7 June 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

**ADVICE**: following a full submission considered under the end of life and orphan equivalent assessment process.

**palbociclib (Ibrance®)** is accepted for use within NHSScotland.

**Indication under review**: for the treatment of 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 submission relates to use in combination with fulvestrant in women who have received prior endocrine therapy.

In a phase III study palbociclib plus fulvestrant, compared with fulvestrant, prolonged progression-free survival in women with HR-positive HER2-negative locally advanced or metastatic breast cancer who had received prior endocrine therapy.

This SMC advice takes account of the benefits of Patient Access Schemes (PAS) that improve the cost-effectiveness of palbociclib and fulvestrant. This advice is contingent upon the continuing availability of these PAS in NHSScotland or list prices that are equivalent or lower.
This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

SMC has previously accepted palbociclib for restricted use in combination with an aromatase inhibitor for first-line treatment of HR-positive HER2-negative locally advanced or metastatic breast cancer (SMC 1276/17). This advice remains valid.

Chairman
Scottish Medicines Consortium
**Indication**

For the treatment of 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.¹

**Dosing Information**

The recommended dose is 125mg of palbociclib orally once daily for 21 consecutive days followed by seven days off treatment to comprise a complete cycle of 28 days. The capsule should be swallowed whole and taken with food. The treatment with palbociclib should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

When co-administered with palbociclib, the recommended dose of fulvestrant is 500mg intramuscular (IM) injection on Days 1, 15, 29, and once monthly thereafter. Treatment of pre / peri-menopausal women with the combination of palbociclib plus fulvestrant, should always be combined with a LHRH agonist.

Dose modification of palbociclib is recommended based on individual safety and tolerability. Management of some adverse reactions may require temporary dose interruptions / delays, and / or dose reductions, or permanent discontinuation as per dose reduction schedules.

Complete blood count should be monitored prior to the start of palbociclib therapy and at the beginning of each cycle, as well as on day 15 of the first two cycles, and as clinically indicated.

Treatment with palbociclib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products. See summary of product characteristics for details.¹

**Product availability date**

9 November 2016

Palbociclib meets SMC orphan equivalent and end of life criteria for this indication.

**Summary of evidence on comparative efficacy**

Palbociclib is a cyclin-dependent kinase (CDK) 4 and 6 inhibitor that reduces cellular proliferation by blocking progression of the cell from G1 into S phase of the cell cycle. It is licensed for HR-positive, HER2-negative locally advanced or metastatic breast cancer: (1) in combination with an aromatase inhibitor; and (2) in combination with fulvestrant in women who have received prior endocrine therapy.¹ Palbociclib in combination with an aromatase inhibitor is already accepted for restricted use. In this submission, the company has requested that SMC considers palbociclib for use in combination with fulvestrant in women who have received prior endocrine therapy.
A double-blind phase III study (PALOMA-3) recruited 521 women with HR-positive, HER2-negative metastatic or locally advanced breast cancer that was not amenable to resection or radiotherapy with curative intent and had progressed during or within 12 months of adjuvant endocrine therapy (aromatase inhibitor in postmenopausal women or tamoxifen in pre- or peri-menopausal women) or had progressed on or within one month of endocrine treatment for metastatic or advanced disease. One previous line of chemotherapy was permitted in addition to endocrine therapy for metastatic or advanced disease. Patients had measurable disease on Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 or bone only disease, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate organ and marrow function and resolution of toxic effects from previous therapy or surgical procedures. Randomisation was stratified by sensitivity to prior endocrine therapy (yes versus no), menopausal status (pre- or peri-menopausal versus postmenopausal) and presence of visceral metastases (yes versus no). Patients were assigned in a 2:1 ratio to palbociclib 125mg orally once daily for first 21 days of each 28-day cycle or placebo and treatment continued until disease progression, unacceptable toxicity or withdrawal of consent. All patients received fulvestrant 500mg IM injection on days 1 and 15 of the first 28-day cycle and on day 1 of each subsequent 28-day cycle. Pre- and peri-menopausal women received the LHRH agonist, goserelin, from at least four weeks before randomisation and continued through the study. The primary outcome, investigator-assessed progression-free survival (PFS) according to RECIST version 1.1, was evaluated in the intention-to-treat (ITT) population, which comprised all randomised patients. Addition of palbociclib to fulvestrant, compared with fulvestrant, significantly prolonged PFS at the first interim analysis, data cut-off date 5 December 2014 (median follow-up 5.6 months), where the pre-specified efficacy stopping boundary (α=0.00135) was crossed and also at subsequent updated analyses at cut-off dates 16 March 2015 and 23 October 2015. At the final analysis of overall survival (OS), (cut-off date 13 April 2018) after a median follow-up of 44.8 months, data were 60% mature. Median OS was longer in the palbociclib plus fulvestrant group, but the difference was not statistically significant. These results are detailed in Table 1 below.

