NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Palbociclib with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using palbociclib 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 palbociclib 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: 24 February 2017

Second appraisal committee meeting: 6 April 2017

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

1 Recommendations

1.1 Palbociclib in combination with an aromatase inhibitor is not recommended for treating hormone receptor-positive, human epidermal growth factor receptor 2-negative, locally advanced or metastatic breast cancer in adults.

1.2 This guidance is not intended to affect the position of patients whose treatment with palbociclib in combination with an aromatase inhibitor 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	Palbociclib (Ibrance, Pfizer) is a selective, small-molecule inhibitor of cyclin-dependent kinases 4 and 6, which prevents DNA synthesis by stopping cell cycle progression from the G1 to S phase.
Marketing authorisation	Palbociclib is indicated for treating 'hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer: • in combination with an aromatase inhibitor; • in combination with fulvestrant in women who have received prior endocrine therapy' 'In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone releasing hormone (LHRH) agonist.' This appraisal only considers the use of palbociclib in combination with an aromatase inhibitor.
Adverse reactions	The most common (20% or more) adverse reactions of any grade reported in patients having palbociclib in randomised clinical studies were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anaemia, alopecia, and diarrhoea. The most common (2% or more) adverse reactions of Grade 3 or over to palbociclib were neutropenia, leukopenia, anaemia, fatigue, and infections. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	The recommended dose is 125 mg of palbociclib, taken orally, once daily for 21 consecutive days followed by 7 days off treatment (Schedule 3/1) to make up a complete cycle of 28 days. Treatment with palbociclib should be continued as long as the patient is having a clinical benefit from therapy or until unacceptable toxicity occurs. Some adverse reactions may need to be managed by temporary dose interruptions or delays, dose reductions, or permanently stopping the treatment. For full details of dose reduction schedules, see the summary of product characteristics.
Price	£2,950 for a 21-capsule pack of 125-mg capsules (excluding VAT; MIMS online, accessed January 2017). Costs may vary in different settings because of negotiated procurement discounts.

3 Evidence

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

4 Committee discussion

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

Clinical management

4.1 The committee was aware that metastatic breast cancer is an incurable condition. First-line treatment for people with metastatic hormone receptor-positive and HER2-negative breast cancer is usually endocrine therapy, but if the symptoms are severe, or the disease is rapidly progressive, people usually have chemotherapy. The committee noted that the marketing authorisation for palbociclib specifies that it is used in combination with an aromatase inhibitor. It discussed the company submission and the evidence from the clinical trials, which investigated palbociclib in combination with letrozole compared with letrozole alone. The committee heard from the clinical experts that in clinical practice the available aromatase inhibitors are essentially interchangeable, because they have similar clinical effectiveness and acquisition costs. The committee also heard that palbociclib in combination with an aromatase inhibitor would be used for people who have not had previous treatment for metastatic breast cancer, and that when the disease progressed most people would then have several lines of further therapy. The committee

concluded that the company submission had palbocilib appropriately placed in the treatment pathway.

Patient experience

4.2 The committee heard from the patient and clinical experts that quality of life is much lower for people whose disease is treated with chemotherapy than with endocrine therapy, because of the side effects of chemotherapy. Endocrine therapies were therefore preferred when possible. Palbociclib, by increasing the effect of aromatase inhibitors, may reduce the number of people who need first-line chemotherapy, and delay such treatment in others. It heard from the patient expert that staying in a progression-free state for as long as possible and being able to continue with normal activities, including working, is very highly valued by patients and their families, and this benefit should not be underestimated. The committee concluded that an important consideration for people who are having treatment is delaying the time to chemotherapy.

Clinical effectiveness

Clinical trial evidence

4.3 The committee noted that the clinical-effectiveness evidence for palbociclib plus letrozole compared with letrozole alone came from 2 studies, PALOMA-1 and PALOMA-2. PALOMA-2 was a larger (666 patients) double-blind trial, and PALOMA-1 was a smaller (165 patients) open-label study. The committee discussed the generalisability of the PALOMA trials to UK clinical practice. It noted that the PALOMA-1 trial contained no UK patients, but 7 of the PALOMA-2 sites were in the UK. The committee heard from the clinical experts that both trials had a greater proportion of people with metastatic disease when first diagnosed than is seen in UK practice (37% in the PALOMA-2 trial compared with about 5% to 10% in UK clinical practice). The committee noted that there was no significant difference in treatment

