NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Abemaciclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer

1 Recommendations

1.1 Abemaciclib with an aromatase inhibitor is recommended, within its marketing authorisation, as an option for treating locally advanced or metastatic, hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer as first endocrine-based therapy in adults. Abemaciclib is recommended only if the company provides it according to the commercial arrangement (see section 2).

Why the committee made these recommendations

Palbociclib or ribociclib, taken with an aromatase inhibitor, are usually the first treatments for locally advanced or metastatic, hormone receptor-positive, HER2-negative breast cancer. They are cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors, as is abemaciclib.

Clinical trial evidence shows that abemaciclib with an aromatase inhibitor increases how long people live without their disease getting worse, compared with an aromatase inhibitor alone. It is not known whether abemaciclib increases the length of time people live, because the final trial results are not available yet. Abemaciclib, palbociclib and ribociclib have different side effects, but they all appear to work as well as each other.

Issue date: January 2019

Taking into account the commercial arrangements for all the CDK 4/6 inhibitors, abemaciclib is a cost-effective use of NHS resources and it can be recommended.

2 Information about abemaciclib

Marketing authorisation	Abemaciclib (Verzenios, Eli Lilly) is indicated for 'the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor … as initial endocrine-based therapy… In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.'
Dosage in the marketing authorisation	The recommended dose is 150 mg taken orally, twice daily, alongside treatment with an aromatase inhibitor. Treatment should be continued as long as the patient is having clinical benefit or until unacceptable toxicity occurs. Some adverse reactions may need to be managed by temporary dose reductions, dose interruptions, or permanently stopping the treatment.
Price	£2,950 for a 58 x 150 mg tablets (excluding VAT; MIMS online, accessed December 2018).The company has a commercial arrangement (simple discount patient access scheme). This makes abemaciclib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 6) considered evidence submitted by Eli Lilly and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Current management

Palbociclib and ribociclib, with an aromatase inhibitor, are the appropriate comparators

3.1 The committee was aware that metastatic breast cancer is an incurable condition. First-line treatment for locally advanced or metastatic, hormone receptor-positive, human epidermal growth factor receptor (HER2)-negative breast cancer is usually a cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitor, currently palbociclib or ribociclib, with an aromatase inhibitor (letrozole or anastrozole). The committee noted that since the CDK 4/6 inhibitors have been recommended, not many patients have an aromatase inhibitor alone. If symptoms are severe or the disease is rapidly progressive, then chemotherapy may be needed in the first instance, and tamoxifen can also be offered to some people in line with NICE's clinical guideline on advanced breast cancer. The committee concluded that the company has placed abemaciclib, which is a new CDK 4/6 inhibitor, appropriately in the treatment pathway. Palbociclib and ribociclib, with an aromatase inhibitor, are the appropriate comparators for this appraisal.

Abemaciclib is a further treatment option that may be preferred by some people

3.2 The patient expert stated that staying progression-free for as long as possible is very highly valued by patients and their families. Abemaciclib shows improved progression-free survival when used with an aromatase inhibitor, compared with an aromatase inhibitor alone (see section 3.4). The committee was aware from past appraisals for advanced breast cancer that patients value improvements in progression-free survival, and this was considered important in the palbociclib and ribociclib appraisals. The clinical experts explained that the dosing regimens and adverse-effect profiles of the 3 CDK 4/6 inhibitors differ. Abemaciclib is taken continuously, twice daily. Palbociclib and ribociclib are taken once daily for

21 days, followed by 7 days off-treatment before restarting a new 28-day cycle. Palbociclib is associated with an increased incidence of neutropenia and needs full blood counts during treatment. Ribociclib is also associated with an increased incidence of neutropenia and needs regular electrocardiogram assessments and liver function tests during treatment. Abemaciclib is associated with an increased incidence of diarrhoea. The patient expert highlighted the importance of patients being involved in choosing the most appropriate treatment option, and that people have different attitudes to risks. The committee acknowledged that abemaciclib provides a further treatment option that may be preferred by some people.

Clinical evidence

MONARCH 3 is relevant to NHS practice, but there is no evidence directly comparing abemaciclib with palbociclib and ribociclib

3.3 MONARCH 3 is a double blind, placebo-controlled, randomised trial comparing abemaciclib with placebo (both taken with letrozole or anastrozole). It included 493 postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer who had not had any treatment for advanced disease. The committee noted that the percentage of patients in the trial presenting at the start with advanced or metastatic disease was larger than would be expected in the NHS. The clinical expert stated that this is not a concern because the treatment benefit was large and was seen in all groups of patients included in the trial. The ERG stated that MONARCH 3 is a well conducted trial but a high frequency of diarrhoea with abemaciclib could have led to unblinding. It also noted that, despite some limitations, the population is representative of women with hormone receptor-positive, HER2-negative breast cancer who have not had treatment for advanced disease. There are no trials directly comparing abemaciclib with palbociclib and ribociclib. The committee concluded that the MONARCH 3 population is generalisable to

NHS clinical practice, but noted that the trial evidence does not provide a comparison of abemaciclib with palbociclib and ribociclib.

