SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
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NHS SCOTLAND

palbociclib 75mg, 100mg and 125mg hard capsules (Ibrance®)

SMC No 1276/17

Pfizer Limited

10 November 2017

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission considered under the end of life process

palbociclib (Ibrance®) is accepted for restricted use within NHS Scotland.

Indication under review: 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 peri-menopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

SMC restriction: in combination with an aromatase inhibitor for first-line treatment of HR-positive HER2-negative locally advanced or metastatic breast cancer.

In an open label phase II study and a double-blind, placebo-controlled phase III study, palbociclib in combination with letrozole increased progression-free survival when compared with letrozole alone in patients with oestrogen receptor-positive, HER2-negative advanced breast cancer.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of palbociclib. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 11 December 2017

Indication

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 peri-menopausal women, the endocrine therapy should be combined with a luteinising 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 letrozole is 2.5mg taken orally once daily continuously throughout the 28-day cycle. Treatment of pre / peri-menopausal women with the combination of palbociclib plus letrozole should always be combined with an 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 14 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 (SPC) for further details.[1]

Product availability date

9 November 2016

Palbociclib meets SMC end of life criteria for this indication.

Summary of evidence on comparative efficacy

Palbociclib is a highly selective, reversible inhibitor of cyclin-dependent kinases (CDK) 4 and 6. It reduces cellular proliferation by blocking progression of the cell from G1 into S phase of the cell cycle. Palbociclib is a first in class medicine and has been shown to have high activity against oestrogen receptor (ER)-positive breast cancers.[1, 2] The submitting company has requested that SMC considers palbociclib when positioned for use in combination with an aromatase inhibitor for first-line treatment of HR-positive HER2-negative locally advanced or metastatic breast cancer.

PALOMA-2 was an international, multi-centre, randomised, double-blind, placebo controlled, phase III study in post-menopausal women with ER-positive, HER2-negative locally recurrent or metastatic breast cancer not amenable to resection or radiation therapy with curative intent, for whom chemotherapy was not clinically indicated and who have not received any prior systemic treatment for advanced disease. Disease was required to be measurable according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 or bone-only disease. Included patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and adequate blood counts and organ function.

Patients were randomised in a 2:1 ratio to receive once daily oral treatment with palbociclib 125mg (n=444) or placebo (n=222) for three weeks in every four week cycle. Both groups received letrozole 2.5mg daily continuously. Randomisation was stratified according to site of disease (visceral versus non-visceral), disease-free interval since the end of (neo)adjuvant treatment to disease recurrence (de novo metastatic, ≤12 months or >12 months), and nature of prior (neo)adjuvant anticancer therapies (prior hormonal therapy versus no prior hormonal therapy). Treatment continued until disease progression, unacceptable toxicity or withdrawal of consent. [2, 3]

The primary outcome was investigator-assessed progression-free survival, defined as the time from randomisation to radiologically confirmed disease progression or death during the study, and assessed according to RECIST version 1.1, in the intention to treat (ITT) population.[2, 3] At the primary analysis, 331 disease progression or death events had been reported, median duration of follow-up was 23 months. The median investigator-assessed progression-free survival was 24.8 months for palbociclib plus letrozole and 14.5 months for placebo plus letrozole. The hazard ratio (HR) was 0.58 (95% CI: 0.46 to 0.72, two-sided p<0.001) in favour of palbociclib plus letrozole. A total of 45% of patients in the palbociclib plus letrozole group were censored due to being in follow up for progression compared with 26% of patients in the placebo plus letrozole group.[2, 3]

A blinded independent central review (BICR) of progression-free survival was also carried out which was 30.5 months in the palbociclib plus letrozole group versus 19.3 months in the placebo plus letrozole group (HR 0.65, 95% CI: 0.50 to 0.84, two-sided p=0.001). Additional key secondary outcomes are presented in table 1. Overall survival data are not yet available due to data immaturity.[2, 3]

Table 1: Additional key secondary outcomes for PALOMA-2 study.[2]

	Palbociclib plus letrozole	**Placebo plus letrozole**
Objective response	42%	35%
	Odds ratio 1.4 (95% CI: 0.98 to 2.01), one sided p=0.0310	
Clinical benefit response rate/disease control rate	85%	70%
	Odds ratio 2.39 (95% CI: 1.58 to 3.59), one sided p<0.0001	
Median duration of response	22.5 months (95% CI: 19.8 to 28.0)	16.8 months (95% CI: 14.2 to 28.5)