response for people with metastatic disease at first diagnosis and were reassured by the clinical experts that a difference would not be expected. The committee agreed that the populations in both PALOMA trials were similar to the population seen in clinical practice in England, but because the PALOMA-2 trial was a blinded larger trial, considered its results more reliable for decision-making. The committee raised concerns that the higher incidence of haematological adverse events in the palbociclib arms of the trials would have resulted in some patients and investigators becoming unblinded to patient allocation during PALOMA-2. The committee heard that to mitigate this, both investigator-assessed and blinded independent central review (BICR) of progression-free survival was carried out. The committee concluded that the BICR results would be more appropriate for decision-making.

PALOMA-1 progression-free and overall survival data

4.4 The committee noted that in the overall intention-to-treat population, the BICR median progression-free survival was 25.7 months for palbociclib plus letrozole, and 14.8 months for letrozole alone. This was reported as statistically significant when using a one-sided p value (p=0.0286), but not if a two-sided p value had been used. The median overall survival was 37.5 months for palbociclib plus letrozole compared with 33.3 months for letrozole alone, which was not a statistically significant difference. The committee concluded that in PALOMA-1, palbociclib improved progression-free survival, but no significant improvement in overall survival had been shown.

PALOMA-2 progression-free and overall survival data

4.5 The committee noted that in the BICR intention-to-treat population, the median progression-free survival was 30.5 months for palbociclib plus letrozole compared with 19.3 months for letrozole alone (hazard ratio 0.653; confidence interval 0.505 to 0.844). The committee heard from the company that they cannot give overall-survival results from this trial

because the required number of events has not been reached, and the company remains blinded to the results. The committee concluded that in PALOMA-2, palbociclib improved progression-free survival but no data on overall survival are available.

Relationship between progression-free and overall survival

4.6 The committee noted that progression-free survival benefits were seen in both trials but no significant benefit was seen in PALOMA-1 for overall survival. It considered that a wider confidence interval is to be expected with the small sample in PALOMA-1, and noted that the overall-survival results are still immature. The clinical experts indicated that they would expect an improved progression-free survival with metastatic breast cancer to have some benefit on overall survival. However, they judged that the situation was complex and difficult to predict because of the number of further lines of treatment that the person would have, and the precise relationship is unclear The committee concluded that palbociclib had a clear and important benefit for improving progression-free survival, and that it was likely that this would result in some improvement in overall survival. However, the size of benefit remained uncertain.

Adverse effects of palbociclib

4.7 The committee noted that the trial evidence suggested a high incidence of haematological adverse events. The committee was aware that the marketing authorisation states that full blood counts must be done during treatment, so extra visits may be needed for monitoring. However, it heard from the clinical and patient experts that the adverse events are reversible and manageable. The committee concluded that, although the incidence was high, the adverse events seemed manageable.

Cost effectiveness

4.8 The committee discussed the cost-effectiveness evidence presented by the company and its critique by the ERG. It accepted the structure of the

economic model developed by the company and considered it appropriate for decision-making.

Data sources in the model

4.9 The committee noted that the company had used overall survival from PALOMA-1, because this is the only source available, but used progression-free survival data from PALOMA-2. It heard from the ERG that they considered the mixing of the 2 data sets to be methodologically flawed, because it implicitly assumed that progression-free survival and overall survival were independent of one another. Therefore, the ERG preferred to use the PALOMA-1 time-to-event data throughout. The committee acknowledged the methodological limitations but recalled that it considered PALOMA-2 to be the more reliable source of clinical data (see section 4.3). The committee was unable to judge whether it is more appropriate to mix PALOMA-1 and PALOMA-2 data or to use PALOMA-1 throughout. It therefore decided to consider the cost-effectiveness results from both approaches.

Modelling progression-free survival

4.10 The ERG highlighted that the company used a Weibull extrapolation for progression-free survival which produced results indicating that the longer a patient remains progression free, the more likely they are to progress or die than they were previously. The ERG considered this to be implausible and that it would be more appropriate to use the available time-to-event data before switching to an extrapolated model. The ERG's model resulted in a mean progression-free survival gain of 13.3 months using the PALOMA-1 data or 11.5 months using the PALOMA-2 data compared with 10.7 months in the company's model. The committee concluded that despite the very differing approaches, these estimates were not very different.