Table 1: Primary and secondary outcomes of PALOMA-3 study.

<table>
<thead>
<tr>
<th></th>
<th>Palbociclib</th>
<th>Placebo</th>
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<tbody>
<tr>
<td><strong>Progression-free survival (PFS) investigator-assessed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data cut-off 5.12.14 First interim analysis of PFS</td>
<td>Events 29% (102/347)</td>
<td>53% (93/174)</td>
</tr>
<tr>
<td></td>
<td>Median (months)</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>0.42 (0.32 to 0.56), p&lt;0.001</td>
</tr>
<tr>
<td>Data cut-off 23.10.15 Updated analysis of PFS</td>
<td>Events 58% (200/347)</td>
<td>76% (133/174)</td>
</tr>
<tr>
<td></td>
<td>Median (months)</td>
<td>11.2</td>
</tr>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>0.50 (0.40 to 0.62), p&lt;0.001</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td>Events 58% (201/347)</td>
<td>63% (109/174)</td>
</tr>
<tr>
<td>Data cut-off 13.4.18</td>
<td>Median (months)</td>
<td>34.9</td>
</tr>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>0.81 (0.64 to 1.03), p=0.09</td>
</tr>
<tr>
<td><strong>Objective response rate</strong></td>
<td></td>
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</tbody>
</table>
Quality of life was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life core-30 (QLQ-C30) and EuroQol EQ-5D (3-level) questionnaires at 5 December 2014 cut-off. The European Medicines Agency (EMA) noted that there was no strategy to account for multiplicity. Also, the results indicated emotional functioning as a driver for overall health related quality-of-life. Unblinding due to the effects of palbociclib on the bone marrow could potentially be associated with hope regarding the benefit of the experimental compound. Therefore the EMA concluded that claims concerning global health status and quality of life were not accepted. However, it was noted that time-to-deterioration in pain from baseline to first increase of ≥10 points in pain symptom score was significantly prolonged with palbociclib and fulvestrant, compared with fulvestrant: median 8.0 versus 2.8 months; hazard ratio of 0.64 [95% CI: 0.49 to 0.85]; p<0.001).

### Summary of evidence on comparative safety

The EMA review noted that the addition of palbociclib to fulvestrant does not appear to give rise to any concerns regarding heightened safety issues from fulvestrant. However, it was associated with a substantial increase in myelosuppression, mainly neutropenia which led to a high proportion of patients undergoing temporary dose interruptions, delays and reductions. Only a small number of patients permanently discontinued study treatment and it was considered that myelosuppression can be effectively managed.

In the PALOMA-3 study at 31 July 2015 data cut-off within the palbociclib plus fulvestrant group and the fulvestrant group, 98% (337/345) and 89% (153/172) of patients had an adverse event, which were grade 3 or 4 in 70% and 18%, serious in 9.6% and 14% and led to study discontinuation in 0.6% and 1.7% of patients, respectively. There were similar rates of discontinuation of fulvestrant, 3.2% and 2.9% and of palbociclib/placebo, 3.8% and 4.1%, in the respective groups. Rates of temporary discontinuation of palbociclib/placebo were higher in the palbociclib group, compared with placebo: 65% versus 8.1%, as were rates of temporary discontinuation of fulvestrant, 24% versus 3.5%. There were also more dose reductions of palbociclib/placebo in the palbociclib group, 31% versus 1.7%, respectively. Most temporary discontinuations of palbociclib were due to reductions in white cells.