CI: confidence interval

PALOMA-1 was an international, multi-centre, open-label, randomised, phase I and II study in post-menopausal women with ER-positive, HER-2 negative advanced breast cancer. Evidence of locally recurrent disease not suitable for resection or radiation therapy with intention to cure, or metastatic disease was required for inclusion into the study. Patients had not received any prior systemic treatment for advanced disease. Disease had to be measurable according to RECIST version 1.0 or bone-only disease. Included patients were required to have an ECOG performance status of 0 or 1, adequate blood counts and organ function, and no brain metastases.

In the phase II part of the study, patients were recruited into two cohorts (cohort 1, n=66 and cohort 2, n=99). Both cohorts were required to have ER-positive and HER-2 negative disease and the second cohort was also required to have amplification of cyclin D1 (CCND1) and / or loss of p16 (also known as INK4A or CDKN2A).[2, 4] Patients were randomised equally in both cohorts to receive palbociclib 125mg orally once daily for three weeks in each four week cycle plus letrozole 2.5mg orally once daily (cohort 1: n=34, cohort 2: n=50) or letrozole 2.5mg orally once daily (cohort 1: n=32, cohort 2: n=49). Randomisation was stratified according to disease site (visceral, bone only, or other) and disease-free interval since the end of (neo)adjuvant treatment to disease recurrence (de novo metastatic, ≤12 months or >12 months). Treatment continued until disease progression, unacceptable toxicity, study withdrawal or death. To manage potential toxic effects, dose interruptions and reductions were allowed.[4]

The primary outcome was investigator-assessed progression-free survival, defined as the time from randomisation to radiological disease progression or death, and analysed in the ITT population (all randomised patients). Analysis of the primary outcome was initially planned to be carried out in cohort 2 only but this was later changed after an unplanned interim analysis to include both cohorts.[2, 4] At data cut-off for the final analysis the median follow up was 29.6 months for patients in both cohorts who received palbociclib plus letrozole and 27.9 months for those who received letrozole alone. In the palbociclib plus letrozole group 23% (19/84) of patients remained on treatment compared with 10% (8/81) in the letrozole group. At final analysis for progression-free survival, 41 events had occurred in the palbociclib plus letrozole group and 59 in the letrozole group.[4]

The amended primary outcome of median progression-free survival in both cohorts was 20.2 months in patients who received palbociclib plus letrozole versus 10.2 months in patients who received letrozole alone (HR 0.49, 95% CI 0.32 to 0.75, one sided p=0.0004).

In cohort 1, median progression-free survival was 26.1 months in the palbociclib plus letrozole group versus 5.7 months in the letrozole group (HR 0.30, 95% CI: 0.16 to 0.57, one sided p<0.0001). In cohort 2, median progression-free survival was 18.1 months in the palbociclib group versus 11.1 months in the letrozole group (HR 0.51, 95% CI: 0.30 to 0.85, one sided p=0.0046).[4]

In addition to the investigator assessed progression-free survival, a BICR identified a median progression-free survival of 25.7 months in the palbociclib plus letrozole group versus 14.8 months in the letrozole group (HR 0.62, 95% CI: 0.38 to 1.02, one sided p=0.0286). The difference between groups was not statistically significant.[2] There were notable differences in the number of progression-free survival events identified in the investigational and control arms when assessed by the investigator and the BICR. The largest difference was in the letrozole arm of cohort 1 where the investigators identified 25 events compared with 9 events identified by the BICR. In cohort 1, the BICR identified a larger proportion of progression-free survival events in the palbociclib plus letrozole group than in the letrozole group (32% versus 28%).[2]

Median overall survival was 37.5 months in the palbociclib plus letrozole group (30 events) compared with 33.3 months (31 events) in the letrozole group. The difference between groups was not statistically significant (HR 0.81, 95% CI: 0.49 to 1.34, two sided p=0.42).[4]

Summary of evidence on comparative safety

In the PALOMA-2 study an adverse event was reported in 99% (439/444) and 96% (212/222) of patients and serious adverse events were reported in 20% (87/444) and 13% (28/222) of patients in the palbociclib plus letrozole and placebo plus letrozole groups respectively.[2, 3]

