NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Everolimus with exemestane for treating advanced breast cancer after endocrine therapy

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using everolimus in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts 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 recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

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 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

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.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 9 September 2016

Second appraisal committee meeting: 29 November 2016

Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 Everolimus, in combination with exemestane, is not recommended within its marketing authorisation for treating advanced human epidermal growth factor receptor 2 (HER2)-negative hormone-receptor-positive breast cancer in postmenopausal women that has recurred or progressed after a non-steroidal aromatase inhibitor.

1.2 This guidance is not intended to affect the position of patients whose treatment with everolimus was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

Description of the technology	Everolimus (Afinitor, Novartis Pharmaceuticals) inhibits the mammalian target of rapamycin, a protein that regulates the division of tumour cells and growth of blood vessels.
Marketing authorisation	Everolimus has a UK marketing authorisation for the 'treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor'.
Adverse reactions	The summary of product characteristics lists the most frequently reported grade 3 or 4 adverse reactions including: anaemia, fatigue, diarrhoea, infections, stomatitis, hyperglycaemia, thrombocytopenia, lymphopenia, neutropenia, hypophosphataemia, hypercholesterolaemia, diabetes mellitus and pneumonitis. For full details of adverse reactions 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 patients benefit clinically, or until they have unacceptable adverse reactions. Adverse reactions that are severe and/or intolerable may be managed by reducing the dosage to 5 mg daily or temporarily stopping treatment then reintroducing it at 5 mg daily.
Price	The price for a pack (30 tablets per pack) of 10 mg tablets and 5 mg tablets is £2,673 and £2,250 respectively (excluding VAT; 'British National Formulary' [BNF]). The company has agreed a patient access scheme with the Department of Health. If everolimus had been recommended, this scheme would provide 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 would not constitute an excessive administrative burden on the NHS.

3 Evidence

3.1 The appraisal committee (section 6) considered evidence submitted by Novartis and a review of this submission by the evidence review group. This appraisal was a Cancer Drugs Fund reconsideration of the published NICE technology appraisal guidance on everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy. Sections 4.1 to 4.27 reflect the committee's consideration of the evidence submitted in the original appraisal (NICE technology appraisal guidance 295). Sections 4.28 to 4.32 reflect the committee's consideration of the additional evidence submitted for the Cancer Drugs Fund reconsideration. It focused on updated overall survival data from the BOLERO-2 trial and cost-effectiveness analyses using a patient access scheme, which provides everolimus at a reduced cost. The level of the discount is commercial in confidence.

3.2 In BOLERO-2 postmenopausal women with advanced HER2-negative hormone-receptor-positive breast cancer without symptomatic visceral disease who had previously had a non-steroidal aromatase inhibitor were randomised to either everolimus plus exemestane or to exemestane alone. The primary end point of the trial was progression-free survival as assessed by a local radiologist (study site specific).

3.3 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 in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy.

4 Committee discussion

4.1 The appraisal committee reviewed the data available on the clinical and cost effectiveness of everolimus plus exemestane, having considered evidence on the nature of locally advanced or metastatic human epidermal growth factor receptor 2 (HER2)-negative hormone-receptor-positive breast cancer after endocrine therapy and the value placed on the benefits of everolimus plus exemestane by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.2 The committee considered the views of the patient expert on their experience of everolimus as a treatment for advanced breast cancer. It heard from the patient expert that patients would value everolimus plus exemestane as a treatment option because it is offered when limited treatment options exist after a woman's disease becomes resistant to endocrine therapy, and because everolimus plus exemestane may delay the need for chemotherapy and its associated toxicity. The committee also heard from the patient expert that patients value increased survival and improved quality of life. The committee was aware of comments from consultees that everolimus is considered to be the 'biggest development in years for treating breast cancer' and also that 'length of life is only worth having if there is a quality of life as well'. The committee recognised the importance of having a range of treatment options for postmenopausal women with locally advanced or metastatic breast cancer.

4.3 The committee considered the marketing authorisation, which specifies that everolimus can be used for 'postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor'. The

committee noted that patients in the BOLERO-2 trial may have had visceral disease, but that it was unclear whether these patients were also symptomatic. The committee heard from the clinical experts that patients with visceral disease may or may not have symptoms but that, for patients with life-threatening symptomatic visceral disease, chemotherapy is the preferred treatment option, usually with an anthracycline-containing regimen (doxorubicin or epirubicin) or a taxane. The committee understood that, in accordance with the marketing authorisation, everolimus was not being appraised for patients with symptomatic visceral disease.

4.4 The committee considered the likely position of everolimus plus exemestane in the treatment pathway for women with locally advanced or metastatic HER2-negative hormone-receptor-positive breast cancer. The committee heard from the clinical experts that, in general, clinical practice reflects the recommendations in NICE's guideline on advanced breast cancer, but that patients whose disease progresses after a non-steroidal aromatase inhibitor (such as anastrozole or letrozole) are often offered further endocrine treatments rather than chemotherapy. The clinical experts confirmed that everolimus plus exemestane would be offered to patients whose disease has progressed on a non-steroidal aromatase inhibitor at a point when a patient might otherwise receive either further endocrine therapy or chemotherapy.

