NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Appraisal consultation document

Everolimus for the second-line treatment of advanced renal cell carcinoma

The Department of Health has asked the National Institute for Health and Clinical Excellence (NICE) to produce guidance on using everolimus for the second-line treatment of advanced renal cell carcinoma in the NHS in England and Wales. The Appraisal Committee has considered the evidence submitted by the manufacturer and the views of non-manufacturer consultees and commentators, and clinical specialists and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see appendix B) and the public. This document should be read along with the evidence base (the evaluation report), which is available from www.nice.org.uk

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using everolimus in the NHS in England and Wales.

For further details, see the 'Guide to the technology appraisal process' (available at www.nice.org.uk).

The key dates for this appraisal are:

Closing date for comments: 2 March 2010

Second Appraisal Committee meeting: 9 March 2010

Details of membership of the Appraisal Committee are given in appendix A, and a list of the sources of evidence used in the preparation of this document is given in appendix B.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Appraisal Committee's preliminary recommendations

1.1 Everolimus is not recommended for the second-line treatment of advanced renal cell carcinoma.

2 The technology

2.1 Everolimus (Afinitor, Novartis Pharmaceuticals) is an active inhibitor of the mammalian target of rapamycin (mTOR) protein, a central regulator of tumour cell division and blood vessel growth in cancer cells. Everolimus has a UK marketing authorisation for the treatment of patients with advanced renal cell carcinoma (RCC), whose disease has progressed on or after treatment with vascular endothelial growth factor (VEGF)-targeted therapy.

2.2 Everolimus is contraindicated in people who have hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients. The summary of product characteristics (SPC) lists the following as special warnings and precautions for everolimus use: non-infectious pneumonitis, localised and systemic infections (including pneumonia, other bacterial infections and invasive fungal infections), hypersensitivity reactions and oral ulcerations. For full details of side effects and contraindications, see the SPC.

2.3 Everolimus is administered orally. The recommended dosage is 10 mg once daily and treatment should continue as long as clinical benefit is observed or until there are unacceptable adverse events. Management of severe and/or intolerable adverse events may

require dose reduction to a suggested dosage of 5 mg daily or temporary withholding of everolimus. The price for a pack of 10-mg tablets (30 tablets per pack) is £2970 (Monthly Index of Medical Specialities [MIMS] December 2009). The daily cost of everolimus is £99, with an 8-week cycle costing £5544. Costs may vary in different settings because of negotiated procurement discounts. The manufacturer of everolimus had agreed a patient access scheme with the Department of Health.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of everolimus and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 The manufacturer presented evidence on the clinical effectiveness of everolimus used within the marketing authorisation and in line with the appraisal scope. The manufacturer also stated that everolimus is the only mTOR inhibitor available in an oral form for the treatment of advanced renal cell carcinoma. The main evidence came from one phase III, multicentre, double-blind randomised controlled trial (RCT). The RCT, RECORD-1, compared everolimus plus best supportive care (277 participants) with placebo plus best supportive care (139 participants). Best supportive care consisted of drug and other types of therapy, including symptom control, palliative care and monitoring of progression. The trial was conducted in adults (18 years or older) with advanced RCC with a clear-cell component confirmed by histology or cytology, whose disease had progressed while on or within 6 months of stopping treatment with sunitinib, sorafenib or both. Previous therapy with a cytokine (for example, interferon alfa or interleukin-2) or bevacizumab was allowed. The participants had a Karnofsky Performance Score of 70% or more, and were

stratified according to whether they had received prior therapy with sunitinib, sorafenib or both and Memorial Sloan Kettering Cancer Centre (MSKCC) prognostic category. The baseline characteristics of the patients in the two treatment arms were generally similar. The arms were relatively well balanced in terms of previous therapy.

3.2 The primary outcome in the RCT was progression-free survival which was defined as time from randomisation to disease progression or death. Tumour assessments were performed using RECIST (Response Evaluation Criteria in Solid Tumours) and were confirmed by an independent central radiology review. Once disease progression was confirmed, patients who previously received placebo plus best supportive care could be offered open-label everolimus plus best supportive care if the treating clinician thought this in the best interests of the patient. The median progression-free survival was 4.90 months (95% confidence interval [CI] 3.98 to 5.52) for patients receiving everolimus plus best supportive care and 1.87 months (95% CI: 1.84 to 1.94) for patients receiving placebo plus best supportive care (hazard ratio [HR] 0.33, [95% CI 0.25 to 0.43]). This meant there was a 67% reduction in risk of disease progression for patients receiving everolimus plus best supportive care compared with those receiving placebo plus best supportive care at the final analysis. The median progression-free survival was statistically significant longer in patients receiving everolimus ($p < 0.001$).

