NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Everolimus for advanced renal cell carcinoma after previous treatment

Cancer Drugs Fund reconsideration of TA219

1 Recommendations

1.1 Everolimus is recommended within its marketing authorisation as an option for treating advanced renal cell carcinoma that has progressed during or after treatment with vascular endothelial growth factor targeted therapy, only if the company provides it with the discount agreed in the patient access scheme.

2 The technology

Description of the technology	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.
Marketing authorisation	Everolimus has a UK marketing authorisation for 'the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF- [vascular endothelial growth factor] targeted therapy'.
Adverse reactions	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 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 summary of product characteristics.
Recommended dose and schedule	Everolimus is administered orally. The recommended dosage is 10 mg once daily, and treatment should continue as long as there is clinical benefit or until there are unacceptable adverse events. Management of severe or intolerable adverse events may need dose reduction to a suggested dosage of 5 mg daily or temporary withholding of everolimus.
Price	The price for a pack of 10–mg tablets (30 tablets per pack) is £2,673 (excluding VAT; 'British national formulary' [BNF] online, December 2016). The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of everolimus, with the discount applied at the point of purchase or invoice. The level 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   Evidence

3.1   The appraisal committee (section 7) considered evidence submitted by Novartis Pharmaceuticals and a review of this submission by the evidence review group. This appraisal was a Cancer Drugs Fund reconsideration of the NICE technology appraisal guidance on everolimus for the second-line treatment of advanced renal cell carcinoma. The company submission focused on cost-effectiveness analyses using a revised patient access scheme, which provides a simple discount to the list price of everolimus. The level of the discount is commercial in confidence.

3.2   See the committee papers for full details of the Cancer Drugs Fund reconsideration evidence and the history for full details of the evidence used for NICE's original technology appraisal guidance on everolimus for the second-line treatment of advanced renal cell carcinoma.

4   Committee discussion

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 renal cell carcinoma (RCC) and the value placed on the benefits of everolimus by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical effectiveness (NICE technology appraisal guidance 219)

4.2   The committee heard from clinical and patient experts that there are limited treatment options for people with advanced RCC.

4.3   The committee heard from the clinical and patient experts that advanced RCC is a relatively rare cancer, and noted the views of

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experts on the severity of the disease. The committee also heard that people having second-line chemotherapy valued the increased life expectancy offered and were prepared to cope with the adverse effects of these treatments. The committee noted the increased frequency of adverse events (including serious adverse events) associated with everolimus treatment in the RECORD-1 trial. In particular, the committee noted that the most common grade 3 or 4 adverse events suspected to be related to everolimus treatment were anaemia, hyperglycaemia, stomatitis, fatigue, hypercholesterolaemia and dyspnoea. However, the committee was advised by the clinical and patient experts that everolimus would be tolerated by most people with advanced RCC, and that people having everolimus would do so after having had sunitinib as a first-line treatment, and so would be prepared for the adverse effects associated with everolimus. The committee discussed the risk of pneumonitis and immunosuppression associated with everolimus. The clinical expert confirmed that, although pneumonitis and immunosuppression had been associated with everolimus in clinical practice, these adverse events would stop on stopping treatment and were therefore considered manageable.

4.4   The committee discussed the evidence of clinical effectiveness (from the RECORD-1 trial) of everolimus in people with advanced RCC whose disease had progressed during, or within 6 months of stopping, vascular endothelial growth factor targeted treatment. The committee noted that most of the trial population had a good performance status. The clinical expert 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 have any active treatment. Therefore, the committee accepted that the trial population was likely to be similar to people considered for second-line therapy in UK clinical practice. The committee also agreed that the

RECORD-1 trial was of good methodological quality and therefore the results could be considered robust.

