacturer were clearer than those in the original submission. It also stated that the delta method used to estimate the confidence intervals for the adjustment factors was appropriate. The ERG stated that the set of confidence intervals that considered uncertainty in the survival
estimates for both the axitinib and best supportive care populations was more appropriate.

3.44 The ERG noted that the differences in the median progression-free survival and overall survival for axitinib and best supportive care had been reported as mean values in the manufacturer’s original submission and then reported as median values in the updated analysis. It emphasised the need for consistency in reporting these results, particularly if the progression-free survival and overall survival ratios are being calculated. The ERG also noted that confidence intervals were not provided for these differences in the original and updated analysis. The ERG noted that in general, the simulated treatment comparison appeared to be well conducted, although it involved some major assumptions, such as the comparability of patients between the trials and that the results of one trial would apply in the setting of the other. The ERG stated that the simulated treatment comparison method was a fairly recent method of analysis and that its robustness and reliability is uncertain.

3.45 With respect to the plausibility of the survival gains of axitinib compared with best supportive care generated by the simulated treatment comparison, the ERG noted that the results of the meta-analysis of 28 studies presented by the manufacturer were based on the earlier published abstract of the study, and that the updated results based on the full published paper (which includes a larger number of studies) were slightly different from those in the abstract published earlier. The progression-free to overall survival relationship based on the subgroup of studies with patients who received prior treatment has been updated from 1 to 1.4 in the abstract to 1 to 1.04 in the full publication, whereas the relationship
reported for the subgroup of studies in which crossover occurred has been updated from 1 to 1.61 in the abstract to 1 to 1.29.

3.46 The ERG noted the impact of the patient access scheme on the manufacturer’s base-case ICER. It also noted that the large impact on the ICER made by varying the post-progression utilities in the prior-cytokine group (see section 3.30) was a result of the manufacturer’s use of specific subgroup utilities in the updated analysis, which has a wider confidence interval. The ERG stated that the inclusion of the statistical uncertainties in the updated simulated treatment comparison analysis increased the impact on the ICER by varying the parameters of the parametric survival curves for the prior-sunitinib group. The ERG agreed with the manufacturer that the difference in the probabilistic sensitivity analysis results for the prior-sunitinib group (see section 3.35) showed that most of the cost-effectiveness uncertainty is due to uncertainty around the median crossover-adjusted (with the RPSFT method) overall survival for best supportive care in the RECORD-1 trial.

3.47 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 axitinib, having considered evidence on the nature of advanced renal cell carcinoma and the value placed on the benefits of axitinib by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
4.2 The Committee considered the clinical need for treatment in people with advanced renal cell carcinoma in whom previous treatments with sunitinib or cytokines have failed. The Committee heard from the clinical specialists that there was a need for more drugs for people whose disease has become resistant to first-line treatment. It noted the comment from the patient experts that there was an unmet clinical need in this group of people because there are currently no second-line drugs approved by NICE. The patient experts also stated that availability of another treatment would offer a sense of hope to patients and their families or carers and also reduce the mental burden associated with the lack of treatment options. The patient experts indicated that patients were aware of the adverse events associated with axitinib and were prepared to cope with them. After consultation on its preliminary recommendation, the Committee further noted the emphasis placed by the consultees on the unmet clinical need for treatment along with the impact, mental burden and uncertainty that limited treatment choice has on people affected by advanced renal cell carcinoma. It took this into full consideration when making its final decisions. It also noted the consultee comments on a potential breach of article 2 (the right to life) of the Human Rights Act (1998). The Committee exercised due regard to NICE’s commitment to promote equality, eliminate unlawful discrimination and actively consider the implications of its guidance for human rights, as stated in section 1.4 of the Guide to the methods of technology appraisal.

4.3 The Committee considered the relevance of the populations covered by the marketing authorisation of axitinib, that is, the prior-cytokine group and the prior-sunitinib group. It heard from the clinical specialists that the use of cytokines is rapidly decreasing in clinical practice and only a few people currently receive them
because most patients begin treatment with sunitinib or pazopanib. The Committee noted the divergent position expressed by some members of the Committee for Medicinal Products for Human Use (CHMP) in the CHMP assessment report regarding the therapeutic value of using axitinib after failure of prior sunitinib. The Committee acknowledged that axitinib had received the marketing authorisation and concluded that there was therapeutic value in using it for people that have been previously treated with sunitinib.