3.3 Sunitinib is the only first-line treatment for advanced and/or metastatic renal cell carcinoma currently recommended by NICE (NICE technology appraisal guidance 169), therefore the manufacturer undertook a final analysis of progression-free survival according to previous VEGF-targeted therapy. Approximately 44%

of patients in each treatment arm had received prior sunitinib treatment, 30% had received sorafenib treatment, and 26% had received both sunitinib and sorafenib. There was a statistically significant improvement in progression-free survival for all subgroups irrespective of prior VEGF-targeted therapy. For people whose disease had failed to respond to sunitinib, there was a 66% reduction in risk of disease progression with everolimus plus best supportive care compared with placebo plus best supportive care.

3.4 During the blinded phase of the RCT, a statistically significant difference in median overall survival was not identified for the two treatment arms. At the final analysis (November 2008), the median overall survival was 14.78 months in the everolimus plus best supportive care arm and 14.39 months in the placebo plus best supportive care arm. The resulting hazard ratio was 0.87 (95% CI 0.65 to 1.17), which was not statistically significant (p = 0.177).

3.5 A total of 76% of patients assigned to receive placebo plus best supportive care had crossed over to receive everolimus plus best supportive care by the time of the final analysis (February 2008). Therefore, the manufacturer adjusted the overall survival results for the crossover by using the Inverse Probability of Censoring Weight (IPCW) method in a post-hoc analysis. This method aims to adjust for crossover by recreating the population that would have been evaluated if crossover had not occurred. People who do not cross over get a greater weighting (in this case a factor of 1.81) in order to correct for the resulting bias. The manufacturer explained that the IPCW method was used to control for crossover because it produces a hazard ratio, it does not require data to be normally distributed, it does not 'borrow' information from crossed over patients and it does not impose a structural model to control for the effect of crossover. The IPCW analysis suggested a statistically

significantly longer mean overall survival for people who received everolimus plus best supportive care (overall survival 10.1 months) compared with those who received placebo plus best supportive care (overall survival 5.1 months) (HR 0.55, 95% CI 0.32 to 0.97).

3.6 In the RCT, health-related quality of life was measured using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire—Core 30 and the Functional Assessment of Cancer Therapy–Kidney Symptom Index, Disease Related Symptoms (FKSI–DRS) score. No generic measures of health-related quality of life were included. More than 65% of patients completed the questionnaires at each time point. Time to deterioration in functioning/symptoms was delayed with everolimus plus best supportive care by 3.5 months compared with placebo plus best supportive care. The median time to deterioration according to FKSI–DSR score was 7.4 months for everolimus plus best supportive care and 3.9 months for placebo plus best supportive care (HR 0.72, p = 0.044).

3.7 The manufacturer used data from the RCT to evaluate the safety profile of everolimus therapy. There were more adverse events and serious adverse events (grades 3 and 4) in the everolimus plus best supportive care arm (40.1%) than the placebo plus best supportive care arm (22.6%). The most frequent adverse events related to everolimus treatment were anaemia (103 events) and stomatitis (103 events). The manufacturer stated that most adverse events reported were reversible, transient and manageable, and that the greater incidence of adverse events in the everolimus plus best supportive care arm was a result of the longer duration of exposure to everolimus. A total of 13.9% of patients randomised to receive everolimus plus best supportive care and 2.9% of patients

randomised to receive placebo plus best supportive care discontinued treatment because of adverse events.

3.8 The manufacturer developed a Markov model to assess the cost effectiveness of everolimus plus best supportive care compared with best supportive care alone. The model used a hypothetical group with advanced RCC whose cancer had progressed on or within 6 months of receiving VEGF-targeted therapy (that is, sunitinib, sorafenib, and/or bevacizumab) and who had demographic characteristics reflecting those of the RECORD-1 trial. The model had four distinct health states: stable disease without adverse events, stable disease with adverse events, progressed disease and death. All people entered the model in the stable disease without adverse events health state. Everolimus treatment (10 mg once daily) was given until disease progression (defined by the RECIST criteria) or unacceptable adverse events were experienced. In the latter case, the dosage was sometimes reduced to 5 mg daily or everolimus treatment was interrupted. Because of this the manufacturer used a dose intensity of 91.8% in the model. The model had a cycle length of 8 weeks and a time horizon of 144 weeks, which the manufacturer stated reflected the maximum life expectancy of the population in the model. Discounting was applied from the second year onwards and a half-cycle correction was not applied. No subgroup analyses were conducted by the manufacturer.