Abemaciclib improves progression-free survival compared with letrozole or anastrozole alone

3.4 Progression-free survival in MONARCH 3 was assessed by the investigators and by independent review. In the interim investigator-assessed progression-free survival analysis, median progression-free survival was not reached for abemaciclib and was 14.7 months for placebo (hazard ratio 0.54, 95% confidence interval 0.41 to 0.72). Similarly, in the interim independent review, median progression-free survival was not reached for abemaciclib and was 19.2 months for placebo (hazard ratio 0.51, 95% confidence interval 0.36 to 0.72). The final progression-free survival analysis was presented to the committee, but the results are confidential until publication. The ERG raised concerns that the investigator review may not be the most objective outcome measure because of the high incidence of diarrhoea and potential unblinding for abemaciclib. However, it noted that independent-review results are usually more conservative than investigator assessment, which was not the case in MONARCH 3. The committee concluded that abemaciclib with an aromatase inhibitor improves progression-free survival compared with letrozole or anastrozole alone.

It is not known whether abemaciclib improves overall survival

3.5 The overall-survival data from MONARCH 3 are immature. At the interim analysis, overall survival was similar between the treatment groups with 32 (9.8%) deaths in the abemaciclib group and 17 (10.3%) in the placebo group (hazard ratio 0.97, 95% confidence interval not reported). A final overall-survival analysis will be done after 315 events. The committee concluded that there are not enough data to decide whether abemaciclib with an aromatase inhibitor improves overall survival, compared with an aromatase inhibitor alone.

Indirect evidence: network meta-analyses

The results suggest similar efficacy for abemaciclib, palbociclib and ribociclib

3.6 The company did network meta-analyses including 18 studies to compare abemaciclib with palbociclib and ribociclib (each with an aromatase inhibitor). Analyses included progression-free survival (8 studies), overall survival (15 studies) and a number of response rates analyses (10 to 17 studies), but networks were not possible for adverse events, treatment duration and quality of life. The results are confidential but similar treatment effects were shown for all 3 CDK 4/6 inhibitors. The company noted a level of heterogeneity among 4 trials of CDK 4/6 inhibitors with an aromatase inhibitor, compared with an aromatase inhibitor alone (MONARCH 3, MONALEESA 2, PALOMA 1 and PALOMA 2) because of differences in the site of disease and the degree of visceral involvement. It also noted that the overall-survival data are immature in 3 out of the 4 trials (final overall-survival data are available in PALOMA 1 only). The ERG agreed with the company and added that because of reporting limitations a full assessment of clinical heterogeneity is not possible. Therefore the effect of clinical heterogeneity on the results is unknown. It also noted that the proportional-hazards assumption does not hold for all analyses, and that the results need to be interpreted with caution. Despite the limitations and uncertainties of the analyses, the clinical experts considered the results to be plausible. The committee agreed that there are no large differences between the 3 CDK 4/6 inhibitors, although it noted some uncertainty in the treatment-effect estimates. It concluded that no real difference in efficacy has been shown between abemaciclib, palbociclib and ribociclib.

Abemaciclib and other CDK 4/6 inhibitors

It is appropriate to consider that abemaciclib, palbociclib and ribociclib have a class effect

3.7 The clinical experts explained that abemaciclib, palbociclib and ribociclib have similar clinical effectiveness. They consider that the 3 CDK 4/6 inhibitors have a class effect, even though they are not identical. They highlighted that although their clinical effectiveness is similar, the safety profiles differ for the 3 treatments (see sections 3.2). However they each have an acceptable safety profile. The company suggested that some of the differences in the safety profiles (for example, bone marrow suppression rather than gastrointestinal problems) can be explained by differences in the proportions of CDK 4 and CDK 6 inhibitors in the 3 drugs. The committee noted that there is an absence of evidence of a difference in clinical efficacy between the 3 treatments (see section 3.6). It agreed with the clinical experts that based on the evidence available, the 3 treatments are clinically similar. The committee therefore concluded that it is appropriate to consider that the CDK 4/6 inhibitors have a class effect.

The company's economic model

The model is different to those seen in the 2 previous CDK 4/6 inhibitor appraisals

3.8 The company submitted a state-transition model with 2 health states (progression-free survival and post-progression survival on first-line treatment) and death, with a 'fixed pay-off' submodel. The submodel is a separate state-transition model with 2 health states (progression-free survival and post-progression survival) and death, representing health outcomes and costs incurred on second-line and subsequent treatments applied post progression. Calibration is used to adjust the time spent in the submodel to reflect the assumed relationship between progression-free survival and overall survival. The ERG noted that this is a new

approach that explicitly models second-line treatments to reduce uncertainty around overall survival. This approach has similarities, but is not identical, to that used in NICE's technology appraisal guidance on ribociclib. The committee acknowledged that this model differs to those used in the 2 previous CDK 4/6 inhibitor appraisals for the same disease area.