4.4 The Committee discussed the population for whom treatment with axitinib would be appropriate in clinical practice, bearing in mind that of the 2 antivascular endothelial growth factor first-line treatments recommended by NICE (sunitinib and pazopanib), only sunitinib had been specified in the marketing authorisation for axitinib. The clinical specialists further stated that although both sunitinib and pazopanib are used interchangeably in clinical practice, patients are increasingly treated with pazopanib. The Committee noted this and was concerned that the exclusion of the prior-pazopanib group from the AXIS trial and the axitinib marketing authorisation could affect choice of first-line therapy in clinical practice, given that a large number of people currently receive pazopanib. It heard from the clinical specialists that in practice, axitinib would be used in the prior-pazopanib group as well, because pazopanib and sunitinib are both tyrosine kinase inhibitors with similar biochemical activities.

**Clinical effectiveness**

4.5 The Committee examined the clinical evidence from the AXIS trial, which compared axitinib with sorafenib, noting that the scope for this appraisal had specified a comparison with best supportive care. The Committee noted that the trial was well conducted and
the relevant outcomes were assessed in line with the scope of the appraisal. However, it noted the difficulties in interpreting the AXIS trial results in this appraisal because of the lack of a best supportive care comparison. The Committee noted that the better progression-free survival results for axitinib (6.7 months for the axitinib group compared with 4.7 months for the sorafenib group [HR 0.67, 95% CI 0.54 to 0.81, p<0.0001]) did not translate into statistically significant overall survival benefits (20.1 months for the axitinib group compared with 19.2 months for the sorafenib group [HR 0.97, 95% CI 0.80 to 1.17, p=0.37]) for the full trial population. The Committee heard the manufacturer’s explanation that this could be a result of the use of subsequent cancer treatments after progression. It was satisfied with the health-related quality-of-life data collected and assessed in the AXIS trial using both generic and disease-specific instruments. The Committee concluded that AXIS was a well-conducted trial, which showed that axitinib provided clinical benefit to people who have been treated previously with sunitinib or a cytokine. Because there was no relevant comparator in the AXIS trial, the Committee concluded that its discussion of the efficacy of axitinib would need to be based on the results of the indirect and the simulated treatment comparisons performed by the manufacturer. It also concluded that it was reasonable to separate out the results for patients who had received only prior cytokines from people who had received prior sunitinib as specified in the marketing authorisation for axitinib.

4.6 The Committee noted, however, that the prior-cytokine population has been diminishing since the introduction of sunitinib and pazopanib and NICE’s approval of these as first-line treatments. It considered that ‘prior-cytokine patients’ would, in practice, be given sunitinib or pazopanib, despite previous treatment with cytokines.
Nevertheless, the Committee examined the indirect comparison performed to generate a best supportive care comparison for axitinib in the prior-cytokine group. It noted that the evidence for the indirect comparison was based on the AXIS trial (which compared axitinib with sorafenib) and the TARGET trial (which compared sorafenib with placebo). The Committee accepted the manufacturer’s use of placebo as a proxy for best supportive care in the indirect and simulated treatment comparisons. It was aware that patient baseline characteristics were not presented separately for the prior-cytokine subgroups in the 2 trials. It noted that the 2 trials were not fully comparable in terms of MSKCC scores, prior treatments and number of metastatic sites reported. The Committee noted that crossover in the TARGET trial was adjusted by censoring the patients who crossed over and considered that this could have resulted in bias and ultimately affected the robustness of the results of the indirect comparison (progression-free survival of 11 months for the axitinib group compared with 3.5 months for the best supportive care group [HR 0.25, 95% CrI 0.17 to 0.38] and overall survival of 33.5 months for the axitinib group compared with 23.5 months for the best supportive care group [HR 0.63, 95% CrI 0.41 to 0.99]). It also noted that an assumption of proportional hazards, which assumes a constant treatment effect over a lifetime, had been used to derive the survival estimates and had not been tested. Therefore, the Committee concluded that although the indirect comparison was adequately performed, the results might not be robust.