4.5   The committee discussed the results of the RECORD-1 placebo-controlled trial. The committee agreed that the results showed that everolimus plus best supportive care had increased progression-free survival by approximately 3 months compared with placebo plus best supportive care. The committee acknowledged that the relative estimates of overall survival according to the intention-to-treat analyses were biased because 81% of people had crossed over to have everolimus in the trial. The committee heard from the clinical expert 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 seen in clinical practice with the introduction of sequential chemotherapy for advanced RCC. The committee noted the meta-analysis submitted by the manufacturer and accepted that a 1.4-month increase in overall survival per 1-month increase in progression-free survival for patients with advanced RCC who had had prior therapy was plausible.

4.6   The committee agreed that it was appropriate to adjust the intention-to-treat results (which gave a median overall survival estimate of 14.8 months for everolimus plus best supportive care and 14.4 months for best supportive care alone) 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.

4.7   The committee acknowledged that the manufacturer had updated both the Inverse Probability of Censoring Weight (IPCW) and the Rank Preserving Structural Failure Time (RPSFT) analyses in response to comments received during consultation. The committee noted that the resulting estimates of overall survival

were 16.2 and 16.1 months with everolimus plus best supportive care and 9.6 and 7.9 months with best supportive care using the IPCW and RPSFT methods respectively. The differences in overall survival were 6.5 months and 8.2 months respectively. The evidence review group (ERG) conducted exploratory analyses of the manufacturer's estimates derived using the RPSFT method and noted that the estimates of overall survival were 14.1 months with everolimus plus best supportive care and 8.9 months with best supportive care (difference in overall survival of 5.2 months). The committee noted that the overall survival estimates for both everolimus and best supportive care were higher with the ERG's exploratory analyses than the manufacturer's analyses. The committee concluded that, although there was sufficient evidence that everolimus increased progression-free and overall survival compared with best supportive care, the exact magnitude of the overall survival gain was uncertain because it was based on modelled data as opposed to data directly seen in the trial. However, the committee accepted that overall survival gain would be more than 3 months.

Cost effectiveness (NICE technology appraisal guidance 219)

4.8   The committee noted that the key factor in determining the cost effectiveness was the estimate of overall survival and discussed the IPCW and the RPSFT methods used to estimate this from the RECORD-1 trial data. It heard from the ERG that it considered the RPSFT method to be more methodologically robust because the IPCW method assumes there are no unmeasured confounders. In addition, the committee understood that the manufacturer's revised IPCW analysis contained a number of unexplained differences between the original and revised models, and so the ERG could not conduct a full critique of the revised IPCW analysis. The committee

also noted that the RPSFT method had been used previously in NICE's technology appraisal guidance on [sunitinib for the treatment of gastrointestinal stromal tumours](). The committee therefore concluded that, in this instance, it was more appropriate to evaluate the cost effectiveness of everolimus based on the estimates generated using the RPSFT method.

4.9   The committee discussed the validity of the estimates of overall survival from the manufacturer's and ERG's RPSFT analyses. The committee noted the ERG's criticism that the manufacturer's extrapolation of long-term survival in the best supportive care arm was still not based on all of the available data (it was based on the mean of cycles 5 and 6 derived from the RPSFT analysis) and that these data may not be representative of the whole trial population. The committee accepted that the use of a Weibull distribution was a more appropriate method for fitting and extrapolating the curve because all available data were used. The committee therefore agreed that this method produced the most plausible estimate of overall survival.

4.10   The committee accepted for this appraisal that the costs and utilities associated with living in the 'progressed disease' health state were similar in patients having everolimus and patients having best supportive care. It also agreed that the incremental difference in overall survival was a key factor in determining the cost effectiveness. The committee acknowledged comments received that overall survival with best supportive care in the ERG's exploratory analyses using the Weibull distribution (8.9 months) was higher that was seen in clinical practice, and that the estimate in the manufacturer's analysis (7.9 months) was more likely to reflect clinical practice. The committee noted that the difference in overall survival between patients having everolimus and those having best supportive care was 8.2 months in the manufacturer's