Key issues with assumptions and inputs in the economic model

The ERG's approach to progression-free survival on first-line treatment, pre-progression death, second-line utility, and overall survival on second-line treatment is preferred

3.9 The company estimated progression-free survival on first-line treatment and pre-progression death using the MONARCH 3 data for abemaciclib (with an aromatase inhibitor) and an aromatase inhibitor alone. It used the hazard ratios for palbociclib and ribociclib from the network meta-analyses relative to the aromatase inhibitor data from MONARCH 3. The ERG noted inconsistency in the company's approach and explained that hazard ratios from the network meta-analyses should be used for all 3 treatments (abemaciclib, palbociclib and ribociclib). The committee agreed with the ERG's approach. It also noted that the company's second-line utility value is higher than the first-line value, and it agreed that the ERG's suggested value of 0.69 (as used in NICE's technology appraisal guidance on ribociclib) for progression-free survival on second-line treatment is more plausible. The ERG also critiqued the company's extrapolation of overall survival on second-line treatment using trial data from both MONARCH 2 (exponential distribution) and CONFIRM (Weibull distribution). It presented another scenario extrapolating overall survival on second-line treatment using MONARCH 2 data only (Gompertz distribution). The committee concluded that it preferred the ERG's approach to modelling progression-free survival on first-line treatment, pre-progression death, second-line utility value, and overall survival on second-line treatment.

Model inputs for time on treatment lack plausibility

3.10 Networks for treatment duration were not available, so MONARCH 3 data were used for abemaciclib (with an aromatase inhibitor) and an aromatase inhibitor alone. Data from the summary of product characteristics were used for palbociclib and ribociclib. The ERG questioned the large difference in the time on treatment for the 3 CDK 4/6 inhibitors (the results are confidential). The clinical experts agreed with the ERG and noted that progression-free survival and treatment duration should be similar. The company was not able to explain the difference in treatment duration. The committee acknowledged that the difference in the modelled time on treatment is unexplained and highly uncertain. It noted that it would be difficult to explain how abemaciclib could produce a similar clinical effect with a shorter time on treatment than palbociclib and ribociclib. The committee concluded that there is no reason to expect a difference in treatment duration between the 3 CDK 4/6 inhibitors.

Cost-effectiveness results

A cost-comparison approach is preferred

3.11 The company presented results using list prices for abemaciclib, palbociclib and ribociclib. The company's deterministic results show that abemaciclib is the cheapest treatment with the highest quality-adjusted life years (QALYs) gained (abemaciclib dominating ribociclib and palbociclib; that is, costs less and works better). The ERG's preferred base case also uses the list prices for all the CDK 4/6 inhibitors but with different assumptions (see section 3.9), and it too shows abemaciclib dominating ribociclib and palbociclib. The results using patient access schemes for all 3 CDK 4/6 inhibitors are confidential. The committee noted that the differences in QALYs between the CDK 4/6 inhibitors are very small, and that the QALY-based ranking of the treatments changes across the company's and ERG's scenario analyses. The committee also recalled that the models use different treatment durations for the 3 CDK 4/6

inhibitors, which it does not consider plausible (see section 3.10). The committee noted that there is no evidence of a difference between the 3 treatments (see section 3.6) and that it is appropriate to consider a class effect for the CDK 4/6 inhibitors (see section 3.7). It concluded that, assuming the clinical effectiveness of abemaciclib, palbociclib and ribociclib is comparable, a cost-comparison approach is preferred.

Abemaciclib with an aromatase inhibitor is a cost-effective use of NHS resources and is recommended for locally advanced or metastatic, hormone receptor-positive, HER2-negative breast cancer

3.12 In response to consultation, consultees and commentators agreed that it is appropriate to consider the 3 CDK 4/6 inhibitors as a class, and therefore the costs associated with the treatments can be compared directly. In response to the consultation document, the company increased the discount in their patient access scheme. Using the company's model and the committees preferred assumptions (see section 3.9), and assuming the same treatment duration for all 3 CDK 4/6 inhibitors (see section 3.10), the ERG calculated the total cost of treatment with abemaciclib, ribociclib and palbociclib using the confidential patient access schemes for all 3 CDK 4/6 inhibitors. The committee concluded that abemaciclib with an aromatase inhibitor is a cost-effective use of NHS resources and it can be recommended as an option for treating hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer.

4 Implementation

4.1 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.

4.2 The Welsh ministers have 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 2 months of the first publication of the final appraisal document.

4.3 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 locally advanced or metastatic, hormone receptor-positive, HER2-negative breast cancer previously untreated in the advanced setting and the doctor responsible for their care thinks that abemaciclib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review by the guidance executive 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, appraisal committee
January 2019

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

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

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

NICE project team

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

Marcela Haasova
Technical Lead

Joanna Richardson
Technical Adviser

Thomas Feist
Project Manager

ISBN: [to be added at publication]