4.7 The Committee considered the simulated treatment comparison performed for the prior-sunitinib subgroup using evidence from the AXIS trial (which compared axitinib with sorafenib) and the RECORD-1 trial (which compared everolimus with placebo). It
noted that this method of comparison was used to create an adjusted indirect comparison of axitinib with best supportive care in the prior-sunitinib group. The Committee discussed whether the use of the simulated treatment comparison method could be considered reliable and valid given that it is a relatively new method of treatment comparison. It noted the ERG’s comment that it was based on a comparison of 2 single treatment arms without random allocations to treatment. The Committee was aware that crossover also occurred in the RECORD-1 trial and although this was adjusted using the RPSFT method, it noted that this method may not be appropriate for subgroups because it assumes the same treatment effect applies across the whole trial population, as well as there being no unobserved factors that should have been controlled for in the analysis. It was also aware that there were key differences between the RECORD-1 trial population and that of AXIS, which could bias the results of the simulated treatment comparison, such as the higher number of prior therapies allowed in RECORD-1, the small number of people in the prior-sunitinib group, the inclusion of sunitinib-intolerant patients who had discontinued sunitinib treatment, and the use of the ITT (rather than the prior-sunitinib) population to estimate overall survival in the placebo arm of the RECORD-1 trial. The Committee was therefore concerned about the validity of the simulated treatment comparison analysis. However, it also noted that the manufacturer performed an alternative indirect comparison for the prior-sunitinib group using evidence from AXIS and the Swedish database (RENCOMP) analyses of sorafenib compared with best supportive care, but noted that the RENCOMP analysis was based on observational data without random allocation to treatments and also needed cautious interpretation. The Committee additionally noted that an assumption of proportional hazards had again been used in the
simulated treatment and RENCOMP analyses to derive the survival estimates and had not been tested. The Committee concluded that there were serious limitations with the indirect comparisons performed for the prior-sunitinib group, and that the outcomes from the simulated treatment comparison (progression-free survival [5.8 months for axitinib compared with 1.7 months for placebo], overall survival [15.2 months for axitinib compared with 8.3 months for placebo]) and indirect comparison (overall survival [HR 0.62, 95% CrI 0.38 to 0.997]) should be interpreted with caution.

4.8 The Committee noted that the manufacturer provided confidence intervals as part of its additional evidence during consultation to account for uncertainty in the results, and it was mindful that the simulated treatment comparison was an unconnected comparison of 2 arms from separate studies. The Committee noted the ERG’s clarification letter in response to the manufacturer’s comment in the submission that similar methodologies have been accepted in a recent NICE appraisal (Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy [NICE technology appraisal guidance 171]). In its letter the ERG stated that the actual meta-analysis in the systematic review performed in the lenalidomide appraisal was based on a pooled analysis of 2 trials comparing the same treatments and that there was a mixed treatment comparison. The Committee also noted that a commentator on the appraisal consultation document stated that the manufacturer’s approach differed from the approaches taken in the indirect comparisons performed in the NICE appraisal of lenalidomide and the Scottish Medicines Consortium appraisal of everolimus for the treatment of pancreatic neuroendocrine tumours because of the lack of a common comparator in this instance.

Furthermore, the Committee was reminded that each appraisal is
conducted separately and that acceptance of a particular methodology in one appraisal does not necessarily create a precedent implying that it is appropriate to use the same approach in another setting. The commentator also highlighted that the use of different data sources to obtain progression-free survival and overall survival data from the RECORD-1 trial and the non-adjustment of the overall survival results for post-progression treatments received in the AXIS and RECORD-1 trials increased the uncertainty in the simulated treatment comparison. The Committee concluded that the robustness and reliability of the estimates from the simulated treatment comparison remained unclear, given the number of uncertainties highlighted.

4.9 The Committee considered the adverse event profile associated with axitinib that was observed in the AXIS trial. The Committee noted that diarrhoea, which was the most common adverse event, occurred with similar frequency in the axitinib and sorafenib groups. It was aware that hypertension, dysphonia, nausea and hypothyroidism occurred more frequently in the axitinib group, although hand–foot syndrome, rash and alopecia occurred more frequently in the sorafenib group. The Committee also noted the comment from the clinical specialists that axitinib was a well-tolerated drug except for the high occurrence rate of hypertension that is common with all tyrosine kinase inhibitors. The patient experts commented that people would be willing to accept these adverse events, and so the Committee concluded that axitinib has a manageable adverse event profile compared with other treatments for advanced renal cell carcinoma.
4.10 The Committee considered the manufacturer’s economic model and the ERG’s critique of the model. It was aware that the economic evaluation considered 2 separate populations based on the subgroups of patients previously treated with sunitinib or a cytokine. It noted that these were the subgroups for whom axitinib has a marketing authorisation. The Committee was satisfied that the best supportive care comparator used reflected UK clinical practice. It was also satisfied with the manufacturer’s use of placebo as a proxy for best supportive care given the lack of any other relevant data. The Committee concluded that the appropriate populations and comparator for the economic evaluation had been captured in the model.