3.9 Rates of adverse events, treatment withdrawal, disease progression, and deaths were taken from the RCT and used to calculate the probabilities that a person would move between health states (transition probabilities). The observed event rates in the RCT were used directly to calculate the number of people entering the ‘stable disease with adverse events’ health state and

the ‘progressed disease’ health state for both treatment arms. Only grade 3 and 4 adverse events associated with everolimus treatment and best supportive care were included in the model. The rates of grade 3 and 4 adverse events were taken directly from the RCT up to cycle seven of treatment. The trial ended after the seventh cycle and the rates after this cycle were assumed to remain constant.

3.10 For health states leading to death, the RCT data were used directly for the everolimus plus best supportive care arm only. For the best supportive care alone arm, the probability of dying was calculated by deriving the IPCW Cox model hazard ratio for mortality (that is, a hazard ratio of 0.55) and then applying this to the transition probabilities in the everolimus arm. The manufacturer explained that the group of patients receiving best supportive care was therefore at a constantly higher relative risk of mortality at any given cycle. Mean overall survival for everolimus plus best supportive care was estimated to be 10.1 months compared with 5.1 months for best supportive care alone.

3.11 The utility values used in the model were taken from the Assessment Group’s estimates for ‘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). These were 0.76 for stable disease without adverse events, 0.71 for stable disease with adverse events, 0.68 for progressed disease and 0 for death. The manufacturer did not use individual disutility (that is, loss of utility) estimates for each adverse event associated with treatment with everolimus, but instead applied a single overall disutility estimate of −0.05 for being in the health state stable disease with adverse events. The manufacturer

clarified that this disutility was maintained throughout all subsequent cycles. The costs of adverse events were assumed to last only for one cycle.

3.12 The manufacturer has agreed a patient access scheme with the Department of Health in which the first treatment pack of everolimus is free to the NHS and following treatment packs cost £2822 (that is, a 5% discount). It was assumed by the manufacturer that there would be no additional costs to the NHS associated with administration of the patient access scheme. The costs associated with best supportive care, monitoring and adverse events were taken from the Assessment Group's estimates for NICE technology appraisal 178. No additional costs were assumed to be associated with tests or special appointments for everolimus administration. Any additional resource use incurred was assumed to be associated with the provision of best supportive care and the underlying cancer. The ongoing cost of resource use was estimated to be £110 for each cycle of everolimus and £182 for a CT scan every three cycles. The estimated cost for best supportive care was £641 per cycle. In addition, 72% of patients in the RCT received other treatments after everolimus treatment had ended (such as sunitinib, sorafenib and bevacizumab). Therefore, an additional cost of £2428.78 per cycle for the other treatments was also incorporated for the progressed disease health state.

3.13 Comparison of everolimus plus best supportive care with best supportive care alone produced a base-case incremental cost-effectiveness ratio (ICER) of £51,613 per quality-adjusted life year (QALY) gained. One-way sensitivity analyses showed that the ICER was most sensitive to the estimate of overall survival in the best supportive care arm. When the hazard ratio for overall survival was taken from the intention-to-treat population (that is, a hazard

ratio of 0.87), the ICER increased to £91,256 per QALY gained (including the patient access scheme). Probabilistic sensitivity analyses suggested that if the maximum acceptable amount to pay for an additional QALY gained was £50,000 then everolimus had a 40% probability of being cost effective (including the patient access scheme).

3.14 The ERG stated that the manufacturer's submission was generally of good quality and appropriate to the decision problem. Although the clinical effectiveness evidence was derived from only one RCT, this was of good quality and demonstrated that everolimus plus best supportive care significantly improved progression-free survival compared with placebo plus best supportive care. The ERG also stated that the economic model developed by the manufacturer appeared appropriate for the decision problem and agreed that a half-cycle correction was not needed.