4.5 The committee considered the chemotherapy treatments that the company had included as comparators in its submission. It understood that the scope listed 'chemotherapy in accordance with NICE guidance' and that the company had included comparisons with docetaxel, doxorubicin and capecitabine, and

after consultation, vinorelbine. The committee heard from the clinical experts that the most relevant chemotherapy comparators for everolimus plus exemestane are likely to be capecitabine and vinorelbine because anthracyclines (doxorubicin) and taxanes (docetaxel) are generally used to treat metastatic breast cancer in patients who have symptomatic and life-threatening visceral disease (see section 4.3). The committee concluded that, of the chemotherapies, the comparison of everolimus plus exemestane with capecitabine was the most relevant for the population in the appraisal, and that a comparison with vinorelbine was also appropriate.

4.6 The committee then discussed the endocrine treatments included as comparators by the company. It heard from the clinical experts that, although fulvestrant is available through the Cancer Drugs Fund, NICE has not recommended it. The committee did not hear any evidence that fulvestrant can be considered routine practice when non-steroidal aromatase inhibitors have failed. The clinical experts stated that tamoxifen and exemestane (alone) were appropriate comparators for everolimus plus exemestane, although tamoxifen is often offered after exemestane. Also, the committee understood from the clinical experts that, although exemestane is used, there are concerns that it is not effective in the population considered in this appraisal because the disease will have already progressed on a non-steroidal aromatase inhibitor. The committee noted that this concern was acknowledged by the European Medicines Agency in the European public assessment report, which stated that patients in the exemestane arm of BOLERO-2 may have received suboptimal treatment. On this basis, the European Medicines Agency requested that the company complete a trial comparing everolimus plus exemestane with everolimus alone

and with capecitabine alone. Despite these issues, the committee concluded that exemestane alone was the most relevant endocrine comparator for everolimus plus exemestane for the purpose of this appraisal.

Clinical effectiveness (NICE technology appraisal guidance 295)

4.7 The Committee discussed the data on clinical effectiveness from BOLERO-2. It heard from the clinical experts that the trial population represented patients who would be offered everolimus in the UK. The committee understood from the trial publication and from the statistical analysis plan of the trial that the primary end point of the trial was progression-free survival based on radiographic assessment by local investigators, and that central assessment by an independent radiology committee was used in supportive analyses. However, in its submission, and at the committee meeting, the company stated that the primary end point was progression-free survival based both on local and central radiological assessment. The committee noted that the company's statistical analysis plan stated that the primary end point of BOLERO-2 was amended to local assessment from central assessment 5 months after the original protocol was approved. The company explained that this protocol amendment was implemented after approximately 100 events, but could not provide the reasons for the change. The committee was aware that median progression-free survival was longer (both relatively and absolutely) when estimated using central rather than local assessment and that the company had chosen to use centrally assessed estimates of progression-free survival in its economic model. The committee heard from the company that central assessment was

associated with fewer biases. However, it was aware that women in the UK who would receive everolimus plus exemestane would have progression assessed locally, not centrally. The company agreed with the committee that disease progression would be assessed locally in routine clinical practice. The committee was aware that, ideally, trials give unbiased estimates of relative treatment effects, but that biases with central assessment may have existed in this particular trial. The committee agreed that it was important to consider in detail the different approaches related to, and issues around, local and central assessment.

4.8 The committee then discussed the approaches to analysing the BOLERO-2 data when assessed locally or centrally. It was aware that the trial protocol stipulated that, once a patient's disease was assessed locally as having progressed, study treatment would have stopped (and the patient may have gone on to other treatments), whether or not the central radiological committee had considered the disease to have progressed. The committee heard from the company that the analysis followed the statistical analysis plan, that patients deemed to have progressed only by local assessment were censored in Kaplan–Meier analyses based on central assessment, and that the company's statistical analysis plan acknowledged the potential for informative censoring when the analysis was based on central review. The committee understood that censoring occurs in a trial when the event of interest, in this case, disease progression, is not seen during the follow-up. It appreciated that censoring in some circumstances can be 'informative', that is, patients censored for one reason are more likely to have disease progression than patients censored for another reason. The censoring in the analysis based on central assessment may

have been informative because these patients would plausibly fare more poorly (given that they had disease severe enough for the local radiologists to have deemed their disease to have progressed) than would patients censored by other means. The committee heard from the evidence review group (ERG) that informative censoring may have biased the treatment effect because it violates the statistical assumption that censoring is random and therefore unrelated to prognosis. The ERG noted that this is of greater concern in unblinded trials, but the committee was also aware of the analysis provided by the ERG that concluded there was no evidence that local investigators acted in a way to suggest that unblinding occurred in BOLERO-2. The committee was also aware of analyses presented by the company after consultation, in which patients randomised to everolimus and censored by central review were instead recorded as having progressed which, according to the company, did not reveal informative censoring. However, the committee noted that these sensitivity analyses resulted in a hazard ratio of 0.55, reflecting a smaller treatment effect compared with when effectiveness was addressed centrally (0.36) or locally (0.43). The ERG explained to the committee that it could not verify the sensitivity analysis described by the company without access to the Kaplan–Meier analyses requested at the clarification stage. It concluded that, as a means to avoid informative censoring, local assessment without risk of informative censoring was superior to central assessment with imputed data. In addition, the committee was aware of a meta-analysis by Amit et al. (2011), which showed that local evaluation provides a reliable measure of treatment effect when compared with central assessment, even when trials are unblinded. The committee concluded that it was more