Adverse events reported more frequently in the palbociclib plus fulvestrant group, compared with the fulvestrant group, included reductions in blood counts: neutropenia (66% versus 2.3%), white blood cell reduction (29% versus 4.1%), anaemia (29% versus 13%), leucopenia (26% versus 1.2%), neutrophil count decreased (23% versus 1.7%), thrombocytopenia (13% versus 0) and platelet count decreased (10% versus 0). Others were fatigue (41% versus 29%), headache (26% versus 20%), nausea (34% versus 28%), diarrhoea (24% versus 19%), constipation (20% versus 16%).
cough (19% versus 13%), alopecia (18% versus 6.4%), decreased appetite (16% versus 8.1%), dyspnoea (13% versus 8.7%), nasopharyngitis (13% versus 8.1%) stomatitis (13% versus 2.9%), pyrexia (13% versus 5.2%), oropharyngeal pain (12% versus 7.0%), insomnia (11% versus 8.1%) and rash (11% versus 5.2%), respectively.²

Summary of clinical effectiveness issues

Palbociclib was the first CDK4/6 inhibitor licensed for treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer. In addition to palbociclib, there are now two other CDK4/6 inhibitors marketed in the UK, ribociclib and abemaciclib. These are indicated for the treatment of women with HR-positive, HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy. In pre- or perimenopausal women the endocrine therapy should be combined with a LHRH agonist.⁷,⁸ As these medicines are recently licensed they do not fall within the timeframe to be eligible as comparators within this submission.

A consensus guideline was published in 2018 by the European School of Oncology (ESO) and the European Society for Medical Oncology (ESMO). The guidance recommends that for oestrogen receptor (ER)-positive HER2-negative advanced breast cancer pre-menopausal women should have adequate ovarian function suppression or ovarian function ablation and should then be treated in line with post-menopausal women. For patients with ER-positive HER2-negative advanced breast cancer the preferred first line treatment is endocrine therapy, unless there is visceral crisis or endocrine resistance. Type of previous adjuvant endocrine therapy, response and time lapsed from end of therapy guide the choice of endocrine therapy in advanced disease. The guideline notes that the optimal sequence of endocrine-based therapy is uncertain. Options include: monotherapy with aromatase inhibitors (exemestane, letrozole, anastrozole), tamoxifen (which has anti-oestrogen effects) or fulvestrant (oestrogen receptor antagonist); CDK4/6 inhibitor in combination with an aromatase inhibitor or with fulvestrant; and everolimus (a mammalian target of rapamycin [mTOR] inhibitor) in combination with an aromatase inhibitor or tamoxifen or fulvestrant.¹⁰

Clinical experts consulted by SMC advise that women with advanced breast cancer that has progressed on endocrine therapy have a variety of treatment options. For women with higher volume disease and/or a shorter disease-free interval chemotherapy may be considered (most commonly capecitabine or weekly paclitaxel). For patients with lower volume disease second-line endocrine therapy (such as aromatase inhibitor monotherapy) may be considered. It was noted that patients respond in varying degrees and to varying durations with aromatase inhibitor monotherapy and ultimately may require chemotherapy to control their disease.

In the key PALOMA-3 study, addition of palbociclib to fulvestrant, compared with fulvestrant alone, increased PFS and OS, although the latter result was not statistically significant, with hazard ratio of 0.50 and 0.81 for the respective outcomes.²,⁶ The PFS data were available during the EMA review and were considered clinically relevant.² It is possible that anti-cancer medicines given
after disease progression may have confounded the analyses of OS. Fewer patients in the palbociclib plus fulvestrant group, compared with the fulvestrant group, received a CDK4/6 inhibitor after disease progression, 4% (14/347) versus 17% (30/174).  

Subgroup analysis suggests that the addition of palbociclib to fulvestrant may have less benefit in women with disease that was not sensitive to prior endocrine therapy, i.e. disease that has relapsed or progressed during the first two years of adjuvant therapy or disease that did not respond (defined as complete or partial response or stable disease for at least six months) to endocrine therapy in the advanced setting. In this subgroup, which comprised 21% of the study population, the hazard ratio for PFS was 0.69 (95% CI: 0.43 to 1.09) and for OS was 1.14 (95% CI: 0.71 to 1.84), whereas in women classed as sensitive to endocrine therapy, the hazard ratio for PFS was 0.46 (95% CI: 0.36 to 0.59) and for OS was 0.72 (95% CI: 0.55 to 0.94).  