4.11 The Committee discussed the assumptions made by the manufacturer in developing the economic model. It noted that when alternative survival distributions for progression-free and overall survival were tested in the scenario analysis, they resulted in sizeable changes to the base-case result for the prior-cytokine population and moderate changes for the prior-sunitinib population. The Committee concluded that the model results were highly sensitive to the distributions used to extrapolate survival.

4.12 The Committee discussed the plausibility of the survival gains estimated for the prior-cytokine group from the economic model. It heard from the clinical specialists and the patient experts that the overall survival gain of approximately 24 months in the best supportive care group of the prior-cytokine group is not seen clinically. It noted the manufacturer’s comment that the implausibility observed may have resulted from the overall survival of 14 months in the placebo arm of TARGET, which was not
properly adjusted for crossover. The Committee considered that this possible over-estimation of the overall survival in TARGET was carried over into the overall survival results in the indirect comparison and ultimately affected the model results for the best supportive care group. It also noted that the ICER was sensitive to some of the parameters and assumptions used in the model (such as the utility values, the value of the survival parameters and the type of distribution used to extrapolate survival). The Committee concluded that the ICER of approximately £55,300 per QALY gained (with the patient access scheme applied) may have been over-estimated based on the unlikely overall survival gains with best supportive care in the prior-cytokine population, but that there were other uncertainties that might push the ICER higher.

4.13 The Committee considered the uncertainty around the base-case estimates in the prior-sunitinib group. It recognised that the use of the simulated treatment comparison method to derive a best supportive care comparison for axitinib in the group was the greatest source of uncertainty. The Committee discussed the plausibility of the survival gains estimated for the prior-sunitinib group (figures are commercial-in-confidence). It noted that the median survival gain difference between axitinib and best supportive care estimated directly from the trials was increased by 63% when modelled, although no such modelling increase was estimated in the prior-cytokine group. Furthermore, the Committee noted that an implausibly high proportion of the total QALY gains with axitinib (compared with best supportive care) in the prior-sunitinib group was observed after progression when active treatment with axitinib has stopped. It noted that this was not a feature in either the prior-cytokine analysis or the AXIS trial results. The Committee examined the exploratory analysis performed by
the ERG and manufacturer in which it was assumed that there was no QALY difference between axitinib and best supportive care in the prior-sunitinib group after progression. When it was also assumed that there was no cost difference after progression the resultant ICER was approximately £52,900 per QALY gained (with the patient access scheme applied). The Committee concluded that the results from the simulated treatment comparison and the post-progression model outputs for the prior-sunitinib group should be interpreted with caution because they lacked clinical plausibility.

4.14 The Committee also noted that use of the RENCOMP indirect comparison of axitinib and best supportive care gave higher ICER values than the manufacturer’s base case result. When the RENCOMP method was used rather than the simulated treatment comparison, the ICER increased to over £40,000 per QALY gained (with the patient access scheme applied) using the Weibull and Gompertz distributions, suggesting that that the method of obtaining a best supportive care comparison was a key driver of the results in this population. The Committee concluded that the results for the prior-sunitinib group should be interpreted with caution because not all the uncertainties had been fully considered.