appropriate to use effectiveness data derived from local assessment in the modelling than from central assessment because local assessment represented the primary end point of the trial, reflected clinical practice and minimised the potential for bias from informative censoring. Overall, the committee concluded that everolimus plus exemestane is effective in prolonging progression-free survival compared with exemestane alone.

4.9 The committee considered the results for overall survival in BOLERO-2 and that the median overall survival had not yet been reached. It therefore agreed that the immaturity of the data resulted in considerable uncertainty associated with the longer-term benefits of everolimus plus exemestane.

4.10 The committee considered the safety data from BOLERO-2, which showed that patients receiving everolimus plus exemestane had more adverse reactions, specifically stomatitis and anaemia, than patients receiving exemestane alone. The committee heard from the clinical experts that, although everolimus can lead to several different adverse reactions, it is generally well tolerated. The clinical experts noted that, because everolimus was associated with pneumonitis, it was likely that patients would need additional monitoring. The committee heard from the patient expert that people vary in their willingness to accept the risks of treatment with chemotherapy because it can significantly worsen a patient's health-related quality of life, and highlighted the importance of providing information on treatments to patients.

4.11 The committee discussed the results of the indirect treatment comparison that estimates the clinical effectiveness of everolimus plus exemestane compared with fulvestrant. It heard

from the ERG that it should regard the results with caution. The committee was aware that the company's indirect treatment comparison included studies that may have assessed progression-free survival locally (which differed from the company's preference for central assessment for everolimus plus exemestane), and that the estimated incremental cost-effectiveness ratio (ICER) for everolimus plus exemestane compared with fulvestrant depended on the results of the indirect treatment comparison. The committee noted its previous conclusion that, because fulvestrant is not used routinely in clinical practice (see section 4.6), and is not currently recommended by NICE (NICE's appraisal of fulvestrant included a different patient population; see fulvestrant for the treatment of locally advanced or metastatic breast cancer), it did not consider fulvestrant to be a relevant comparator. The committee concluded that, for this technology appraisal, the results of the indirect treatment comparison were not key to its decision-making.

4.12 The committee discussed the company's approach of using the TAMRAD trial, which compared everolimus plus tamoxifen with tamoxifen alone, to inform a comparison of everolimus plus exemestane with tamoxifen alone. The committee understood from the company that it used the hazard ratios from TAMRAD in its economic model and assumed that the hazard ratios for everolimus plus exemestane compared with tamoxifen alone would be the same as those for everolimus plus tamoxifen compared with tamoxifen alone. The clinical experts noted that they could not determine whether the assumption was valid because exemestane and tamoxifen have different mechanisms of action. The committee concluded that there was considerable uncertainty about the validity of the comparison of everolimus

plus exemestane with tamoxifen. Therefore no conclusions were possible on the effectiveness of everolimus plus exemestane compared with tamoxifen.

4.13 The committee considered the results of the naive chained indirect analysis, which estimated the clinical effectiveness of everolimus plus exemestane compared with chemotherapy. It heard from the ERG that it had several concerns about the methodology associated with this analysis, which relied on untested assumptions and on a systematic review (Wilcken et al. 2003) that included studies that no longer reflect clinical practice. The clinical experts agreed that the studies in the systematic review reflect outdated clinical practice, but also stated there was little evidence comparing endocrine therapies with chemotherapies. Indeed, the ERG had not identified any evidence that would have allowed the company to have completed a more appropriate analysis. The committee concluded that it was not possible to make robust comparisons between everolimus plus exemestane and chemotherapies based on the available evidence. Therefore it was not possible to separately develop recommendations for everolimus plus exemestane compared with chemotherapy.

Cost effectiveness (NICE technology appraisal guidance 295)

4.14 The committee considered the company's economic model and the ERG's critique of the company's comparison of everolimus plus exemestane and exemestane alone. Firstly, it discussed the company's economic model and their choice of a Weibull function to extrapolate overall survival data from BOLERO-2. It noted that the Weibull function did not provide the best statistical fit, but heard from the company that its clinical advisers

suggested that the Weibull function estimated the proportion of patients alive over time more accurately than the other functions explored. The committee was aware of numerous uncertainties about extrapolating survival beyond the end of BOLERO-2, for example, that few patients died during the median 18-month follow-up of BOLERO-2, making data sparse, and whether mortality rates would plausibly differ after treatment stops between postmenopausal women who had or did not have previous treatment with everolimus. The committee concluded that statistical fit is only one way to choose a parametric function, and that how well a curve fits the natural history of locally advanced and metastatic breast cancer treated with standard treatment would also be important, particularly when overall survival data are immature.