revised RPSFT analysis and 5.2 months in the ERG's revised RPSFT analysis. It noted the earlier conclusion that an increase in overall survival of 1.4 months per 1 month of increased progression-free survival was plausible. Therefore, the committee agreed that the incremental overall survival derived using the manufacturer's revised RPSFT analysis (8.2 months) was greater than expected, based on the increase in progression-free survival of 3 months seen in the RECORD-1 trial. The committee accepted that the ERG's estimate of overall survival for patients having best supportive care using the RPSFT analysis was higher than seen in clinical practice, but the incremental difference in overall survival for everolimus versus best supportive care (5.2 months) was more plausible than that derived by the manufacturer and was based on all of the available data.

4.11   The committee then discussed the manufacturer's updated estimate of cost effectiveness derived using the RPSFT analysis. The revised deterministic base-case analysis resulted in an incremental cost-effectiveness ratio (ICER) for everolimus plus best supportive care compared with best supportive care alone of £49,300 per quality-adjusted life year (QALY) gained. The committee understood that the updated estimate also included a revised patient access scheme that had been agreed with the Department of Health. The committee then discussed the results of the manufacturer's probabilistic sensitivity analysis using the adjusted 95% confidence interval around the hazard ratio for overall survival, which gave a mean ICER of £49,500 per QALY gained. The committee noted that this analysis incorporated confidence intervals for the hazard ratio for overall survival adjusted by the manufacturer, rather than the limits as derived directly from the RPSFT analysis. The committee noted that the lower limit of the 95% confidence interval for the hazard ratio for overall survival (0.27) had been derived from clinical opinion data collected by the

manufacturer. The committee noted that these data were from a small sample of clinicians and details about the distribution of values within the dataset had not been provided. The committee therefore agreed that these data were likely to be biased. The committee therefore agreed that it would not consider further the results of this analysis.

4.12   The committee discussed the ERG's critique of the manufacturer's probabilistic and one-way sensitivity analyses and accepted that the ERG's criticisms of these analyses were valid. The committee noted that the ERG's re-run of the probabilistic sensitivity analysis, which incorporated the 95% confidence interval obtained from the RPSFT analysis, resulted in a mean ICER for everolimus plus best supportive care compared with best supportive care alone of £51,700 per QALY gained. This gave a 24.0% and 52.7% probability of everolimus plus best supportive care being cost effective compared with best supportive care alone if the maximum acceptable amount to pay for an additional QALY gained was £30,000 or £50,000 respectively. The committee concluded that, because of the errors identified in the manufacturer's analysis, the ERG's probabilistic analysis was the most plausible.

4.13   The committee then discussed other aspects of the manufacturer's model and the critique by the ERG. The committee considered that the time horizon and discounting in the analyses were appropriate. However, the committee had concerns about the validity of some of the assumptions used in the economic model. Firstly, it noted that all patients entered the economic model in the 'stable disease without adverse events' health state. The committee heard from the clinical expert that, in practice, patients eligible for treatment would present with progressed disease and it was likely that some people starting a second-line therapy for advanced RCC experienced adverse events. Secondly, the committee was concerned about the

model assumption that the costs of managing associated adverse events would apply for only 1 treatment cycle. However, the committee heard from the clinical expert 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 expert that the primary ongoing adverse event with everolimus was fatigue, but that this was common to all cancer treatments and there were currently no treatments for its management. Therefore, the committee agreed that the cost estimates used for adverse events in the model were acceptable.

4.14   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 accepted that 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 agreed that, although the utility estimates were subject to some uncertainty, the utility assumptions in the economic model were acceptable.

4.15   The committee was aware of the supplementary advice from NICE that should be taken into account when appraising treatments that 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.

4.16   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 who would be eligible for treatment with everolimus was less than 4,000. The committee heard from the clinical expert that the life expectancy for people with advanced RCC having best supportive care alone was unlikely to be greater than 24 months and was potentially as low as 5 months. The committee also noted that the evidence from the RPSFT analysis suggested that 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.

