NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using abemaciclib 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?

Issue date: October 2018

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 document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using abemaciclib 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: 8 November 2018

Second appraisal committee meeting: 15 November 2018

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Abemaciclib with an aromatase inhibitor is not recommended, within its anticipated 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.

1.2 This recommendation is not intended to affect treatment with abemaciclib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

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

Clinical trial evidence shows that abemaciclib plus 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. However, taking into account the patient access schemes for all CDK 4/6 inhibitors, abemaciclib is not considered to be a cost-effective use of NHS resources and is not recommended.

2 Information about abemaciclib

Anticipated 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.' In July 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product abemaciclib intended for the treatment of locally advanced or metastatic breast cancer.
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	The price is confidential. The company has a commercial arrangement, which would apply if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 5) 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, 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 now begin treatment with an aromatase inhibitor alone. If symptoms are severe or the disease is rapidly progressive then chemotherapy may be needed first-line, 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 for more details). 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 requires full blood counts during treatment. Ribociclib is also associated with an increased incidence of neutropenia and requires regular electrocardiogram assessments and liver function tests during treatment. Abemaciclib is associated with an increased incidence of diarrhoea (see section 3.7). 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 de novo 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 insufficient 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 but there is a high level of uncertainty

3.6 The company did network meta-analyses with 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 response rates (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 impact 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 a high level of uncertainty in the treatment-effect estimates. It concluded that that there is no real difference in efficacy for abemaciclib, palbociclib and ribociclib.

Adverse events

Abemaciclib has an acceptable adverse-effects profile

3.7 In MONARCH 3 abemaciclib was associated with an increased incidence of diarrhoea, infections, neutropenia, fatigue, nausea, anaemia, abdominal pain and vomiting. Diarrhoea was experienced by most patients, however it was controlled with medications and only a small proportion of patients needed dose interruptions. The clinical experts noted that adverse events are more common when starting treatment, and are usually resolved with dose reductions and interruptions. The clinical and patient experts stated that although there are side effects for all the CDK 4/6 inhibitors these are generally managed quite easily, and overall

these drugs are well tolerated. The committee acknowledged the risks associated with abemaciclib and concluded that it has an acceptable adverse-effect profile.

Abemaciclib and other CDK 4/6 inhibitors

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

3.8 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 section 3.2 and section 3.7). 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. With regard to clinical efficacy, the committee noted that there is an absence of evidence of a difference 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

3.9 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 the ribociclib appraisal. 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

3.10 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 the ribociclib appraisal) 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 prefers 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 are highly uncertain

3.11 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 the results of the network meta-analyses are also highly uncertain (see section 3.6) and concluded that there is high uncertainty in the clinical inputs for first-line treatment. The committee concluded that there is no reason to suspect a difference in treatment duration between the 3 CDK 4/6 inhibitors.

Cost-effectiveness estimates

Results are uncertain and not suitable for decision making

3.12 The company presented results using list prices for all 3 treatments. 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). The ERG's preferred base case also uses the list prices for all the CDK 4/6 inhibitors but with different assumptions (see section 3.10), and it too shows abemaciclib dominating ribociclib and palbociclib. However, in the ERG's and the company's base-case analyses using the patient access schemes for all 3 CDK 4/6 inhibitors, the incremental cost-effectiveness ratios (ICERs) for abemaciclib are significantly higher than £30,000 per QALY gained. The

ICERs are confidential because of patient access schemes for all 3 CDK 4/6 inhibitors. 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 3.11). It concluded that the cost-effectiveness results are uncertain and not suitable for decision making.

Cost comparison

A cost-comparison approach is preferred

3.13 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 3.8). The committee recalled that uncertainty in the model inputs makes the cost-effectiveness results uncertain (see sections 3.9 to 3.11). It concluded that, assuming the clinical effectiveness of abemaciclib, palbociclib and ribociclib is comparable, a cost-comparison approach is preferred.

Conclusion

Abemaciclib with an aromatase inhibitor cannot be recommended for locally advanced or metastatic, hormone receptor-positive, HER2-negative breast cancer

3.14 The committee agreed that it is appropriate to consider the 3 CDK 4/6 inhibitors as a class and that a cost-comparison approach is preferred. It noted that the cost-effectiveness results show that treatment with abemaciclib is not a cost-effective use of NHS resources. Therefore, it concluded that abemaciclib cannot be recommended in routine commissioning as first endocrine-based therapy for locally advanced or metastatic, hormone receptor-positive, HER2-negative breast cancer.

4 Proposed date for review of guidance

4.1 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.

Jane Adam
Chair, appraisal committee
October 2018

5 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

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