4.15 The committee discussed whether it was appropriate for the company to adjust overall survival with a factor it took from Beauchemin et al. (2012) to address the anomalous result when estimating the number of women in the 'progressed disease' health state from the progression-free survival and overall survival data, and whether it was appropriate to apply this adjustment only to people who had everolimus plus exemestane. The committee heard from the ERG that this adjustment increased the length of overall survival in the everolimus plus exemestane arm of the economic model by 17%. The company clarified that it took the factor from a conference poster, which it considered to be the most up-to-date source of evidence. The committee understood that the most recent evidence was not necessarily the most robust, and that other studies exist and had been reviewed by the NICE Decision Support Unit (A review of studies examining the relationship between progression-free survival and overall survival in

advanced or metastatic cancer). Also, the committee concluded that it was not reasonable for the company to apply this adjustment factor only to the everolimus plus exemestane arm of the economic model, and that the anomalous result for post-progression survival showed that the company had either used the wrong parametric model or had applied the functions incorrectly in the model. The committee noted that the company had removed the adjustment in the additional analyses it provided after consultation.

4.16 The committee noted that the company had originally applied a background mortality rate (age-related mortality) after 4 years in the economic model. It heard from the ERG that this double counted deaths from causes other than locally advanced or metastatic breast cancer because these were seen in BOLERO-2. The committee concluded that it was not appropriate for the company to model additional background mortality and noted that this was removed in the additional analyses provided by the company after consultation.

4.17 The committee discussed the implications of using local or central assessment for progression-free survival in the modelling. It would expect progression-free survival from the economic model and the trial to be similar, but noted that the centrally assessed mean progression-free survival with everolimus plus exemestane was 3.8 months longer than that observed in BOLERO-2, whereas progression-free survival for exemestane alone was only 0.5 months longer in the economic model than in the trial. The committee noted that this indicated that the economic model did not reflect the patient population in BOLERO-2. Also, the committee noted that the estimates for locally assessed progression-free survival were similar between

the economic model and the trial. The committee concluded that the company's economic model based on centrally assessed progression-free survival is unlikely to provide a robust basis for calculating a valid estimate of cost effectiveness.

4.18 The committee discussed the ERG's exploratory survival analyses. The ERG chose a 'piecewise approach' because the mortality risk associated with advanced breast cancer is likely to be different before progression than it is after progression when a treatment has stopped. The committee understood from the ERG that the company did not provide the post-progression survival data that it requested and therefore the ERG could not assess whether everolimus prolongs survival after disease progression. The committee agreed that fitting multiple parametric curves to the overall survival data may be appropriate when there is a high degree of uncertainty associated with estimating the survival gain from immature data. However, the committee could not be confident that this markedly diminished the uncertainty inherent in the data. It noted the ERG's observation that mortality rates were similar in both treatment arms after approximately 10 months, and so the ERG fitted an exponential model that assumed parallel long-term hazard trends and, after consultation, an alternative scenario that assumed everolimus plus exemestane provides a survival benefit compared with exemestane alone (that is, the 'non-parallel exponential model'). The committee heard from the ERG that it was unable to assess the goodness of fit of the exploratory survival analyses because the company did not provide access to the patient-level data. It agreed that the company's estimated 10.5 months' survival benefit with the Weibull analysis was likely to be optimistic, and that the estimated 1.4 months' survival benefit with the ERG's

exploratory parallel exponential model was likely to be pessimistic. The committee acknowledged that the overall survival benefit of everolimus plus exemestane is uncertain but probably lies between these estimates, as seen in the overall survival benefit from the ERG's non-parallel exponential model (4.6 months), which reflects the longer progression-free survival with everolimus plus exemestane compared with exemestane alone. The committee agreed to use the ERG's exploratory non-parallel exponential survival analyses in its discussions.

4.19 The committee discussed the utility values for the 'stable disease' health state used by the company in its economic model. It noted that, in its original submission, the company had chosen utility values (taken from Lloyd et al. 2006) for the health states that were not estimated in line with the NICE reference case because it used vignettes to describe the health states and the standard gamble technique to estimate the utility values. The committee was aware that these utility values had been used by other companies in NICE's previous appraisal of breast cancer (fulvestrant for the treatment of locally advanced or metastatic breast cancer). The ERG noted that the company had incorrectly calculated the utility estimate for 'stable disease' in its original submission because it had not calculated utility separately for each treatment. The committee understood that correcting this had a small effect on the ICER. It understood that the company had measured health-related quality of life using a disease-specific instrument, but made no attempt to map this to the preferred generic EQ-5D instrument, despite several algorithms being available. It heard from the company that this was because BOLERO-2 evaluated health-related quality of life only until disease progressed. The committee acknowledged this limitation, but concluded that it would have been appropriate

for the company to present estimates for the 'stable disease' health state from BOLERO-2 alongside its base-case analysis.