4.17   The committee then discussed whether, in view of the estimates of cost effectiveness, everolimus was an appropriate use of NHS resources for a life-extending, end-of-life treatment. The committee considered 2 key issues: first the central estimate of the ICERs,

and second the robustness and certainty of the ICER. It noted that the deterministic ICER of £49,300 per QALY gained was high and close to the range considered acceptable for end-of-life treatments. The committee also noted the wide confidence intervals and uncertainty introduced by the novel methodology used to obtain this ICER. Therefore the committee considered the importance of considering the mean probabilistic ICER of £51,700 per QALY gained from the ERG's exploratory probabilistic sensitivity analysis (incorporating the revised patient access scheme). It noted that this ICER was higher than those considered acceptable for end-of-life treatments to date. The committee noted that the ERG's probabilistic sensitivity analysis had indicated that, if the maximum acceptable amount to pay for an additional QALY gained was £30,000, the probability that everolimus was cost effective compared with best supportive care alone was only 24.0%. It also noted that, if the maximum acceptable amount to pay for an additional QALY gained was £50,000, the probability that everolimus was cost effective compared with best supportive care alone was only 52.7%. The committee concluded that, because 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 it could not recommend everolimus for the second-line treatment of advanced RCC as a cost-effective use of NHS resources.

Equality issues (NICE technology appraisal guidance 219)

4.18   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.

Cancer Drugs Fund reconsideration

4.19   This appraisal was a Cancer Drugs Fund reconsideration of the published NICE technology appraisal guidance on everolimus for the second-line treatment of advanced RCC. Everolimus has been available through the Cancer Drugs Fund. In its revised submission updating its cost-effectiveness analysis, the company:

- introduced a revised patient access scheme that provides a simple discount to the list price of everolimus (the level of the discount is commercial in confidence)
- updated unit cost data to 2016 values and
- presented evidence comparing everolimus with axitinib, based on the updated NICE scope for the Cancer Drugs Fund reconsideration.

Clinical management

4.20 The committee recognised that the treatment pathway for advanced RCC has changed since the publication of NICE's original technology appraisal guidance on everolimus. New treatments recommended by NICE are now available: axitinib is recommended as an option after treatment failure with a first-line tyrosine kinase inhibitor or a cytokine. This was reflected in the updated NICE

scope for the Cancer Drugs Fund reconsideration. Axitinib and best supportive care were considered to be comparators for everolimus. In addition, nivolumab was recommended for previously treated advanced RCC in adults in November 2016 and can be now used at this place in the pathway. The committee heard from clinical experts that there is still unmet clinical need for some patients with advanced RCC. The committee agreed that everolimus remains a valuable treatment option for people with advanced RCC.

4.21   No new clinical evidence comparing everolimus with best supportive care was submitted (sections 4.2–4.7 describe the clinical effectiveness in NICE technology appraisal guidance 219). The company presented evidence comparing everolimus and axitinib using matched indirect comparison of RECORD-1 subgroup of patients who had previously had sunitinib and data from the AXIS trial (comparing axitinib and sorafenib). The median progression-free survival was 5.1 months for everolimus and 4.8 months for axitinib. The company did not do the matched indirect comparison for overall survival as no statistically significant results were reported in the RECORD-1 and AXIS trials for overall survival. The ERG also identified a published matched indirect comparison with a median progression-free survival of 4.7 months for everolimus and 4.8 months for axitinib. The company suggested that progression-free survival and overall survival for everolimus and axitinib can be considered the same. The ERG agreed that this assumption is plausible. The committee noted the conclusion in the original appraisal that everolimus increased progression-free and overall survival compared with best supportive care (section 4.7). The committee concluded that it was reasonable to assume similar progression-free survival and overall survival for everolimus and axitinib.