4.15 The Committee considered the manufacturer’s comments from consultation that some evidence exists from metastatic renal cell carcinoma trials that show that there are QALY gains in the post-progression period above those gained in the progression-free period when targeted therapies are compared with best supportive care. It heard from the manufacturer that active targeted treatments are associated with higher response rates and tumour shrinkage compared with best supportive care. The Committee examined the plausibility of a post-progression survival gain with axitinib in the context of the progression-free and overall survival relationship
presented by the manufacturer (see section 3.26). It compared the relationship between progression-free survival and overall survival estimated from the manufacturer’s simulated treatment comparison (1 to 1.6) and that originally modelled by the ERG (1 to 1). It noted that the relationship reported in the earlier version of the meta-analysis referenced by the manufacturer had been weakened by the inclusion of more studies in which crossover occurred in the updated meta-analysis (1 to 1.04 for the subgroup of trials with prior treatment and 1 to 1.29 for the subgroup in which crossover was adjusted). The Committee discussed whether it was plausible that a relationship of 1 to 1.6 would be observed when a tyrosine kinase inhibitor is used after failure of a previous tyrosine kinase inhibitor. It also noted the lack of post-progression benefit in the AXIS trial for the prior-sunitinib group, as well as for the prior-cytokine group derived from the manufacturer’s model. The Committee concluded that the progression-free survival and overall survival relationship for the prior-sunitinib group was likely to lie between the manufacturer’s estimate and the ERG’s estimate, although probably closer to the ERG’s estimate.

4.16 The Committee considered whether axitinib reflected a cost-effective use of NHS resources. It noted that the manufacturer’s base-case ICER of approximately £55,300 per QALY gained (with the patient access scheme applied) generated for the prior-cytokine group may have been an over-estimate (see section 4.12), but there were uncertainties that might increase or decrease the ICER and the most plausible ICER was still likely to be above the usual threshold considered a cost-effective use of NHS resources in NICE technology appraisals. For the prior-sunitinib population, the Committee noted the uncertainty in the simulated treatment comparison method, and the large QALY gains assumed to
accumulate after progression in this group of people (section 4.13) and after discontinuation of the drug. It considered that the more plausible ICER for the prior-sunitinib group was likely to lie between the base-case estimate with a survival relationship of 1 to 1.6 (approximately £33,500 per QALY gained) and the estimate assuming no survival gain with a survival relationship of 1 to 1 (approximately £52,900 per QALY gained). Given the balance of the evidence, the Committee considered that the ICER would be closer to the higher estimate. The Committee thus concluded that axitinib could not be considered to be a cost-effective use of NHS resources in either the prior-cytokine population or the prior-sunitinib population when the health-related quality-of-life valuation for these patients is considered without any QALY weighting for end of life.

4.17 The Committee therefore discussed whether axitinib for advanced renal cell carcinoma fulfilled the criteria for a life-extending, end-of-life treatment, which are that:

- 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 and
- the treatment is licensed or otherwise indicated for small patient populations.

In addition, 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.
4.18 The Committee agreed that the life expectancy of people with advanced renal cell carcinoma in whom prior cytokines and sunitinib have failed was less than 24 months. It also noted the manufacturer’s evidence to indicate that the treatment offers an extension to life of at least an additional 3 months in the case of the prior-sunitinib population, compared with the current NHS treatment of best supportive care. However, in the case of the prior-cytokine group, the Committee considered that these were people who could receive sunitinib or pazopanib but no comparison had been available to establish the true benefit of axitinib in this group. It noted that the manufacturer’s estimation of the eligible population for whom axitinib is licensed (most in the prior-sunitinib group), that is, 1580 people in year 1 and up to 1743 people in year 5, represented a small patient population. The Committee concluded that axitinib was only shown to be a life-extending, end-of-life treatment for the prior-sunitinib population.

4.19 The Committee then discussed whether the valuation of the health-related quality of life necessary for axitinib to be considered a cost-effective use of NHS resources for the prior-sunitinib population was reasonable. It discussed both the range of ICER valuations available and the degree of certainty around the estimates. The range of valuations was £33,500 to £52,900 per QALY gained, but the most plausible valuations were at the higher end of this range. The Committee concluded that as the ICERs were subject to considerable uncertainty and were high, the magnitude of additional weight that would need to be assigned to the original QALY benefits in this patient group was too high for the cost effectiveness of the drug to fall within the range currently considered a cost-effective use of NHS resources. Taking into account both the value of the ICERs and the uncertainty around the
ICERs, the Committee concluded that axitinib could not be considered a cost-effective use of NHS resources in the prior-sunitinib population even under the supplementary criteria for appraising life-extending, ‘end-of-life’ treatments.

4.20 The Committee noted the comments made by the manufacturer and patient organisations regarding the ‘innovativeness’ of axitinib. They stated that axitinib was expected to offer a step-change in the second-line management of advanced renal cell carcinoma by improving survival beyond what is expected with best supportive care, while maintaining health-related quality of life. The Committee understood this, as well as noting the needs of patients for further treatment options, but considered that there were no additional gains in health-related quality of life over those already included in the QALY calculations. Therefore, the Committee concluded that the innovative aspects of axitinib with regard to patient benefits were already incorporated in the economic model and analyses.