Modelling overall survival

4.11 For modelling overall survival, the company tried to reconcile the overall survival gain from PALOMA-1 with the modelled median progression-free survival gain from PALOMA-2. The company adjusted the curve of the palbococlib arm so that the median gain for overall survival was the same as the median gain for progression-free survival in PALOMA-2. The ERG's preferred method is to use only the PALOMA-1 data and this resulted in a mean overall-survival gain of 6.6 months compared with a gain of 11.2 months in the company model. The committee recalled that the relationship between progression-free and overall survival was complex and difficult to predict, but that palbociclib would be expected to improve overall survival. The committee therefore concluded it was plausible that the overall survival gain is within the range of estimates made by the ERG and the company.

Incremental cost-effectiveness results

4.12 It noted that the company's base-case incremental cost-effectiveness ratio (ICER) is £150,869 per quality adjusted life year (QALY) gained. Despite the very different methods used by ERG for modelling cost effectiveness, including using PALOMA-1 data alone, and implementing 10 changes in total, the ERG's revised base-case ICER was not very different at £132,872 per QALY gained. The ERG also did a scenario analysis using the available PALOMA-2 data, which resulted in an ICER of £213,206 per QALY gained. The committee judged that all the ICERs presented were considerably above the range usually considered to be a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Company's scenario analyses

4.13 The committee noted that the company had submitted several scenario analyses, some of which reduced the ICER for palbociclib. The committee noted that for palbociclib to fall within the range considered to be a cost-

effective use of NHS resources it would need a scenario that included all 4 of the following assumptions:

- the comparator had the same acquisition costs as palbociclib
- palbociclib resulted in an overall-survival gain of 24 months
- the utility value of the pre-progression state was increased by 0.1
- no post-progression costs were included.

The committee considered each of these assumptions in turn.

Acquisition cost of comparator

4.14 The committee discussed the company's suggestion that they assume that the comparator had the same cost to the NHS as palbociclib. This assumption would reduce the base-case ICER by £97,795 per QALY gained. The company stated that it had explored this scenario because palbociclib is an add-on therapy, which means that all of the drug acquisition costs contribute to the incremental costs. The committee was aware that its remit was to consider costs from a current NHS and personal social services perspective, and it could not calculate cost effectiveness based on a hypothetical more expensive comparator than is used in current NHS practice. The committee concluded that the assumption of a higher cost for the comparator treatment was not appropriate and could not be considered.

Overall-survival gain of 24 months

4.15 The committee noted that the progression-free survival gain in the trials was 10 months, and that the company's base case calculated an overall-survival gain of 11.2 months. Given the unclear relationship between progression-free and overall survival, and that no overall-survival benefit had been shown in the PALOMA-1 trial, the committee concluded that an overall-survival gain of 24 months was both much higher than modelled by the company, and not clinically plausible.

Increased utility value of 0.1 in the pre-progression state

4.16 The committee then discussed the company's assumption of an increased utility value in the pre-progression state by 0.1 for both the group having pabloclicib plus letrozole and the group having letrozole alone. The company stated that the progression-free-survival state is consistently undervalued in health technology appraisals, and that people place a greater value on staying in a progression-free state and not progressing to further lines of therapy than is captured in the EQ-5D questionnaire. The committee agreed that it had heard that there is a strong preference for people wanting to delay starting chemotherapy (see section 4.2). It noted that because the EQ-5D measures the health state of people at points in time, it may not fully capture a person's preference to avoid future events. However, the committee noted that the company's utility values were based on data collected in PALOMA-2, and were in line with those used in other appraisals. Moreover, having disagreed with the company's first 2 scenarios, the committee concluded that including such a change would not reduce the ICER to a level considered cost effective.

No post-progression costs

4.17 This scenario has a large effect when combined with the clinically implausible overall-survival scenario (see section 4.15), but because it results in only a small reduction in the base-case ICER of £566 per QALY gained, the committee did not consider it further.