3.15 The ERG highlighted that the main driver of cost effectiveness was the estimate of overall survival used in the economic model. The ERG agreed that it was important to correct the data for the confounding caused by the crossover that occurred. However, the ERG stated that the manufacturer had made two key errors in applying the IPCW method in the economic model. Firstly the manufacturer had failed to convert the transition probabilities to rates before applying the hazard ratio multiplier, leading to transition probabilities greater than one. The ERG stated that using the correct approach the base-case ICER was increased from £51,613 to £53,479 per QALY gained (with the patient access scheme applied). Secondly, the ERG stated that in applying the mortality hazard ratio, the manufacturer overestimated the mortality in the best supportive care arm. This is because there was a higher level of progression in the best supportive care arm and more

deaths in the progressed disease state. The ERG stated that this in effect 'double-counted' some of the deaths in the best supportive care arm and in effect improved the overall mortality hazard ratio in favour of the everolimus arm (and therefore improved the cost-effectiveness estimates). The ERG stated that correcting for this, in addition to converting the transition probabilities to rates as described above, the base-case ICER increased further from £53,479 to £64,988 per QALY gained (with the patient access scheme applied).

3.16 The ERG stated that the discounting should have been applied from the second cycle (not from the second year as in the model). When the ERG changed the manufacturer's model by discounting costs and benefits (at 3.5%) in this way the amended ICERs described in 3.15 increased from £64,988 to £65,231 per QALY gained (with patient access scheme). The ERG also highlighted concern about the assumption that patients experiencing adverse events were assumed to experience a utility decrement for only one cycle, after which their utility is assumed to return to a level equivalent to the state without adverse events. Costs for treatment were however assumed to remain. Therefore only one episode of adverse events for each patient is supported in the model. The ERG also considered that the difference in utility between stable disease and progressed disease (0.76 versus 0.68) may understate the benefit demonstrated for everolimus in delaying progression.

3.17 In response to the factual check of the ERG report, the manufacturer also produced analyses using the Rank Preserving Structural Failure Time (RPSFT) method to derive estimates of overall survival. This method had been used previously in 'Sunitinib for the treatment of gastrointestinal stromal tumours' (NICE technology appraisal guidance179). The RPSFT method estimates

the overall survival of patients randomised to receive placebo assuming that they had not crossed over (that is, they had remained on placebo for the duration of the trial). This method is therefore based on a comparison of the groups according to the way they were randomised. The RPSFT method proportionally 'shrinks' the estimated amount of additional survival conferred to patients who crossed over to receive everolimus, thereby changing the mortality hazard ratio used in the economic model. This analysis was conducted at a later time point than the IPCW analysis, at this later time point 81% of patients who were allocated to placebo plus best supportive care had crossed over to receive everolimus plus best supportive care.

3.18 The RPSFT method estimated that survival was nearly twice as long with everolimus plus best supportive care compared with best supportive care alone (relative risk 1.93, 95% CI 0.50 to 8.50). This equated to a mean overall survival of 15.18 months with everolimus plus best supportive care and 7.67 months with best supportive care alone (a non-statistically significant gain of 7.51 months). The manufacturer also presented updated cost-effectiveness estimates using the RPSFT method to derive overall survival estimates with all other base-case assumptions in the model unchanged. The analysis produced an ICER of £53,128 per QALY gained (including the patient access scheme) for everolimus plus best supportive care compared with best supportive care alone.

3.19 The ERG highlighted that in the additional analysis provided by the manufacturer the RPSFT method had been applied to the economic model incorrectly. The ERG stated that the mortality risk in the best supportive care arm had been overestimated. This was because the longer-term extrapolation of the overall survival curve for patients receiving best supportive care only was based on a

single trial data point. The ERG conducted an exploratory analysis using revised transition probabilities for the best supportive care arm of the model. The ERG calculated the new transition probability for cycles 6 to 18 as the mean of the probabilities in cycles 4 and 5 and stated that it provided a more realistic interpretation of the overall survival in the best supportive care arm. All other model transition values were the same as those used in the manufacturer's analysis. The resulting ICER was £75,725 per QALY gained (including the patient access scheme and discounting) and £74,935 per QALY gained (including the patient access scheme but without discounting).

3.20 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/guidance/TAXXX

4 Consideration of the evidence

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

Clinical effectiveness

4.2 The Committee heard from clinical specialists and patient experts that there are limited treatment options for people with advanced RCC. The Committee noted that currently sunitinib is the only first-line treatment recommended by NICE and there are no second-line treatments recommended by NICE for people whose disease has stopped responding to sunitinib.