4.21 The Committee discussed potential equality issues and gave particular consideration to avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity. The Committee noted the following potential equality issues raised by the patient experts, patient organisations and NHS organisations:

- Older patients with additional health issues may find adverse effects more difficult to tolerate.
- People with rare cancers such as kidney cancer have inequity of access to NHS-funded treatments.
- The scope does not consider axitinib for people for whom first-line immunotherapy is unsuitable.
The Committee considered that these were not equality issues under the legislation. It therefore concluded that its recommendations did not have a particular impact on any of the groups whose interests are protected by the legislation and that there was no need to alter or add to its recommendations.

**Summary of Appraisal Committee’s key conclusions**

<table>
<thead>
<tr>
<th>Key conclusion</th>
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<tr>
<td>Axitinib is not recommended within its marketing authorisation, that is, for the treatment of adults with advanced renal cell carcinoma after failure of prior treatment with sunitinib or a cytokine. The Committee concluded that the ICER of approximately £55,300 per QALY gained (with the patient access scheme applied) may have been over-estimated based on the unlikely overall survival gains with best supportive care in the prior-cytokine population, but that there were other uncertainties that might push the ICER higher. The Committee concluded that the results from the simulated treatment comparison and the post-progression model outputs for the prior-sunitinib group should be interpreted with caution because they lacked clinical plausibility. The Committee concluded that axitinib could not be considered a cost-effective use of NHS resources even under the supplementary criteria for appraising life-extending, end-of-life treatments.</td>
<td>1.1 4.12 4.13 4.19</td>
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### Current practice

| Clinical need of patients, including the availability of alternative treatments | The patient experts stated that there was an unmet clinical need for people whose disease has become resistant to first-line treatment. This is because there are currently no second-line drugs for renal cell carcinoma approved by NICE.

The Committee took into full consideration the impact, mental burden and uncertainty that limited treatment choice has on people affected by advanced renal cell carcinoma, along with the unmet clinical need for treatment, when making its final decisions. It also noted the consultee comments on a potential breach of article 2 (the right to life) of the Human Rights Act (1998). The Committee exercised due regard to NICE’s commitment to promote equality, eliminate unlawful discrimination and actively consider the implications of its guidance for human rights as stated in section 1.4 of the Guide to the methods of technology appraisal. | 4.2 |

### The technology

| Proposed benefits of the technology

How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits? | The Committee understood that axitinib was expected to improve survival beyond what is currently expected with best supportive care in the second-line management of advanced renal cell carcinoma, but considered that there were no additional gains in health-related quality of life over those already included in the QALY calculations. | 4.20 |

| What is the position of the treatment in the pathway of care for the condition? | Axitinib has a marketing authorisation for ‘the treatment of adult patients with advanced renal cell carcinoma, after failure of prior treatment with sunitinib or a cytokine’. | 2.1 |

| Adverse reactions | The Committee concluded that axitinib has a manageable adverse event profile compared with other treatments for advanced renal cell carcinoma. | 4.9 |
### Evidence for clinical effectiveness

| Availability, nature and quality of evidence | The Committee noted that the AXIS trial was well conducted and the relevant outcomes were assessed in line with the scope of the appraisal. However, it noted the difficulties in interpreting the AXIS trial results in this appraisal because of the lack of a best supportive care comparison. The Committee concluded that although the indirect comparison used to generate a best supportive care comparison for the prior-cytokine group based on the AXIS trial (which compared axitinib with sorafenib) and the TARGET trial (which compared sorafenib with placebo) was adequately performed; there were serious limitations with the simulated treatment comparison performed for the prior-sunitinib group using evidence from the AXIS trial and the RECORD-1 trial (which compared everolimus with placebo), and with the indirect comparison using evidence from AXIS and the Swedish database (RENCOMP). | 4.5 |
| Relevance to general clinical practice in the NHS | The Committee heard from the clinical specialists that the use of cytokines is rapidly decreasing in clinical practice and only a few people currently receive them because most patients begin treatment with sunitinib or pazopanib. The Committee noted the divergent position expressed by some members of the Committee for Medicinal Products for Human Use (CHMP) in the CHMP assessment report and concluded that there was therapeutic value in using axitinib for people that have been previously treated with sunitinib. | 4.3 |