A temporary discontinuation of palbociclib due to an adverse event occurred in 75% (332/444) of patients while in the investigational arm while a temporary discontinuation of placebo occurred in 16% (35/222) of the control arm. A permanent discontinuation due to adverse events occurred in 9.7% and 5.9% of the investigational and control groups respectively. A dose reduction of palbociclib due to adverse event occurred in 36% (160/444) of patients compared with dose reduction of placebo due to adverse events in 1.4% (3/222) of patients.[2]

The most frequently reported treatment-emergent adverse event in the palbociclib plus letrozole group was neutropenia, reported in 66% of patients compared with 3.2% of patients in the placebo plus letrozole group. Fatigue was reported in 37% and 28%, nausea in 35% and 26%, arthralgia 33% and 34%, alopecia 33% and 16%, diarrhoea 26% and 19%, cough 25% and 19%, leucopenia 24% and 0.5% and anaemia 23% and 9% of patients in the palbociclib plus letrozole and the placebo plus letrozole groups respectively.[2]

Adverse events reported in PALOMA-1 were similar and no additional safety concerns were identified.[2] The European Medicines Agency (EMA) concluded that the addition of palbociclib to letrozole is associated with a larger risk of toxicity however, with dose adjustment as appropriate, is fairly tolerable.[2]

Summary of clinical effectiveness issues

Breast cancer is the most common cancer in women. Advanced breast cancer includes both locally advanced and metastatic breast cancer. Approximately two thirds of breast cancer cases are ER-positive which is a significant predictive factor used to identify patients that may benefit from endocrine therapy. Endocrine therapy, such as letrozole, anastrozole, exemestane, fulvestrant, or tamoxifen is recommended as first-line therapy in post-menopausal patients with ER-positive, HER2-negative advanced breast cancer. In patients with life threatening, rapidly progressing or symptomatic visceral disease or where endocrine resistance is a concern chemotherapy would be used first-line.[2] SMC clinical experts have advised that currently within NHS Scotland letrozole is recommended, when appropriate, as the first-line choice of endocrine therapy. Median overall survival in the PALOMA-1 study was 33 months for patients receiving standard of care, letrozole therapy,[4] therefore palbociclib meets SMC end of life criteria. Clinical experts consulted by SMC considered that there is unmet need in this area. The submitting company has requested that SMC considers palbociclib when positioned for use in combination with an aromatase inhibitor for first-line treatment of HR-positive HER2-negative locally advanced or metastatic breast cancer.

In the phase III PALOMA-2 study the primary outcome of median investigator assessed progression-free survival was 10.3 months longer in the palbociclib plus placebo group compared with the placebo plus letrozole group (24.8 months versus 14.5 months). Progression-free survival is not a direct health outcome but was considered appropriate by the EMA. The EMA guidelines on the investigation of anti-cancer medicines note that although favourable effects on survival are the most persuasive outcome of a clinical study, prolonged progression-free survival is considered to be of benefit to the patient. Overall survival results are not yet available due to data immaturity therefore no overall survival conclusions can be made.[2]

In the phase II PALOMA-1 study, the primary outcome of investigator assessed progression-free survival was 10 months longer in the palbociclib plus letrozole group compared with the letrozole group (20.2 months versus 10.2 months). The EMA concluded that results from PALOMA-1 that included cohort 1 were at a high risk of bias. In cohort 2, investigator assessed progression-free survival was 7.1 months longer in the palbociclib plus letrozole group compared with the letrozole group (18.1 months versus 11.1 months). Median overall survival, a key secondary outcome in PALOMA-1, was 4.2 months longer in the palbociclib plus letrozole group compared with the letrozole group (37.5 months versus 33.3 months) however the difference was not statistically significant.[2, 4]