4.3 The Committee heard from the patient experts and clinical specialists that advanced RCC is a relatively rare cancer and noted the views of patient experts and clinical specialists on the severity of the disease. The Committee also heard that people undergoing second-line chemotherapy particularly valued the increased life expectancy offered and were prepared to cope with the other effects of these treatments. The Committee noted the number of adverse events associated with everolimus treatment in the RECORD-1 trial. However, the Committee was advised by the patient experts and clinical specialists that everolimus would be tolerated by most people with advanced RCC, and the adverse events would not be significantly worse than those experienced with first-line sunitinib therapy. The Committee discussed the risk of pneumonitis and immunosuppression associated with everolimus. The clinical specialist confirmed that although pneumonitis and immunosuppression had been associated with everolimus in clinical practice, these adverse events would stop on discontinuation of treatment and were therefore considered manageable.

4.4 The Committee discussed the clinical effectiveness of everolimus in people with advanced RCC whose disease had progressed within 6 months of stopping VEGF-targeted treatment. The Committee noted that the most of the trial population had a good performance status. However, the clinical specialist highlighted that in clinical practice only people with a good performance status would be considered for second-line therapy because people with a poorer performance status would be too ill to receive any active treatment. Therefore the Committee agreed that the trial population was likely to be similar to people considered for second-line therapy in UK clinical practice.

4.5 The Committee discussed the results of the RECORD-1 placebo-controlled trial. The Committee agreed that the results demonstrated that everolimus plus best supportive care had increased progression-free survival by approximately 3 months compared with placebo plus best supportive care.

4.6 The Committee then discussed the estimates of overall survival gain obtained from the RECORD-1 trial. The Committee acknowledged that the estimates of overall survival according to the intention-to-treat analyses had been confounded because (due to crossover) only 20% of people had not received everolimus in the trial. The Committee heard from the clinical specialist that an increase in progression-free survival would be expected to result in an increase in overall survival because gains in overall survival had been observed in clinical practice with the introduction of sequential chemotherapy for advanced RCC.

4.7 The Committee agreed that it was appropriate to adjust the results to control for the crossover using statistical modelling techniques. However, the Committee agreed that any estimate of overall survival obtained using statistical modelling would be subject to uncertainty because a number of assumptions would have to be made. The Committee therefore concluded that although there was sufficient evidence that everolimus increased progression-free and overall survival compared with best supportive care, the magnitude of the overall survival gain was uncertain.

Cost effectiveness

4.8 The Committee discussed the manufacturer's model and the critique by the ERG. The Committee agreed that best supportive care alone was the appropriate comparator for use in the model. The Committee noted that the ERG had identified several

limitations in the submitted economic model. The Committee had concerns about the modelling of adverse events. Firstly it did not agree with the assumption that people starting everolimus therapy would all have stable disease without adverse events. The Committee heard from the clinical specialist that in clinical practice eligible patients would present with progressed disease and a proportion of these would experience adverse events when starting everolimus therapy. Secondly, the Committee was concerned about the model assumption that the costs of managing associated adverse events would apply for only one treatment cycle. However, the Committee heard from the clinical specialist that adverse events would be managed by 'drug holidays' or dose reduction and therefore treatment of adverse events would not be expected to incur significant ongoing costs. The Committee also heard from the clinical specialist that the primary ongoing adverse event with everolimus was fatigue but that this was common to all chemotherapy agents and there were no current treatments for its management. Therefore the Committee agreed that the cost estimates used for adverse events in the model were acceptable.

4.9 The Committee noted that the utility estimates in the model were neither directly obtained nor mapped from the RECORD-1 trial. The Committee noted that the estimates of utility for each of the disease states were similar. The Committee discussed whether a larger decrement in utility may be plausible when a person moves from a stable disease health state to a progressed disease health state. The Committee noted comments from the ERG and the results of the one-way sensitivity analyses which showed changes in utility estimates had little effect on the ICERs. The Committee therefore agreed that although the utility estimates were subject to some uncertainty they were not a key issue in determining the cost-effectiveness of everolimus compared with best supportive care.

4.10 The Committee discussed the discounting method employed by the manufacturer. The Committee agreed with the ERG that discounting should have been applied from the second cycle in the model rather than after the first year only. However, the Committee acknowledged that making this change to the model increased the incremental cost by £405 per QALY gained in the manufacturer's base case. The Committee therefore agreed that this was not a key issue in determining the cost effectiveness of everolimus compared with best supportive care.