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**Evidence for clinical effectiveness**

**Availability, nature and quality of evidence**

The Committee noted that the AXIS trial was well conducted and the relevant outcomes were assessed in line with the scope of the appraisal. However, it noted the difficulties in interpreting the AXIS trial results in this appraisal because of the lack of a best supportive care comparison. The Committee concluded that although the indirect comparison used to generate a best supportive care comparison for the prior-cytokine group based on the AXIS trial (which compared axitinib with sorafenib) and the TARGET trial (which compared sorafenib with placebo) was adequately performed; there were serious limitations with the simulated treatment comparison performed for the prior-sunitinib group using evidence from the AXIS trial and the RECORD-1 trial (which compared everolimus with placebo), and with the indirect comparison using evidence from AXIS and the Swedish database (RENCOMP).
| Uncertainties generated by the evidence | The Committee noted that crossover in the TARGET trial was adjusted by censoring the patients who crossed over and considered that this could have resulted in bias and ultimately affected the robustness of the indirect comparison. The Committee was concerned about the validity and reliability of the simulated treatment comparison because it was an unconnected comparison of 2 arms from separate studies. The RENCOMP analysis was based on observational data without random allocation to treatments and also needed cautious interpretation. An assumption of proportional hazards had been used in the indirect comparisons and simulated treatment comparison to derive the survival estimates and had not been tested. | 4.6 |
| Are there any clinically relevant subgroups for which there is evidence of differential effectiveness? | N/A | 4.7, 4.8, 4.7, 4.7 |
| Estimate of the size of the clinical effectiveness including strength of supporting evidence | The Committee noted that the better progression-free survival results for axitinib patients (6.7 months for the axitinib group compared with 4.7 months for the sorafenib group [HR 0.67, 95% CI 0.54 to 0.81, p<0.0001]) did not translate into statistically significant overall survival benefits (20.1 months for the axitinib group compared with 19.2 months for the sorafenib group [HR 0.97, 95% CI 0.80 to 1.17, p=0.37]) for the full trial population.

The Committee noted that crossover in the TARGET trial was adjusted by censoring the patients who crossed over and considered that this could have resulted in bias and ultimately affected the robustness of the results of the indirect comparison (progression-free survival of 11 months for the axitinib group compared with 3.5 months for the best supportive care group [HR 0.25, 95% CrI 0.17 to 0.38] and overall survival of 33.5 months for the axitinib group compared with 23.5 months for the best supportive care group [HR 0.63, 95% CrI 0.41 to 0.99]).

The Committee concluded that there were serious limitations with the indirect comparisons performed for the prior-sunitinib group, and that the outcomes from the simulated treatment comparison (progression-free survival [5.8 months for axitinib compared with 1.7 months for placebo], overall survival [15.2 months for axitinib compared with 8.3 months for placebo]) and indirect comparison (overall survival [HR 0.62, 95% CrI 0.38 to 0.997]) should be interpreted with caution. |
| --- |

| Evidence for cost effectiveness | The economic evaluation was based on the 2 separate populations specified in the marketing authorisation for axitinib (the groups of people in whom prior treatment with sunitinib or cytokines has failed, also referred to as the prior-sunitinib and the prior-cytokine groups).

A 3-state Markov cohort model was developed based on previous modelling of metastatic cancer using Microsoft Excel. |
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<tr>
<td>Uncertainties around and plausibility of assumptions and inputs in the economic model</td>
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<td>Incorporation of health-related quality-of-life benefits and utility values</td>
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<tr>
<td>Are there specific groups of people for whom the technology is particularly cost effective?</td>
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<td>What are the key drivers of cost effectiveness?</td>
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### Most likely cost-effectiveness estimate (given as an ICER)

The Committee noted that the manufacturer’s base-case ICER of £55,300 per QALY gained may have been an over-estimate for the prior-cytokine group, but it noted that the most plausible ICER was still likely to be above the usual threshold considered a cost-effective use of NHS resources in NICE technology appraisals. It considered that the more plausible ICER for the prior-sunitinib group was likely to lie between the base-case estimate of £33,500 per QALY gained and the estimate assuming no survival gain (£52,900 per QALY gained). Given the balance of the evidence, the Committee considered that the ICER would be closer to the higher estimate.