PALOMA-1 was an open-label study which is a potential source of bias. In cohort 2, patients were required to have amplification of cyclin D1 (CCND1) and / or loss of p16 (also known as INK4A or CDKN2A CDK4/6). The results did not support the hypothesis that this improved patient selection. The primary outcome was changed during the study to progression-free survival in both cohorts combined instead of cohort 2 only. At this point, recruitment to cohort 2 was stopped. Results that include cohort 1 and also the full study population (cohort 1 and 2) are at a high risk of bias. The EMA stated that only results from cohort 2 are relevant to the efficacy assessment and that PALOMA-1 should be considered as a supportive rather than pivotal study. The statistical analysis plan in PALOMA-1 used a one-sided α of 0.10 rather than the traditional two-sided threshold of 0.05. The planned final analysis for progression-free survival was due to occur after 114 events however this was changed during the study to occur after 95 events. There were some imbalances in baseline data in PALOMA-1 which may have favoured the palbociclib plus letrozole arm.[2, 4]

In PALOMA-1, assessment of tumour response to determine the primary outcome of progression-free survival was carried out by investigators who were not blinded to treatment arm. A BICR of tumour response to determine progression-free survival was also carried out as a secondary outcome. The difference in progression-free survival between groups was not statistically significant when assessed by the BICR. BICR assessment showed the palbociclib plus letrozole arm to be less efficacious than control for cohort 1. There were notable differences in the number of progression-free survival events identified in the experimental and control arms when assessed by the investigator and the BICR. Investigator assessment of events was not confirmed by blinded assessors for a substantial proportion of events. The EMA stated that analysis of discordance of investigator assessed and BICR progression-free survival events indicates a bias favouring the palbociclib plus letrozole arm.[2]

In PALOMA-2, assessment of tumour response to determine the primary outcome of progression-free survival was also carried out by investigators who were not blinded to treatment arm. An independent (blinded to treatment) review of tumour response to determine progression-free survival was also carried out as a secondary outcome. This identified a longer duration of progression-free survival in both groups but with a similar difference between groups in favour of palbociclib plus letrozole and these results were statistically significant.

Post-menopausal women only were included in PALOMA-1 and PALOMA-2. However the EMA concluded that the results could be extrapolated to include pre / peri-menopausal women. Palbociclib would be given in combination with an aromatase inhibitor and LHRH agonist which is an established first line treatment regime in this patient population. There are no data available for patients with hepatic or renal impairment. No patients from the UK were included in PALOMA-1, however patients were recruited from sites in the UK for PALOMA-2. There were limited patient reported or quality of life outcomes in both studies.

The submitting company presented Bayesian network meta-analyses (NMA) comparing palbociclib plus letrozole with capecitabine for the outcomes progression-free survival (11 studies) and overall survival (12 studies). The pivotal PALOMA-2 study was excluded from the NMA and the only study of palbociclib included was PALOMA-1 which the EMA considered to be at high risk of bias. Capecitabine was considered by the company to be an appropriate proxy for all chemotherapy. Due to data limitations, studies have been included that were up to 25 years old and include populations not relevant to the licensed indication or proposed positioning (i.e. patients who did not have HR-positive, HER2-negative disease or status was unknown). Results of the analysis favour palbociclib plus letrozole over capecitabine. According to guidelines and SMC clinical expert feedback, chemotherapy is unlikely to be a relevant comparator therefore the NMAs are of limited importance.

Clinical experts consulted by SMC considered that palbociclib is a therapeutic advancement due to the benefit over single agent hormone therapy. The addition of palbociclib to letrozole would provide an additional treatment option for patients with advanced breast cancer. Introduction of palbociclib will impact patients and have service implications as treatment with palbociclib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products (i.e. secondary care) unlike hormone therapy which can be managed in primary care. Full blood count should be monitored before palbociclib commences, at the beginning of each cycle, on day 14 of the first two cycles and thereafter when clinically indicated.

Summary of patient and clinician engagement

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 medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- HR-positive, HER2-negative locally advanced or metastatic breast cancer is a major health problem affecting a significant number of patients. It is an incurable and life-limiting condition with a median survival of 24 to 36 months. Symptoms can be significant and have a negative impact on quality of life, for example affecting mobility and causing exhaustion. In addition, patients have reported a severe fear of progression and anxiety relating to the impact of their disease on their family.
- Current treatment options are limited. First-line therapy is usually with an aromatase inhibitor. The next stage of treatment may involve further endocrine therapy with a different agent prior to chemotherapy, which is associated with considerable toxicity and a negative impact on quality of life.
- Palbociclib is an oral medication which is easy to administer alongside an aromatase inhibitor. It could offer an additional ten months of high quality time where patients' disease doesn't progress, reducing symptoms and potentially improving quality of life compared to current standard of care. Patients may be able to continue to work and participate in family activities over this time. This extended period on first-line therapy also delays the need for chemotherapy.
- Clinicians considered the side-effect profile of palbociclib to be manageable and less toxic than chemotherapy.
- It was noted that hospital visits would be required for patients receiving palbociclib and this would be expected to impact on outpatient clinic workload.