4.20 In its meeting after consultation, the committee discussed the alternative utility value from Launois et al. (1997) included by the company for the 'progressed disease' health state. The committee heard from the company that it had increased the utility value for 'progressed disease' after discussions with the Scottish Medicines Consortium. The company explained that Launois et al. (1997) was the only publication relevant to advanced breast cancer that it could find. The committee discussed the anomalous finding in Launois et al. (1997), which showed a lower quality of life for 'early progression' compared with 'progression'. It heard from the clinical experts that this was unlikely to reflect reality. The committee further discussed whether it is more valid to assume a decrease in utility from stable to progressed disease of approximately 0.28 (if using Lloyd et al. 2006) or approximately 0.12 (if using Launois et al. 1997). The patient expert commented that they were unable to approximate the decrease in quality of life resulting from disease progression in patients with advanced breast cancer. The committee stated that the estimates for quality of life for the 'progressed disease' state from both Lloyd et al. (2006) and Launois et al. (1997) relied on the descriptions used for the vignettes in the studies but the company could not provide information on how the vignettes had been described. The committee heard from the ERG that Lloyd et al. (2006) better reflected NICE's guide to the methods of technology appraisal (2008), in that it used valuations from the UK general public, than did Launois et al. (1997), which surveyed French nurses. The committee concluded that neither valuation of utility for the 'progressed disease' health state was without uncertainty, but

that the data from Lloyd et al. (2006) were more appropriate than the data from Launois et al. (1997).

4.21 The committee discussed whether the company provided valid cost inputs for the 'stable' and 'progressed' health states in its economic model. It was aware that the company may have used drug costs of chemotherapy (particularly docetaxel) that were higher than the costs in the NHS, achieved through national agreements. The committee agreed with the ERG's decision to adjust the time on treatment to reflect the longer follow-up period of BOLERO-2, and to include costs for a quarterly appointment to assess whether patients with stable disease had progressed. The committee was aware that these exploratory analyses decreased and increased the base-case ICER respectively. It noted that the univariate sensitivity analysis included in the company's economic model (although not presented in its written submission) showed that the ICERs were sensitive to the costs for the 'progressed disease' health state but that this did not include costs associated with subsequent therapies (namely, chemotherapy). After consultation, the company included the costs associated with subsequent therapies in its economic model. It heard from the ERG that there is no evidence to suggest the probability of receiving subsequent therapies after disease progression differed significantly between treatment arms. The committee concluded that the inclusion of costs associated with subsequent therapies would have a small effect on the estimation of the ICER.

4.22 The committee discussed whether it was appropriate to include costs and disutilities associated with adverse events in the model, noting that the company had included these in its

analyses of everolimus plus exemestane compared with chemotherapies, but not when compared with endocrine therapies. The committee heard from the clinical experts that mild adverse events would not lead to a break from treatment, but that patients may need other medicines (for example, mouthwash for stomatitis). The clinical experts noted that patients who have grade 3 or 4 adverse events would need a temporary break in treatment and that the cost of pneumonitis appeared to be underestimated in the company's model for both diagnosis and treatment. Having previously concluded that, given the side-effect profile of everolimus, costs and disutilities associated with adverse events should be included for each of the comparisons in its economic model, the committee noted that the company included them in the additional analyses it provided after consultation.

4.23 The committee discussed the most plausible ICER, noting that a robust comparison was available only for everolimus plus exemestane compared with exemestane alone. It agreed that the most plausible ICER should be based on an analysis using the following assumptions:

- using exponential functions to estimate progression-free survival and the non-parallel model of overall survival
- omitting the adjustment factor from Beauchemin et al. (2012)
- using locally assessed trial data
- including adverse reactions
- using rates of adverse reactions as documented in the European public assessment report
- recalculating time on treatment
- including costs of monitoring disease that has not progressed
- correcting discounting and utility values for stable disease

- using the utility value for 'progressed disease' from Lloyd et al. (2006) and
- omitting extra mortality from non-cancer causes.

The committee noted that the ICER was most sensitive to the modelling of overall survival and the progression-free survival assessment method. The committee concluded that the ERG's estimate of the ICER (including the patient access scheme for everolimus) of £68,000 per quality-adjusted life year (QALY) gained for everolimus plus exemestane compared with exemestane alone was more plausible than the company's base-case estimate. The committee concluded that everolimus (plus exemestane) could not be considered a cost-effective use of NHS resources for treating locally advanced or metastatic HER2-negative hormone-receptor-positive breast cancer, after recurrence or progression following a non-steroidal aromatase inhibitor.