Cost effectiveness

4.22   The company presented updated cost-effectiveness analyses, which included all committee's preferred assumptions and a revised patient access scheme that provides a simple discount to the list price of everolimus as in [breast cancer (HER2 negative, oestrogen receptor positive, metastatic) – everolimus (with aromatase inhibitor) (review of TA295) [ID1011] - CDF rapid reconsideration](#) (the level of the discount is commercial in confidence). The updated [NICE scope](#) for the Cancer Drugs Fund reconsideration included axitinib and best supportive care as the comparators for everolimus. However, the model compared everolimus with best supportive care only. The resulting ICERs cannot be reported here because they are commercial in confidence. The committee concluded that the most plausible ICER for everolimus compared with best supportive care would be less than £30,000 per QALY gained.

4.23   The company also provided cost-minimisation analyses comparing everolimus with axitinib. These analyses assumed progression-free survival and overall for everolimus and axitinib to be equivalent and compared the cost of axitinib and everolimus treatments. Similarly, the ERG proposed that, given that progression-free survival and overall survival for everolimus and axitinib can considered to be the same, a cost-minimisation analysis would be an appropriate approach. The committee agreed that cost-minimisation analyses comparing everolimus and axitinib were suitable for its decision-making. In the cost-minimisation analyses, the cost of everolimus treatment was lower than the cost of axitinib treatment. The committee concluded that everolimus compared with axitinib is a cost-effective use of NHS resources for advanced RCC.

End-of-life considerations

4.24   The committee noted the conclusion in the original appraisal that the end-of-life criteria for everolimus compared with best supported care had been met (section 4.16); and considered whether this was still the case. The committee was aware that the most plausible ICER for this comparison would be less than £30,000 per QALY gained (section 4.22) and therefore that advice about life-extending treatments for people with a short life expectancy was not needed for the economic analyses. It also noted that the evidence suggesting that everolimus increased survival by more than 3 months compared with best supportive care (section 4.16) had not changed. The committee earlier concluded that similar survival can be assumed for everolimus and axitinib (section 4.21). Overall, the committee considered the end-of-life criteria to be fulfilled but only when everolimus was compared with best supportive care.

Conclusion

4.25   Taking into account the cost-effectiveness analyses, including the revised patient access scheme, the committee recommended everolimus as a cost-effective use of NHS resources within its marketing authorisation as an option for treating advanced renal cell carcinoma that has progressed during or after treatment with vascular endothelial growth factor targeted therapy, only if the company provides it with the discount agreed in the patient access scheme.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Everolimus for advanced renal cell carcinoma after failure of a prior systemic treatment	Section
Key conclusion (Cancer Drugs Fund reconsideration of TA219)		
Everolimus is recommended within its marketing authorisation as an option for treating advanced renal cell carcinoma (RCC). The drug is recommended only if the company provides it with the discount agreed in the patient access scheme. The committee understood that, in the company's Cancer Drugs Fund reconsideration submission, it provided an updated cost-effectiveness analysis. The committee concluded everolimus was a cost-effective use of NHS resources.		1.1 4.19 4.25
Current practice (TA219)		
Clinical need of patients including the availability of alternative treatments	The committee heard from the clinical and patient experts that advanced RCC is a relatively rare cancer and noted the views of clinical and patient experts on the severity of the disease. The committee also heard that people having second-line chemotherapy valued the increased life expectancy offered and were prepared to cope with the adverse effects of these treatments.	4.3
The technology (TA219)		
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 acknowledged that there are no second-line treatments recommended by NICE for people whose disease has stopped responding to sunitinib and that everolimus could offer an option for the second-line treatment of advanced RCC in people whose disease has progressed on first-line treatment with sunitinib.	4.2
What is the position of the treatment in the pathway of care for the condition?	The committee acknowledged that everolimus could offer an option for the second-line treatment of advanced RCC in people whose disease has progressed on first-line treatment with sunitinib.	4.2
Adverse events	The committee noted the increased frequency of adverse events (including serious adverse events) associated with everolimus treatment in the RECORD-1 trial. The committee concluded that, although there were adverse events that had been associated with everolimus in clinical practice, these adverse events would stop on stopping treatment and were therefore considered manageable.	4.3