Subgroup analysis of PFS and OS by age suggests a possibly greater effect in older women. In women aged at least 65 years, who comprised a quarter of the study population, the hazard ratio for PFS was 0.32 (95% CI: 0.20 to 0.51) and for OS was 0.52 (95% CI: 0.33 to 0.82). In remaining three quarters of the study population aged less than 65% the hazard ratio for PFS was 0.59 (95% CI: 0.45 to 0.75) and for OS was 0.91 (95% CI: 0.70 to 1.20). There were significant p-values for interaction for both outcomes.  

Women were excluded from PALOMA-3 if they had advanced or metastatic symptomatic visceral spread causing risk of life-threatening complications or active uncontrolled or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease. Therefore, there were no data for palbociclib plus fulvestrant in these women with more extensive or uncontrolled disease. Also, women were excluded if they had ECOG performance status of at least 2 or unresolved acute toxic effects of prior therapy or surgical procedures. This may limit application of results to women with poorer health.  

Quality of life data were limited by lack of a strategy to handle multiplicity and potential unblinding due to myelosupression. The latter issue may have had an impact on other subjective outcomes such as adverse events.  

Direct comparative data were only available versus fulvestrant, with no direct comparisons to other relevant comparators, such as aromatase inhibitor monotherapy or everolimus (mTOR inhibitor) plus exemestane (aromatase inhibitor).  

To provide comparative data for palbociclib plus fulvestrant versus everolimus plus exemestane an indirect comparison was performed using network meta-analyses (NMA). There were a number of weaknesses in the NMA. The PFS NMA included 20 studies, with 11 for chemotherapies and five for endocrine therapies not relevant to the comparison and not required to link these main comparators. One of the studies linking the main comparators was a small phase II study with unexpected results. The OS NMA included 8 studies. Two of the studies provided OS estimates
based on immature data (i.e. only 14% and 30% of patients had died) with one deriving the estimate (via conversion formula) from an odds ratio for progression or death, which could further limit validity of the data input. There was a potentially relevant study omitted from both NMA that could have addressed some of these issues. Sensitivity analyses were provided to address some of these issues. In both NMA there was some heterogeneity in study design, baseline demographic and disease characteristic and outcomes. The indirect comparison did not address quality-of-life or safety outcomes. Although the company states that the NMA indicate superiority of palbociclib plus fulvestrant versus everolimus plus exemestane, results do not support this and suggest similar PFS and OS.

Clinical experts consulted by SMC consider addition of palbociclib to fulvestrant a therapeutic advance in the treatment of women with HR-positive HER2-negative advanced or metastatic breast cancer previously treated with endocrine therapy. This is due to its effects on PFS and opportunity for benefit in OS. They note that for some women use of palbociclib plus fulvestrant may delay the need to start more toxic chemotherapy. They highlighted that currently some women may not have had the opportunity to receive a CDK4/6 inhibitor in the first-line setting.

### Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of palbociclib, as an end of life and orphan-equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Palbociclib plus fulvestrant, compared with fulvestrant alone, provides an improvement in PFS of about 7 months, which is a substantial benefit for patients with metastatic breast cancer where the life expectancy is just 2 to 3 years. There may also be an opportunity for increased OS with potentially greater benefits in certain subgroups, such as women with sensitivity to prior endocrine therapy.

- Improved PFS provides psychological and practical benefits and in particular it delays the need for chemotherapy, which has a more gruelling treatment schedule and side-effects.

- Benefits are achieved with a manageable side-effect profile and patients receiving palbociclib plus fulvestrant feel generally well with normality in their life, especially during the “week off” treatment (only receiving treatment 21 out of every 28 days).

- There are benefits for a patient’s family and carers associated with increased PFS as they have more high quality time together with the patient.