4.24 The committee discussed the innovative nature of everolimus and whether the economic analysis had captured all changes in health-related quality of life. In its submission, the company stated that everolimus was innovative because it is administered orally, may slow the rate of disease progression in the bone, increases productivity and reduces healthcare-resource use when compared with chemotherapy. The committee noted that a number of the comparator treatments are also administered orally, that bone markers were only an exploratory end point in BOLERO-2, and that gains in productivity were currently outside of the NICE reference case. The committee considered that differences in the use of healthcare resource are expected to be adequately captured in the company's economic model. Although the committee acknowledged that the mechanism of

action of everolimus may offer a step change in treatment by restoring the sensitivity of the tumour to endocrine therapy, it concluded that the company had not submitted convincing evidence that everolimus (plus exemestane) provides health-related quality-of-life benefits exceeding that calculated in the QALY, as defined in NICE's guide to the methods of technology appraisal (2008). The committee concluded that the case for innovation made by the company did not change the committee's conclusions about the cost effectiveness of everolimus plus exemestane.

4.25 The committee considered supplementary advice from NICE, which should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all of 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 show 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 that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.26 The committee discussed whether everolimus plus exemestane fulfilled the criteria for a life-extending end-of-life treatment. It acknowledged the uncertainty associated with estimated life expectancy but, given that the company's model estimated a mean overall survival of 28.9 months for exemestane alone, the committee was not convinced that the life expectancy of women offered everolimus plus exemestane based on the marketing authorisation was convincingly less than 24 months. The committee heard from the company that it chose not to present a case for end-of-life treatment in its original submission because discussions with the clinical experts identified no clinically plausible subgroups of patients with a life expectancy of less than 24 months. The committee was aware that the meta-analysis of the SoFEA and EFECT trials provided by the company during consultation suggested a median survival of 22.6 months in patients with advanced breast cancer treated with exemestane alone. However, the committee understood that the company's original submission showed at least a third of the patients in the SoFEA trial had HER2-positive tumours (the EFECT trial did not report the proportion of patients with HER2-negative tumours). It heard from the clinical experts that HER2-positive tumours have a worse prognosis, that is, patients with HER2-positive tumours on average die sooner than patients with HER2-negative tumours. The committee concluded that these 2 trials were not relevant in determining life expectancy in women with HER2-negative tumours, and that everolimus plus exemestane did not convincingly fulfil this criterion for an end-of-life therapy as defined. Having established that everolimus did not meet the short life expectancy criterion, the committee decided that it was not necessary to make a decision about the extension-to-life or

population size criteria. It concluded that, on this basis, everolimus plus exemestane did not fulfil the criteria for being a life-extending, end-of-life treatment.

4.27 The committee discussed whether subgroups existed in which everolimus plus exemestane offered a cost-effective use of NHS resources. The ERG had identified 3 subgroups. The committee noted that, although the statistical analysis plan of the trial included no plans to test for interaction, the company had stated that it had not identified any statistically significant differences in progression-free survival between subgroups. The committee heard from the ERG that it believed these subgroups may be relevant because, even though the relative effectiveness of everolimus plus exemestane might be similar across subgroups, differences in baseline risk could improve the cost effectiveness. The committee noted that the ERG had been unable to quantify the effect on the ICER of the different subgroups. The committee was also aware that the efficacy analyses in subgroups performed by the company were purely exploratory and intended to explore the uniformity of any overall treatment effects, and that the company had not included any cost-effectiveness analyses for subgroups in its original or revised submission. The committee concluded that the available evidence did not allow it to make any recommendations specific to subgroups of patients.

Cancer Drugs Fund reconsideration of NICE technology appraisal guidance 295

4.28 This appraisal was a Cancer Drugs Fund reconsideration of the published NICE technology appraisal guidance on everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after

endocrine therapy. The committee considered the company's submission for the Cancer Drugs Fund reconsideration that:

- included a revised patient access scheme that provides a simple discount to the list price of everolimus
- provided new analyses reflecting longer follow-up data on overall survival from BOLERO-2
- revised the approaches for extrapolating progression-free survival and overall survival in the economic model
- addressed the committee's preferred assumptions (see sections 4.15, 4.16, 4.17, 4.21, 4.22 and 4.23)
- used up-to-date unit cost data.

The committee also considered the ERG's critique of the company's reconsideration submission and the ERG's exploratory analyses. The committee was aware that the ERG had corrected an error when implementing the time horizon in the company's economic model.

Extrapolating progression-free survival from BOLERO-2

4.29 The committee noted that the company used progression-free survival based on assessment by a local radiologist, as preferred in the original appraisal (see sections 4.8 and 4.17). It also noted that the company used the same data cut for progression-free survival in its original submission and its reconsideration submission. The committee understood that this was because the data were already mature at the time of the original data cut. However, the committee was aware that the company and ERG used different methods to model the same progression-free survival data in this reconsideration compared with the original appraisal. The committee asked why the company and ERG had chosen to change their methods. The

committee understood that the company now used the function that provided the best statistical fit (log-logistic) rather than the function that was considered the most plausible by the company's clinical advisers (Weibull) and used it to extrapolate, but also to replace, the trial Kaplan–Meier data. The committee considered that the log-logistic function was likely to overestimate the progression-free survival benefits of everolimus plus exemestane compared with exemestane alone beyond the end of BOLERO-2. The committee noted that the ERG took a different approach to modelling progression-free survival by using the Kaplan–Meier data directly from BOLERO-2 and then applying a simple exponential model to both treatment arms from the time when the number of data events from BOLERO-2 was small. The committee heard from the ERG that the trial data and the simple exponential model corresponded closely. The committee agreed that the ERG's approach was reasonable given the maturity of the progression-free survival data and the ERG's preference for using real data when possible. It concluded that it preferred the ERG's method for modelling progression-free survival rather than the company's method.