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Evidence for clinical effectiveness (TA219)		
Availability, nature and quality of evidence	The committee agreed that the RECORD-1 trial was of good methodological quality and therefore the results could be considered robust.	4.4 to 4.7
	The committee agreed that everolimus plus best supportive care had increased progression-free survival by approximately 3 months compared with placebo plus best supportive care.	
	The committee acknowledged that the relative estimates of overall survival according to the intention-to-treat analyses were biased because 81% of people had crossed over to have everolimus in the trial. Therefore, the committee agreed that it was appropriate to adjust the results to control for the crossover using statistical modelling techniques.	
	The committee noted that the resulting estimates of overall survival were 16.2 and 16.1 months with everolimus plus best supportive care and 9.6 and 7.9 months with best supportive care using the Inverse Probability of Censoring Weight (IPCW) and the Rank Preserving Structural Failure Time (RPSFT) methods respectively. The evidence review group (ERG) conducted exploratory analyses of the manufacturer's estimates derived using the RPSFT method and noted that the estimates of overall survival were 14.1 months with everolimus plus best supportive care and 8.9 months with best supportive care.	
	The committee therefore concluded that, although there was sufficient evidence that everolimus increased progression-free and overall survival compared with best supportive care, the exact magnitude of the overall survival gain was uncertain because it was based on modelled data as opposed to data directly seen in the trial, but accepted that it would be more than 3 months.	
Relevance to general clinical practice in the NHS	The committee accepted that the trial population was likely to be similar to people considered for second-line therapy in UK clinical practice.	4.4

Uncertainties generated by the evidence	The committee agreed that any estimate of overall survival obtained using statistical modelling would be subject to some uncertainty because a number of assumptions would have to be made. However, the committee concluded that there was sufficient evidence that everolimus increased progression-free and overall survival compared with best supportive care. It noted that the exact magnitude of the overall survival gain was uncertain because it was based on modelled data as opposed to data directly seen in the trial, but accepted that it would be more than 3 months.	4.6, 4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee did not identify any specific groups of people for whom the technology was considered particularly effective.	4.18
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee concluded that there was sufficient evidence that everolimus increased progression-free and overall survival compared with best supportive care. It noted that the exact magnitude of the overall survival gain was uncertain because it was based on modelled data as opposed to data directly seen in the trial, but accepted that it would be more than 3 months.	4.7
Evidence for cost effectiveness (TA219)		
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. The committee noted that the key factor in determining the cost effectiveness was the estimate of overall survival and heard from the ERG that it considered the RPSFT method to be more methodologically robust because the IPCW method assumes there are no unmeasured confounders. In addition, the committee understood that the manufacturer's revised IPCW analysis contained a number of unexplained differences between the original and revised models, and so the ERG could not conduct a full critique of the revised IPCW analysis. The committee therefore concluded that, in this instance, it was more appropriate to evaluate the cost effectiveness of everolimus based on the estimates generated using the RPSFT method.	3.2 4.8

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| Uncertainties around and plausibility of assumptions and inputs in the economic model | The committee acknowledged comments received that overall survival with best supportive care in the ERG's exploratory analyses using the Weibull distribution (8.9 months) was higher than was seen in clinical practice, and that the estimate in the manufacturer's analysis (7.9 months) was more likely to reflect clinical practice. The committee noted that the difference in overall survival between patients having everolimus and those having best supportive care was 8.2 months in the manufacturer's revised RPSFT analysis and 5.2 months in the ERG's revised RPSFT analysis. The committee accepted that the ERG's estimate of overall survival for patients having best supportive care using the RPSFT analysis was higher than seen in clinical practice, but the incremental difference in overall survival for everolimus compared with best supportive care (5.2 months) was more plausible than that derived by the manufacturer, and it was based on all of the available data.