Additional Patient and Carer Involvement

We received a joint patient group submission from Breast Cancer Care and Breast Cancer Now, both are registered charities. Breast Cancer Care has received 1.94% pharmaceutical company funding in the past two years, including from the submitting company. Breast Cancer Now has received 0.62% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from both charities participated in the PACE meeting. The key points of their submission have been included in the full PACE statement.

Summary of comparative health economic evidence

The company submitted a cost- utility analysis comparing palbociclib plus letrozole to letrozole alone for first line use in postmenopausal women with HR-positive HER2-negative locally advanced or metastatic breast cancer who have never received systemic therapy in the advanced/metastatic setting. SMC clinical experts have indicated that palbociclib will not displace any therapy but will be used as an add-on treatment. Most experts have noted that letrozole is currently used for this patient group. As a secondary analysis the company provided a comparison versus capecitabine and a blended comparator i.e. capecitabine/letrozole. It is worth noting that the results versus the blended comparator were derived by using a weighted average of the incremental cost-effectiveness ratios (ICERs) for palbociclib plus letrozole versus letrozole (80%) and capecitabine (20%) respectively.

A partitioned survival Markov model was submitted containing three primary health states ie pre-progression, post- progression and death. The post- progression health state was further subdivided to account for treatment lines which can be given post progression. It was assumed that patients could receive up to four treatment lines. A lifetime horizon was used in the analysis which was assumed to be 40 years.

The clinical data used in the economic analysis were taken from the PALOMA-1 study.[4] Progression-free survival for the palbociclib plus letrozole arm was extrapolated using a piece wise approach ie an exponential function was appended to Kaplan- Meier data. Progression- free survival data for the letrozole arm were complete in the PALOMA-1 study and therefore the analysis used the Kaplan-Meier data from the study without any extrapolation. In terms of overall survival, the company extrapolated data from PALOMA-1 using the Weibull parametric function for both treatment arms. For the comparison versus capecitabine, the economic analysis used the results from the NMA.

Treatment- specific utility values were applied to the pre- progression health state (0.71 and 0.74 for the letrozole and palbociclib plus letrozole arms respectively). These values were derived from the PALOMA-2 study, whereby EQ-5D was used to elicit health-related quality of life values. The baseline utility value applied to the post- progression health state was 0.46 and the same post-progression value was used in all arms of the analysis. In addition, this value was derived from the general UK population using the standard gamble approach and taken from a published study.[5] The base case analysis did not include adverse event disutilities on the basis that the EQ-5D data would have reflected any adverse events.

Medicine costs associated with palbociclib and letrozole were based on patient level time to discontinuation data from PALOMA-1 ie costs were not calculated according to treatment until progression. The post- progression health state included the cost of subsequent treatment lines. Background resource use such as community nurse home visits, consultant visits, GP visits and clinical nurse specialist visits were included in the model as well as the cost of grade 3 and 4 adverse events.

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The key base case results and sensitivity analyses are presented in the tables below.

Table 2: Base case results with PAS

Comparator	Incremental life year gain	Incremental cost-effectiveness ratio (ICER) with PAS
Letrozole	0.28	£26,706
Blended comparator	0.51	£19,241
Capecitabine	1.51	£25,306

Table 3: One-way sensitivity analysis for palbociclib plus letrozole versus letrozole

Parameter varied	ICER with PAS
PFS parametric model coefficients (lower coefficient)	£59,156
Time to treatment discontinuation (Upper coefficient)	£54,383

Table 4: Scenario analyses for palbociclib plus letrozole versus letrozole

Parameter varied	ICER with PAS
Overall survival: Assumed no overall survival gain associated with palbociclib plus letrozole	£25,870
Time horizon: 5 years	£35,893
Baseline pre progressed utility equal in both arms	£28,398
Costs based on treatment until progression	£54,274