4.11 The Committee discussed the results of the manufacturer's and ERG's one-way sensitivity analyses and noted that the key driver in determining the cost effectiveness was the estimate of overall survival. The Committee acknowledged that using a statistical technique to model overall survival was necessary because of the large amount of crossover in the trial. The Committee understood that the manufacturer had originally used the IPCW method and had provided analysis using the RPSFT method in response to a factual check of the ERG report. The Committee noted that the estimates of clinical and cost effectiveness generated by the manufacturer using the IPCW and the RPSFT methods differed only slightly. It heard from the ERG that it considered the RPSFT method to be more methodologically robust than the IPCW method because it does not make the assumption of no unmeasured confounders. However, the ERG highlighted that both methods have advantages and disadvantages, and all available statistical methods used to adjust for the effects of crossover were associated with some limitations and uncertainty.

4.12 The Committee went on to discuss the manufacturer's cost-effectiveness estimate of £51,600 per QALY gained which incorporated estimates of clinical effectiveness using the IPCW

method. The Committee understood that this estimate also included a patient access scheme which had been agreed with the Department of Health. The Committee understood from the ERG that, when using the IPCW method, the manufacturer had failed to convert the transition probabilities to rates before applying the hazard rate multiplier. Moreover, when applying the mortality hazard ratio the manufacturer had overestimated the mortality in the best supportive care arm. The manufacturer acknowledged that the survival of people receiving best supportive care had been underestimated when calculating the transition probabilities used in the model. Therefore, the Committee agreed that the ICER of £65,200 per QALY gained calculated by the ERG using the IPCW method (and including discounting from the second cycle) was more plausible than the manufacturer's estimate of £51,600 per QALY gained.

4.13 The Committee then discussed the manufacturer's cost-effectiveness estimate of £53,100 per QALY gained which incorporated estimates of clinical effectiveness using the RPSFT method. The Committee understood that this estimate also included a patient access scheme which had been agreed with the Department of Health. The Committee heard concerns from the ERG that the RPSFT method had been applied incorrectly by the manufacturer. The application of the transition probabilities led to overestimation of the mortality risk in the best supportive care arm and the survival curve for the best supportive care arm was not consistent with what would have been expected with a constant hazard ratio or with survival curves typically seen in other NICE technology appraisals. Therefore, the Committee agreed that the ERG's ICER of £75,700 per QALY gained when using the RPSFT method (and including discounting from the second cycle) was

more plausible than the manufacturer's estimate of £53,100 per QALY gained.

4.14 The Committee was aware of the supplementary advice from NICE that should be taken into account when appraising treatments which may extend the life of people with a short life expectancy and which are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

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

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

4.15 The Committee then discussed whether everolimus as a second-line treatment for advanced RCC fulfilled the criteria for consideration as a life-extending, end-of-life treatment. It was aware that in England and Wales the total number of people concerned was less than 4000. The Committee heard that the life expectancy for people with advanced RCC receiving best supportive care alone was unlikely to be greater than 24 months and was potentially as low as 6 months. The Committee also noted that the evidence from the IPCW and RPSFT analyses suggested that everolimus increased survival by more than 3 months

compared with best supportive care. In summary, the Committee was satisfied that everolimus met the criteria for being a life-extending, end-of-life treatment, and that the evidence presented for this consideration was sufficiently robust.

4.16 The Committee considered whether there were any subgroups of patients for whom everolimus would be considered a cost effective use of NHS resources, and whether NICE's duties under the equalities legislation required it to alter or to add to its recommendations in any way. The Committee noted that no subgroups of patients had been identified and agreed that that there are no specific equality issues relevant to this appraisal.

4.17 The Committee then discussed the most plausible cost-effectiveness estimates of everolimus of £65,200 and £75,700 per QALY gained, in light of an appraisal of a life-extending, end-of-life treatment. It considered the impact of giving a greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy person of the same age. The Committee also considered the magnitude of additional weight that would need to be assigned to the original QALY benefits in this patient group for the cost effectiveness of the drug to fall within the current threshold range. The Committee concluded that the QALY weighting needed would be too great, even when the patient access scheme was incorporated. Therefore the Committee concluded that it could not recommend everolimus for the second-line treatment of advanced RCC as a cost-effective use of NHS resources.