The ERG reviewed the manufacturer's updated RPSFT analysis, which incorporated the revised patient access scheme. The ERG was satisfied that the model appropriately incorporated the conditions of the revised scheme. The ERG was also satisfied that the other changes made to the manufacturer's model had been satisfactorily incorporated (adopting the assumptions used in the ERG's RPSFT analysis). The ERG expressed concern that the hazard ratio for overall survival between treatment arms had wide confidence intervals and therefore this was the major source of uncertainty in the model.

The committee concluded that, because of the errors identified in the manufacturer's analysis, the ERG's probabilistic analysis was the most plausible. | 3.2, 4.9, 4.10, 4.12 |

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Incorporation of health-related quality of life benefits and utility values	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 accepted that 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 agreed that, although the utility estimates were subject to some uncertainty, the utility assumptions in the economic model were acceptable.	4.14
Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	No potential health-related benefits have been identified that were not included in the economic model.	
Are there specific groups of people for whom the technology is particularly cost effective?	The committee noted that no subgroups of patients had been identified.	4.18
What are the key factors in determining cost effectiveness?	The committee noted that the key factor in determining the cost effectiveness was the estimate of overall survival.	4.8
Most likely cost-effectiveness estimate (given as an ICER)	The committee considered the deterministic incremental cost-effectiveness ratio (ICER) of £49.300 per quality-adjusted life year (QALY) gained (derived by the manufacturer) and the mean probabilistic ICER of £51,700 per QALY gained (derived by the ERG).	4.11, 4.12

Additional factors taken into account (TA219)		
Patient access scheme	The manufacturer 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 £2,822 (that is, a 5% discount on the acquisition cost of everolimus). A revised patient access scheme was subsequently agreed, the details of which are confidential.	3.2
End-of-life considerations	The committee concluded that everolimus for advanced RCC 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
Equalities considerations, social value judgements	No equality issues relating to population groups protected by equality legislation were highlighted when the scope for this appraisal was developed, or during the appraisal.	4.18
Cancer Drugs Fund reconsideration of TA219		
Current practice	Everolimus remains a valuable treatment option for people with advanced RCC.	4.20
Evidence for cost effectiveness	The committee concluded that the most plausible ICER for everolimus compared with best supportive care would be less than £30,000 per QALY gained including the revised patient access scheme. The committee concluded that everolimus compared with axitinib is a cost-effective use of NHS resources.	4.21 4.23
Additional factors taken into account	The committee acknowledged that the Cancer Drugs Fund reconsideration submission included the patient access scheme as in breast cancer (HER2 negative, oestrogen receptor positive, metastatic) – everolimus (with aromatase inhibitor) (review of TA295) [ID1011] - CDF rapid reconsideration	4.19

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2   The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

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

5.4   The Department of Health and Novartis Pharmaceuticals have agreed that everolimus will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to [NICE to add details at time of publication]

6   Review of guidance

6.1   The guidance on this technology will be considered for review 3 years after publication. 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, TA219 appraisal committee

November 2010

Andrew Stevens

Chair, Cancer Drugs Fund reconsideration of TA219 appraisal committee

January 2016

7 Appraisal committee members and NICE project team

Appraisal committee members

The technology appraisal committees are standing advisory committees of NICE. This topic was considered by members of the existing standing committees who have met to reconsider drugs funded by the Cancer Drugs Fund. The names of the members who attended are in the [minutes](#) of the appraisal committee meeting, which are posted on the NICE website.

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.

NICE project team

Each technology appraisal is assigned to a team consisting of a health technology analyst (who acts as technical lead for the appraisal), a technical adviser or an associate director, and a project manager.

TA219

Helen Tucker

Technical Lead

Rebecca Trowman

Technical Adviser

Lori Farrar

Project Manager

Cancer Drugs Fund reconsideration of TA219

Marcela Haasova

Technical Lead

Frances Sutcliffe

Associate Director

Jenna Dilkes

Project Manager