There were a number of weaknesses with the analysis which include the following

- There is some uncertainty surrounding the modelled overall survival estimate associated with palbociclib due to the lack of mature, statistically significant overall survival data. In the economic case, the company extrapolated overall survival using mortality data from PALOMA-1. This study was not powered to detect a significant difference in overall survival and no significant difference for this outcome versus letrozole alone was demonstrated. Sensitivity analysis was provided to show the impact of assuming no overall survival advantage. This had the impact of lowering the ICER. This was caused by the effect of reduced overall survival and therefore lower costs in the progressed survival period. (see Table 4 above).
- The clinical data supporting the economic case were from the phase II PALOMA-1 study not the phase III PALOMA-2 study. The results from the PALOMA-1 study were considered by the EMA to be at high risk of bias.
- Progression- free survival in the palbociclib treatment arm was extrapolated using the exponential function. Based on a review of goodness of fit statistics alternative functions may have been a more appropriate or similar fit to the data.
- The results were sensitive to palbociclib treatment costs; these were calculated using time to treatment discontinuation data from the clinical studies. For completeness, the company

provided a sensitivity analysis whereby costs reflect treatment until progression (see Table 4 above) but noted that in practice, as in the clinical studies, patients may discontinue treatment for reasons other than progression.

- There are some uncertainties surrounding the baseline utility values for both the pre- progression and post- progression health states within the model. The company has provided sensitivity analysis whereby the same baseline utility is used for the pre- progression health state in both treatment arms and results are presented in Table 4 above.
- As a secondary analysis the company compared palbociclib plus letrozole to capecitabine and a blended comparator. Based on SMC expert responses these comparisons may not be of primary importance. Furthermore, the comparison versus capecitabine is based on an indirect comparison with considerable limitations.

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

*Other data were also assessed but remain commercially confidential.**

Additional information: guidelines and protocols

The European Society of Medical Oncology (ESMO). 3rd ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). 5 December 2016.
This guideline states that endocrine therapy is the preferred option for ER-positive, HER2-negative advanced breast cancer, even if there is visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance. First-line endocrine therapy can include an aromatase inhibitor, tamoxifen or fulvestrant. The choice would be influenced by the type and duration of adjuvant endocrine therapy and the time since the end of adjuvant endocrine therapy.

The addition of palbociclib to an aromatase inhibitor, as first line therapy, for post-menopausal patients (except patients relapsing <12 months from the end of adjuvant aromatase inhibitor), is recommended as a treatment option. This combination provided a significant improvement in progression-free survival, with an acceptable toxicity profile. Overall survival results are still awaited. For pre/peri-menopausal patients, an LHRH-agonist must also be used.

At present, no predictive biomarker other than hormone receptor status exists to identify patients who will benefit from these type of agents and research efforts must continue.

The optimal sequence of endocrine agents after first line endocrine therapy is uncertain. It depends on which agents were used in the (neo)adjuvant and first line advanced breast cancer settings. Available options include aromatase inhibitor, tamoxifen, fulvestrant, palbociclib, everolimus, tamoxifen, everolimus, fulvestrant, megestrol acetate and oestradiol.[6]

The American Society of Clinical Oncology (ASCO). Endocrine Therapy for Hormone Receptor–Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. 1 September 2016.
These guidelines state that sequential hormone therapy is the preferential treatment for most women with HR-positive metastatic breast cancer. With the exception of immediately life-threatening disease, hormone therapy should be used as initial treatment. The choice of treatment would be made depending on adjuvant treatment, the disease-free interval and organ function. Aromatase inhibitors are recommended as first-line therapy with or without palbociclib in post-menopausal women.[7]

Additional information: comparators

Letrozole.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per cycle(£)
Palbociclib plus letrozole	Palbociclib 125mg daily for 21 days in each 28 day cycle plus letrozole 2.5mg daily	2,954
Letrozole	2.5mg daily	4

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 02 August 2017. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 260 patients eligible for treatment with palbociclib in year 1 rising to 327 patients in year 5 to which confidential estimates of treatment uptake were applied.

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 commercially confidential.**

References

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This assessment is based on data submitted by the applicant company up to and including 21 September 2017.

**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_statements/Policy_Statements*

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.

Advice context:

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug 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 NHS Scotland 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 NHS Scotland 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.

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.