Conclusion

4.18 The committee concluded that all plausible ICERs presented were considerably above the level that could be considered to be a cost-effective use of NHS resources, and therefore the committee could not recommend palbociclib for treating hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer in adults in combination with an aromatase inhibitor for routine commissioning.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

4.19 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: Palbociclib with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer**	**Section**
Key conclusion		
Palbociclib in combination with an aromatase inhibitor is not recommended for treating hormone receptor positive, human epidermal growth factor receptor 2-negative, locally advanced or metastatic breast cancer in adults. The committee concluded that all plausible ICERs presented were considerably above the level that could be considered to be a cost-effective use of NHS resources.		1.1 4.18
Current practice		
Clinical need of patients, including	First-line treatment for people with metastatic hormone receptor-positive and HER2-	4.1

the availability of alternative treatments	negative breast cancer is usually endocrine therapy, but if the effects of the disease are too difficult for the person or the disease is rapidly progressive, people usually have chemotherapy. An important consideration for people who are having treatment is delaying the time to chemotherapy.	4.2
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?	Palbociclib, by increasing the effect of aromatase inhibitors, may reduce the number of people who need first-line chemotherapy, and delay such treatment in others.	4.2
What is the position of the treatment in the pathway of care for the condition?	Palbociclib, in combination with an aromatase, inhibitor would be a first-line treatment for people with metastatic hormone receptor-positive and HER2-negative breast cancer	4.1
Adverse reactions	Although the incidence was high, the adverse events seemed manageable.	4.7
Evidence for clinical effectiveness		

Availability, nature and quality of evidence	Clinical-effectiveness evidence for palbociclib plus letrozole compared with letrozole alone came from 2 studies, PALOMA-1 and PALOMA-2. Because the PALOMA-2 trial was a blinded larger trial, the committee considered its results more reliable for decision-making.	4.3
Relevance to general clinical practice in the NHS	The relevance to general clinical practice was not raised during this appraisal.	-
Uncertainties generated by the evidence	Data from the trials showed that palbociclib improved progression-free survival, but no significant improvement in overall survival had been shown. An improved progression-free survival with metastatic breast cancer would be expected to have some benefit on overall survival. However, the size of benefit remained uncertain.	4.4–4.6
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No specific groups of people were presented for whom the technology is particularly clinically effective.	-

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee concluded that palbociclib had a clear and important benefit for improving progression-free survival, and that it was likely that this would result in some improvement in overall survival. However, the size of benefit remained uncertain.	4.6
Evidence for cost effectiveness		
Availability and nature of evidence	It accepted the structure of the economic model developed by the company and considered it appropriate for decision-making.	4.8
Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee were unable to judge whether it is more appropriate to mix PALOMA 1 and PALOMA 2 data or to use PALOMA 1 throughout. It therefore decided to consider the cost-effectiveness results from both approaches. The company used a Weibull extrapolation for progression-free survival which produced results indicating that the longer a patient remains progression free, the more likely they are to progress or die than they were previously. The ERG considered this to be implausible and that it would be more appropriate to use the available time-to-event data before switching to an extrapolated model. The committee concluded that despite the very differing approaches, the estimates were much the same.	4.9 4.10

	For modelling overall survival, the company tried to reconcile overall survival from PALOMA-1 with the modelled median progression-free survival from PALOMA-2, whereas the ERG's preferred method is to use the PALOMA-1 data, which reduces the overall-survival gain. The committee considered that the relationship between progression-free and overall survival was complex and difficult to predict, and that it was plausible that the overall survival gain is within the range of estimates made by the ERG and the company.	4.11
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 company stated that the progression-free-survival state is consistently undervalued in health technology appraisals, and that people place a greater value on staying in a progression-free state and not progressing to further lines of therapy than is captured in the EQ 5D questionnaire. The committee noted that the company's utility values were based on data collected in PALOMA-2, and were in line with those used in other appraisals.	4.16

Are there specific groups of people for whom the technology is particularly cost effective?	No specific groups of people were presented for whom the technology is particularly cost effective.	-
What are the key drivers of cost effectiveness?	The acquisition cost of the drugs and the use of PALOMA-1 or PALOMA-2 progression-free survival data were the key drivers of the cost-effectiveness results.	4.12, 4.14
Most likely cost-effectiveness estimate (given as an ICER)	The committee concluded that all plausible ICERs presented were considerably above the level that could be considered to be a cost-effective use of NHS resources.	4.18
Additional factors taken into account		
Patient access schemes (PPRS)	The company did not submit a patient access scheme.	-
End-of-life considerations	No end-of-life considerations were raised during the appraisal.	-
Equalities considerations and social value judgements	No equality issues were raised during the appraisal.	-

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.

Jane Adam
Chair, appraisal committee
January 2017

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.

Thomas Strong

Technical Lead

Joanna Richardson

Technical Adviser

Liv Gualda

Project Manager

ISBN: [to be added at publication]