### Additional factors taken into account

| **Patient access schemes (PPRS)** | The manufacturer of axitinib has agreed a patient access scheme with the Department of Health. The size of the discount is commercial in confidence. | 2.3 |
| **End-of-life considerations** | For the prior-cytokine group, the Committee considered that these were people who could receive sunitinib or pazopanib but no comparison had been available to establish the true benefit of axitinib in this group.  

The Committee concluded that axitinib was only shown to be a life-extending, end-of-life treatment for the prior-sunitinib population. However, taking into account both the value of the ICERs and the uncertainty around the ICERs, the Committee concluded that axitinib could not be considered a cost-effective use of NHS resources even under the supplementary criteria for appraising life-extending, end-of-life treatments. | 4.18, 4.19 |
| **Equalities considerations and social value judgements** | The Committee noted the potential equality issues raised by the patient experts, patient organisations and NHS organisations, but concluded that its recommendations did not have a particular impact on any of the groups whose interests are protected by the legislation and that there was no need to alter or add to its recommendations. | 4.21 |
5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 The technology in this appraisal may not be the only treatment for advanced renal cell carcinoma. If a NICE technology appraisal recommends use of a technology, it is as an option for the treatment of a disease or condition. This means that the technology should be available for a patient who meets the clinical criteria set out in the guidance, subject to the clinical judgement of the treating clinician. The NHS must provide funding and resources (in line with section 5.1) when the clinician concludes and the patient agrees that the recommended technology is the most appropriate to use, based on a discussion of all available treatments.

5.3 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
• Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
• A costing statement explaining the resource impact of this guidance.
• Audit support for monitoring local practice.

6 Related NICE guidance

Published
• Pazopanib for the first-line treatment of advanced renal cell carcinoma. NICE technology appraisal 215 (2011)
• 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. NICE technology appraisal guidance 178 (2009).

Under development
There is no related guidance under development for this technology.

7 Proposed date for review of guidance

7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive in May 2016. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Andrew Stevens
Chair, Appraisal Committee
April 2013
Appendix A: Appraisal Committee members, guideline representatives and NICE project team

A  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.

Professor Andrew Stevens (Chair)
Professor of Public Health, University of Birmingham

Professor Gary McVeigh (Vice Chair)
Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr David Black
Medical Director, NHS South Yorkshire and Bassetlaw

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, London
David Chandler
Lay Member

Dr Mary Cooke
Lecturer, School of Nursing, Midwifery and Social Work, University of Manchester

Professor Peter Crome
Honorary Professor, Department of Primary Care and Population Health, University College London

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

Dr Greg Fell
Consultant in Public Health, Bradford and Airedale Primary Care Trust

Dr Wasim Hanif
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

Dr Janice Kohler
Senior Lecturer and Consultant in Paediatric Oncology, Southampton University Hospital Trust

Emily Lam
Lay Member

Dr Grant Maclaine
Director, Health Economics and Outcomes Research, BD, Oxford

Dr Andrea Manca
Health Economist and Senior Research Fellow, University of York
C  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.

Nwamaka Umeweni
Technical Lead

Dr Bhash Naidoo
Technical Adviser

Lori Farrar
Project Manager
Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by Kleijnen Systematic Reviews:


B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Manufacturer/sponsor:

- Pfizer

II. Professional/specialist and patient/carer groups:

- James Whale Fund for Kidney Cancer
- Kidney Cancer UK
- Cancer Research UK
- Royal College of Nursing
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS Devon
- NHS Norfolk
- Welsh Government
IV. 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
- Healthcare Improvement Scotland
- National Cancer Research Institute
- Kleijnen Systematic Reviews Ltd
- National Institute for Health Research Health Technology Assessment Programme
- National Collaborating Centre for Cancer

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on axitinib by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the ACD.

- Dr Janet Brown, Senior Lecturer, Honorary Consultant Medical Oncology, nominated by Royal College of Physicians – clinical specialist
- Professor Robert Hawkins, Director of Medical Oncology, nominated by Royal College of Physicians – clinical specialist
- Dr Pat Hanlon, nominated by Kidney Cancer UK – patient expert
- Jacqueline Lowe, nominated by Kidney Cancer UK – patient expert

D Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Pfizer