Extrapolating overall survival from BOLERO-2

4.30 The committee noted that the company had submitted more mature evidence for overall survival in its Cancer Drugs Fund reconsideration submission than it had originally. The committee recognised that new data would mean that the company would revisit the most appropriate method for modelling overall survival. The new data were based on a median follow-up of 39.3 months, by which time 56.6% of patients had died. This compared with the company's original submission based on a median follow-up of 16 months, when 25.1% of patients had

died. Noting that the hazard ratio declined from 0.77 to 0.89 in the analyses, the committee highlighted that the more mature overall survival data suggested everolimus plus exemestane compared with exemestane alone was less clinically effective than it appeared in the company's original submission. The committee recognised that the company fitted a log-logistic function to the curve representing the more mature data to model overall survival. It commented that the company chose the log-logistic function because it considered this to be the best statistical fit. The committee understood that the ERG modelled overall survival differently using a landmark analysis based on the assumption that patients would not gain benefit (increased life expectancy) from everolimus after disease progression and after stopping treatment. The committee agreed that the ERG's approach was reasonable and the landmark method was likely to provide a reasonable approximation of the incremental survival, which reflected BOLERO-2. The committee noted that both the company's and ERG's methods for modelling overall survival had a small effect on the ICER. However, it concluded that it preferred the ERG's method for modelling overall survival rather than the company's method.

End-of-life considerations

4.31 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's final Cancer Drugs Fund technology appraisal process and methods. The committee noted that the company provided a subgroup analysis of people with HER2-negative hormone-receptor-positive tumours randomised to exemestane alone in the SoFEA trial. Median overall survival was less than 24 months. The committee was aware that the mean life expectancy would exceed the median life expectancy. The committee noted that

the median overall survival for people receiving exemestane alone was 26.6 months in BOLERO-2. It was also aware that the company's model had estimated a mean survival of over 30 months. The committee was aware that the ERG's exploratory analyses similarly estimated a mean life expectancy of more than 30 months for exemestane alone. Therefore, the committee agreed with its conclusion in the original technology appraisal that everolimus plus exemestane did not fulfil the short life expectancy criterion for an end-of-life therapy (see section 4.26). It concluded that everolimus plus exemestane did not fulfil the criteria for being a life-extending, end-of-life treatment.

Conclusion

4.32 The committee discussed the most plausible ICER for everolimus plus exemestane compared with exemestane alone. The ICERs including the patient access scheme were considered commercial in confidence in order to protect the level of discount, and cannot be presented here. The committee agreed that the most plausible ICER should be based on the ERG's exploratory analyses to estimate progression-free survival and overall survival and the corrected time horizon. It stated that the availability of more mature evidence from BOLERO-2 resolved considerable clinical uncertainty. However the committee considered that everolimus plus exemestane, with the discount in the revised patient access scheme, did not have plausible potential to be cost effective. Therefore, it could not recommend everolimus for use within the Cancer Drugs Fund or for routine commissioning in the NHS.

Summary of appraisal committee's key conclusions

TAXXX	Appraisal title: Everolimus with exemestane for treating advanced breast cancer after endocrine therapy	Section
Key conclusion: Cancer Drugs Fund reconsideration of TA295		
Everolimus, in combination with exemestane, is not recommended within its marketing authorisation for treating advanced human epidermal growth factor receptor 2 (HER2) negative hormone receptor positive breast cancer in postmenopausal women that has recurred or progressed after a non-steroidal aromatase inhibitor. The committee stated that the availability of more mature evidence from BOLERO-2 resolved considerable clinical uncertainty. However, the committee considered that everolimus plus exemestane, with the discount in the revised patient access scheme, did not have plausible potential to be cost effective. Therefore, it could not recommend everolimus for use within the Cancer Drugs Fund or for routine commissioning in the NHS.		1.1 4.32
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee heard from the patient expert that patients would value everolimus as a treatment option because it is offered when limited treatment options exist after a woman's disease becomes resistant to endocrine therapy, and because everolimus may delay the need for chemotherapy and its associated toxicity. The committee also heard from the patient expert that patients value increased survival and improved quality of life. The clinical experts stated that tamoxifen and exemestane (alone) were appropriate comparators for everolimus plus exemestane, although tamoxifen is often offered after exemestane. The committee concluded that exemestane alone was the most relevant endocrine comparator for everolimus plus exemestane.	4.2 4.6
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee acknowledged that the mechanism of action of everolimus may offer a step change in treatment by restoring sensitivity of the tumour to endocrine therapy.	4.24