- There are no additional service requirements associated with the introduction of palbociclib. PACE participants highlighted that in future this regimen may provide an opportunity to move treatment to a local community setting offering potential benefits for patients/carers and the cancer units.
Additional Patient and Carer Involvement

We received a patient group submission from Breast Cancer Care and Breast Cancer Now (a new charity formed from a merger between Breast Cancer Care and Breast Cancer Now), which is a registered charity. In the past two years, Breast Cancer Care has received 0.69% pharmaceutical company funding and Breast Cancer Now has received 10% pharmaceutical company funding in the past two years, both including from the submitting company. A representative from the merged organisation participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing palbociclib in combination with fulvestrant versus fulvestrant monotherapy as treatment for women who have developed resistance to previous endocrine therapy. A separate comparison with everolimus plus exemestane was also presented. In each analysis a standard three-state partitioned survival model was used over a lifetime (40 year) time horizon, with states of progression-free and post-progression, and death. For post-progression the state was sub-divided to accommodate a first and second subsequently line of therapy, prior to best supportive care. For the primary comparison with fulvestrant, parametric functions were fitted independently to each arm of the PALOMA-3 study for PFS and OS, with treatment duration represented by Kaplan-Meier data.6,11

The economic analysis is based on the latest data cut-off (October 2015) for PFS and a planned final OS data cut-off (April 2018). For the comparison to fulvestrant, the whole study population for PALOMA-3 (regardless of prior therapy) was used to inform efficacy inputs in the model, which the submitting company describes as reflecting the real-world patients treated with fulvestrant in the NHS in Scotland, i.e. the whole endocrine resistant population. For PFS the submitting company reported the best fitting curves (based on statistical goodness of fit) as the log-normal and generalized gamma for both palbociclib and fulvestrant with the former selected as base case. The submitting company highlights the Weibull and log-logistic as the best fitting overall survival functions, which again are independently fitted. The Weibull was deemed to produce a more plausible (and conservative) overall survival gain and was adopted for the base case. Duration of treatment was extrapolated by attaching exponential functions to the tails of the observed Kaplan-Meier data in PALOMA-3.

For the comparison with everolimus plus exemestane a network of evidence was constructed linking PALOMA-3 to BOLERO-2.11,12 A NMA was employed to estimate OS. Given the non-proportional hazards for PFS in PALOMA-3, a fractional polynomial approach was employed for this endpoint, and functions fitted for palbociclib in combination with fulvestrant and everolimus plus exemestane. Consequently results for palbociclib in combination with fulvestrant differ between the two comparisons.
EuroQol EQ-5D (3-level) data were available directly from PALOMA-3 and were employed in the economic model for the PFS health state. The overall EQ-5D index scores while on treatment were 0.74 (95% CI: 0.72 - 0.76) for the palbociclib in combination with fulvestrant arm and 0.69 (95% CI: 0.67 - 0.72) for the fulvestrant arm (p-value 0.0037). The company assumed patients treated with exemestane plus everolimus would have the same utility value as patients treated with fulvestrant. A systematic literature review identified a published study\textsuperscript{13} which was used in the economic model for the post-progression health state resulting in a utility value of 0.51. The PALOMA-3 stable disease estimates were deemed to capture the negative impact of treatment related adverse events and therefore in the base-case no disutility due to adverse events is applied to either arm. Applying utility decrements due to adverse events was explored in the sensitivity analysis.

The model assumes that treatment continues until disease progression. Monitoring of each therapy was modelled to involve regular blood tests and in the case of fulvestrant GP surgery nurse visits for each intramuscular administration. The post progression state allows for up to two subsequent lines of therapy. The assumption is made that 75% of patients at each progression take up further therapy (the remainder not doing so due to e.g. frailty). Costs at each line are based on mixed distributions of therapies and amount to £973 for the first post-progression therapy per cycle, and £860 for the second post-progression therapy. Costs of treating adverse events were also included.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. PAS discounts are in place for fulvestrant and everolimus these were included in the results used for decision-making by using estimates of the comparator PAS prices.

SMC would wish to present the cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS and the comparator PAS estimates, SMC is unable to publish these results.