Summary of Appraisal Committee's key conclusions

TAXXX (STA)	**Appraisal title: Everolimus for the second-line treatment of advanced renal cell carcinoma**	**ACD section**
Key conclusion		
The Appraisal Committees preliminary recommendation is that everolimus is not recommended for the second-line treatment of advanced renal cell carcinoma.		1.1
Current practice		
Clinical need of patients	The main aim of treatment of advanced renal cell carcinoma (RCC) is to extend progression-free and overall survival with the fewest adverse events and with the best quality of life possible for the remaining months of life.	4.3
Availability of alternative treatments	There are currently no second-line treatment options recommended by NICE for people whose disease has stopped responding to sunitinib.	4.2
What is the position of the treatment in the pathway of care for the condition	Based on NICE guidance, first-line drug treatment is sunitinib. Everolimus would be used as a second-line treatment after VEGF-targeted therapy in people with advanced RCC whose condition has failed to respond to sunitinib.	2.1 and 4.2
The technology		
Proposed benefits of the technology from the manufacturer, clinician and patient perspective	The technology provides a treatment option for people whose disease has progressed with sunitinib therefore potentially increasing life expectancy.	4.2
How innovative is the technology	Everolimus is a selective kinase inhibitor that blocks the action of the mammalian target of rapamycin (mTOR) protein, which plays an important role in regulating key cellular functions, such as cell proliferation, survival, growth, and	2.1 to 2.3 and 3.1

	angiogenesis. It is the only mTOR inhibitor available in an oral form for the treatment of patients with advanced RCC.	
Adverse events	The safety profile of everolimus is similar to that of first-line sunitinib therapy.	4.3
Evidence for clinical effectiveness		
Availability and nature of evidence	Compared with best supportive care, everolimus increases progression-free survival in people with advanced RCC with a clear-cell component and whose disease has progressed while on or within 6 months of stopping treatment with sunitinib, sorafenib or both. There was no statistically significant difference in overall survival in the trial arms, however a large proportion of people who were randomised to receive placebo plus best supportive care crossed over to receive everolimus plus best supportive care. Therefore the Committee agreed that it was appropriate to adjust the results to control for the crossover using statistical modelling techniques. However, the Committee agreed that any estimate of overall survival obtained using statistical modelling would be subject to uncertainty because a number of assumptions would have to be made. The Committee therefore concluded that although there was sufficient evidence to conclude that everolimus had greater clinical effectiveness in terms of increased progression-free and overall survival compared with best supportive care, the magnitude of the overall survival gain was uncertain.	4.4 4.7
Quality of the evidence	Only one randomised controlled trial, however this was considered to be generally of good quality	3.14
Relevance to general clinical practice in the NHS	The Committee agreed that the trial population was similar to people likely to be considered for second-line treatment in UK clinical practice.	4.4

Uncertainties generated by the evidence	There is uncertainty about the magnitude of the overall survival gain obtained with everolimus plus best supportive care compared with best supportive care alone.	4.6 and 4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness	Not applicable	
Evidence for cost effectiveness		
Availability and nature of evidence	The manufacturer developed a Markov model to assess the cost effectiveness of everolimus plus best supportive care compared with best supportive care alone.	3.8 to 3.11
Uncertainties around and plausibility of assumptions and inputs in the economic model	Uncertainty generated by use of utility values taken from the Assessment Group's estimates from a previous NICE technology appraisal '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 178), rather than values taken from everolimus trials. The Committee agreed that any estimate of overall survival obtained using statistical modelling would be subject to uncertainty because a number of assumptions would have to be made. The Committee understood from the ERG that, when using the IPCW method, the manufacturer had failed to convert the transition probabilities to rates before applying the hazard rate multiplier, leading to an overestimation of the mortality risk for best supportive care. The Committee heard concerns from the ERG that the RPSFT method had been applied incorrectly by the manufacturer leading to an overestimation of the mortality risk for best supportive care.	3.11 4.7, 4.12 to 4.13
Incorporation of health-	The utility values used were 0.76 for	

related quality of life benefits and utility values	stable disease without adverse events, 0.71 for stable disease with adverse events, 0.68 for progressed disease and 0 for death. The manufacturer did not use individual disutility estimates for adverse events associated with treatment with everolimus, but instead applied a single overall disutility estimate of −0.05 for being in the health state stable disease with adverse events. The manufacturer clarified that this disutility was maintained throughout all subsequent cycles.	3.11
Are there specific groups of people for whom the technology is particularly cost-effective?	Not applicable	
Most likely cost-effectiveness estimate (given as an ICER)	The Appraisal Committee agreed that that the incremental cost-effectiveness ratio (ICER) is likely to be higher than the estimates provided by the manufacturer. The Appraisal Committee agreed that the ERG's ICER of £65,2000 per QALY gained using the IPCW method to estimate overall survival and £75,7000 per QALY gained using the RPSFT method were more plausible than the ICERs provided by the manufacturer	4.16
Additional factors taken into account		
Patient access scheme	The Appraisal Committee was advised that a patient access scheme had been approved in which the first treatment pack of everolimus is free to the NHS and following treatment packs cost £2822 (that is, a 5% discount).	3.12
End-of-life considerations	The Committee heard that the life expectancy for people with advanced RCC receiving best supportive care alone was unlikely to be greater than 24 months and was potentially as low as 6 months. The Committee also noted that the evidence from the IPCW and RPSFT analyses suggested that everolimus increased survival by more than 3 months compared	4.15