What is the position of the treatment in the pathway of care for the condition?	The clinical experts confirmed that everolimus plus exemestane would be offered to patients whose disease has progressed on a non-steroidal aromatase inhibitor at a point when a patient might receive either further endocrine therapy or chemotherapy.	4.4
Adverse reactions	The committee noted that the BOLERO-2 trial showed that patients receiving everolimus plus exemestane experienced more adverse reactions, specifically stomatitis and anaemia, than patients receiving exemestane alone. However, the committee heard that everolimus is generally well tolerated.	4.10
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee discussed the data on clinical effectiveness from BOLERO-2. The committee noted that the company had submitted more mature evidence for overall survival in its Cancer Drugs Fund reconsideration submission than it had originally.	4.7 4.30
Relevance to general clinical practice in the NHS	The committee heard from the clinical experts that the BOLERO-2 trial population represented patients who would be offered everolimus plus exemestane in the UK.	4.7
Uncertainties generated by the evidence	The committee was aware that the company and ERG used different methods to model the same progression-free survival data in this reconsideration compared with the original appraisal.	4.29
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee noted that, although the company included no plans to test for interaction in its statistical analysis plan, it had stated that it had not identified any statistically significant differences in progression-free survival between subgroups.	4.27

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee concluded that everolimus plus exemestane is effective in prolonging progression-free survival compared with exemestane alone. Noting that the hazard ratio declined from 0.77 to 0.89 in the analyses, the committee highlighted that the more mature overall survival data suggested everolimus plus exemestane compared with exemestane alone was less clinically effective than it appeared in the company's original submission.	4.8 4.30
Evidence for cost effectiveness		
Availability and nature of evidence	The committee considered the company's submission for the Cancer Drugs Fund reconsideration that included a revised patient access scheme, provided new analyses reflecting longer follow-up data on overall survival from BOLERO 2, revised the approaches for extrapolating progression-free survival and overall survival in the economic model, addressed the committee's preferred assumptions and used up-to-date unit cost data. The committee also considered the ERG's critique of the company's reconsideration submission and the ERG's exploratory analyses.	4.28
Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee agreed that the most plausible ICER should be based on an analysis using the following assumptions: using exponential functions to estimate progression-free survival; omitting the adjustment factor from Beauchemin et al. (2012); using locally assessed trial data; including adverse reactions; using rates of adverse reactions as documented in the European public assessment report; recalculating time on treatment; including costs of monitoring disease that has not progressed; correcting discounting and utility values for stable disease; using the utility value for 'progressed disease' from Lloyd et al. (2006); and omitting extra mortality from non-cancer causes. The committee agreed that the most plausible ICER should be based on the ERG's exploratory analyses to estimate progression-free survival and overall survival and the corrected time horizon.	4.23 4.32

Incorporation of health-related quality-of-life benefits and utility values 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?	The committee concluded that neither valuation of utility for the 'progressed disease' health state was without uncertainty, but that the data from Lloyd et al. (2006) were more appropriate than the data from Launois et al. (1997). Although the committee acknowledged that the mechanism of action of everolimus may offer a step change in treatment by restoring sensitivity of the tumour to endocrine therapy, it concluded that the company had not submitted convincing evidence that everolimus (plus exemestane) provides health-related quality-of-life benefits exceeding that calculated in the quality-adjusted life year (QALY).	4.20 4.24
Are there specific groups of people for whom the technology is particularly cost effective?	The committee concluded that the available evidence did not allow it to make any recommendations specific to subgroups of patients.	4.27
What are the key drivers of cost effectiveness?	Using local or central assessment for progression-free survival in the modelling: The committee concluded that it was more appropriate to use effectiveness data derived from local assessment in the modelling than from central assessment because local assessment represented the primary end point of the trial, reflected clinical practice and minimised the potential for bias from informative censoring.	4.8 4.17
Most likely cost-effectiveness estimate (given as an ICER)	The ICERs including the patient access scheme were considered commercial in confidence, and cannot be presented here.	4.32
Additional factors taken into account		
Patient access schemes (PPRS)	The company of everolimus has agreed a patient access scheme with the Department of Health.	2
End-of-life considerations	The committee was not convinced that the life expectancy of women to whom everolimus plus exemestane would be offered was convincingly less than 24 months. The committee therefore concluded that everolimus plus exemestane did not fulfil the criteria for an end-of-life therapy.	4.25 4.26, 4.32

Equalities considerations and social value judgements	The only potential issue raised was that everolimus should be available to male patients. However, the UK marketing authorisation includes only postmenopausal women and therefore this issue could not be addressed within the remit of this NICE technology appraisal.	n/a

5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. 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.

Amanda Adler
Chair, TA295 appraisal committee, June 2013 and Cancer Drugs Fund reconsideration of TA295 appraisal committee, July 2016

6 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 an associate director, 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

TA295

Martyn Burke

Technical Lead

Zoe Garrett

Technical Adviser

Jeremy Powell

Project Manager

Cancer Drugs Fund reconsideration of TA295

Janet Robertson

Associate Director

Martyn Burke

Technical Adviser

Jenna Dilkes

Project Manager

ISBN: [to be added at publication]