The economic analysis was associated with some limitations:

- The submitting company provided evidence of very similar durations of PFS and time on treatment, whereas the model’s base case approach to these related endpoints resulted in divergent extrapolations. Sensitivity analysis indicated that the results were upwardly sensitive to the use of PFS as a proxy for treatment duration for both comparisons.
- There may be some uncertainty associated with the overall survival estimate included in the analysis. Median OS was longer in the palbociclib plus fulvestrant group but the difference was not statistically significant. It is however noted that OS in PALOMA-3 study was a secondary endpoint and the trial design not optimised to detect statistical significance.
- A quality of life advantage was applied for palbociclib plus fulvestrant relative to comparators in the stable disease (progression- free) state. This reflected a significant difference in EQ-5D scores in the relevant periods of the PALOMA-3 study, however, potential unblinding may have effected quality of life assessment. The submitting company did provide additional
sensitivity analysis setting the PFS utility values equal in each arm of the study and this resulted in modest increases in the cost-effectiveness ratio.

The Committee considered the benefits of palbociclib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as palbociclib is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted palbociclib for use in NHSScotland.

Other data were also assessed but remain confidential.*

Additional information: guidelines and protocols

The European School of Oncology (ESO) and the European Society for Medical Oncology (ESMO) published the 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer in July 2018. The guidance recommends that for ER-positive HER2-negative advanced breast cancer pre-menopausal women should have adequate ovarian function suppression or ovarian function ablation and should then be treated in line with post-menopausal women. For patients with ER-positive/HER2 negative advanced breast cancer the preferred first line treatment is endocrine therapy, unless there is visceral crisis or endocrine resistance. Type of previous adjuvant endocrine therapy, response and time lapsed from end of therapy guide the choice of endocrine therapy in advanced disease. Options include aromatase inhibitors (exemestane, letrozole, anastrozole), tamoxifen, fulvestrant, CDK4/6 inhibitor in combination with an aromatase inhibitor or with fulvestrant, and everolimus in combination with an aromatase inhibitor or tamoxifen or fulvestrant. The guideline notes that the optimal sequence of endocrine-based therapy is uncertain.10

The National Institute for Health and Care Excellence (NICE) published clinical guideline 81, Advanced breast cancer: diagnosis and treatment in 2009. The guidance was subsequently updated in August 2017. The guidance recommends that an aromatase inhibitor be offered as first line treatment to postmenopausal women with oestrogen receptor (ER)-positive advanced breast cancer, unless their disease is imminently life-threatening or needs early symptomatic relief due to significant visceral organ involvement, in which case they should be offered chemotherapy. The guidance does not make any recommendations regarding the use of palbociclib.14

In September 2013 the Scottish Intercollegiate Guidelines Network (SIGN) issued publication number 134, the treatment of primary breast cancer. This provides some recommendations on adjuvant and neoadjuvant endocrine therapy.15
Additional information: comparators

Fulvestrant and everolimus plus exemestane are considered the predominant comparators but exemestane and tamoxifen may also be considered as lesser comparators in this setting.

Cost of relevant comparators

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose Regimen</th>
<th>Cost per year (£)</th>
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</thead>
<tbody>
<tr>
<td>Palbociclib</td>
<td>125mg orally for first 21 days of 28-day cycle</td>
<td>45,141</td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>500mg IM day 0, 14, 28 then every 28 days</td>
<td>(45,664 in year 1)</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Everolimus</td>
<td>10mg orally once daily</td>
<td>34,855</td>
</tr>
<tr>
<td>Exemestane</td>
<td>25mg orally once daily</td>
<td></td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>500mg IM day 0, 14, 28 then every 28 days</td>
<td>6,791</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(7,314 in year 1)</td>
</tr>
<tr>
<td>Exemestane</td>
<td>25mg orally once daily</td>
<td>106</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>20mg orally once daily</td>
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</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online 01 March 2019. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 684 patients eligible for treatment with palbociclib plus fulvestrant in year 1, falling to 324 by year 5 by which time patient numbers are based on anticipated incidence rather than existing prevalence in addition to incidence. The company assumed an uptake rate of 10% in year 1 rising to 40% in years 5, resulting 68 patients estimated to be treated in year 1 and 130 patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

Other data were also assessed but remain confidential.*
References

1. Pfizer. Summary of product characteristics for palbociclib (Ibrance®), last updated 6 August 2018.


7. Summary of product characteristics for ribociclib (Kisqali®), last updated 16.1.19

8. Summary of product characteristics for abemaciclib (Verzenios®), last updated 19.11.18


This assessment is based on data submitted by the applicant company up to and including 12 April 2019.
*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.