	with best supportive care. In summary, the Committee was satisfied that everolimus met the criteria for being a life-extending, end-of-life treatment, and that the evidence presented for this consideration was sufficiently robust.	
Equalities considerations, social value judgements	The Committee noted that no subgroups of patients had been identified and agreed that that there are no specific equality issues relevant to this appraisal	4.16

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must 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. The NHS is not required to fund treatments that are not recommended by NICE.

5.2 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 report and costing template to estimate the 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

- Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. NICE technology appraisal guidance 169 (2009). Available from www.nice.org.uk/guidance/TA169
- Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of renal cell carcinoma. NICE technology appraisal guidance 178 (2009). Available from www.nice.org.uk/guidance/TA178

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Pazopanib for the first-line treatment of metastatic renal cell carcinoma (earliest anticipated date of publication December 2010).
- Pazopanib for the second-line treatment of metastatic renal cell carcinoma (earliest anticipated date of publication January 2011).

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 February 2013. 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.

Gary McVeigh

Vice Chair, Appraisal Committee

February 2010

Appendix A: Appraisal Committee members 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 four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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

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

Dr Kathryn Abel

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

Dr David Black

Director of Public Health, Derbyshire County Primary Care Trust

Dr Daniele Bryden

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

David Chandler

Lay member

Professor Mike Campbell

Statistician, Institute of Primary Care and General Practice, University of Sheffield

Dr Christine Davey

Senior Researcher, North Yorkshire Alliance R & D Unit

Stephen Greep

Chief Executive of Hull and East Yorkshire Hospitals NHS Trust

Dr Alan Haycox

Reader in Health Economics, University of Liverpool Management School

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Henry Marsh

Consultant Neurosurgeon, St George's Hospital, London

Professor Gary McVeigh

Vice Chair, Professor of Cardiovascular Medicine, Queen's University Belfast and Consultant Physician, Belfast City Hospital

Dr Eugene Milne

Deputy Medical Director, North East Strategic Health Authority

Professor Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Dr Richard Nakielny

Consultant Radiologist, Sheffield Teaching Hospitals Foundation Trust

Dr Katherine Payne

Health Economics Research Fellow, University of Manchester

Dr Martin J Price

Head of Outcomes Research, Janssen-Cilag

Miles Scott

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Dr Surinder Sethi

Consultant in Public Health Medicine, North West Specialised Services Commissioning Team

Professor Andrew Stevens

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

John Stevens

Director, Centre for Bayesian Statistics in Health Economics University of Sheffield

Dr Matt Stevenson

Technical Director, School of Health and Related Research, University of Sheffield

Dr Judith Wardle

Lay member

B NICE project team

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

Helen Tucker

Technical Lead

Rebecca Trowman

Technical Adviser

Laura Malone

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by Peninsula Technology Assessment Group (PenTAG)

- Pitt M, Crathorne L, Moxham T, et al., Everolimus for the second-line treatment of advanced and/or metastatic renal cell carcinoma, November 2009

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:

- Novartis Pharmaceuticals

II Professional/specialist and patient/carer groups:

- James Whale Fund for Kidney Cancer
- Kidney Cancer UK
- Macmillan Cancer Support
- Rarer Cancers Forum
- Royal College of Nursing
- Royal College of Physicians, Medical Oncology Joint Special Committee
- United Kingdom Oncology Nursing Society

III Other consultees:

- Department of Health
- Welsh Assembly Government

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

- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- National Institute for Health Research Health Technology Assessment Programme
- Peninsula Technology Assessment Group, University of Exeter (PenTAG)

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 everolimus by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the ACD.

- Dr Kate Fife, Consultant Clinical Oncologist, nominated by Royal College of Physicians – clinical specialist
- Beryl Roberts, Lead Oncology Nurse, nominated by United Kingdom Oncology Nursing Society – clinical specialist
- Pat Hanlon, nominated by Kidney Cancer UK – patient expert
- Jackie Lowe, nominated by Kidney Cancer UK – patient expert
- Bill Savage, nominated by James Whale Fund – 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.

- Novartis Pharmaceuticals