

A.8	Cyclin-dependent kinase 4/6 inhibitors (palbociclib, ribociclib, abemaciclib) for the treatment of patients with hormone receptor positive/ HER2-negative advanced breast cancer
Does the application adequately address the issue of the public health need for the medicine?	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>According to the Global Cancer Patterns 2020, female breast cancer is the most diagnosed cancer (11.7% of total cases). In women, breast cancer is the leading cause of cancer death (Sung 2021). Advanced breast cancer includes both inoperable locally advanced and metastatic breast cancer. Advanced/metastatic breast cancer remains a virtually incurable disease, with a median overall survival (OS) of about 3 years and a 5-year survival rate of around 25%, even in countries without major accessibility problems (Cardoso 2020)</p> <p>Its evolution depends on several factors, such as site and extension of metastasis, histopathological characteristics, and molecular profiles of tumours.</p> <p>Broadly there are three biologic subgroups of breast cancer: 1) those that express the estrogen receptor (ER), 2) those that express the human epidermal growth factor receptor 2 (HER2 [with or without ER expression]), and 3) those express neither of these, nor the progesterone receptor (PR; triple-negative). More than a half of women with breast cancer present a disease that is ER-positive and HER2-negative, both in the early and advanced setting. The biological subtype drives treatment choices.</p> <p>Patients who develop metastatic disease, irrespective of whether they previously had early breast cancer, undergo biopsy of a metastatic lesion to confirm estrogen receptor (ER), progesterone receptor (PR), and HER2 status. This is because up to 15 percent of metastatic cancers may have discordant ER expression compared with the primary cancer.</p>
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	<p>The Application regards the inclusion in the Model List of the Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors palbociclib, ribociclib and abemaciclib in combination with endocrine therapy (ET) for the management of patients with advanced breast cancer positive to the hormone receptor(s) and negative to HER2 - square- boxed as palbociclib (ribociclib, abemaciclib).</p> <p>The request only refers to the metastatic setting as uncertainties for the use in the early setting preclude firm conclusions on the implementation of these medicines in the (neo-)adjuvant setting. The benefit of inclusion of effective treatments in this setting would have a greater impact on the overall management of breast cancer. Thus, a better definition of the benefit risk ratio of CDK4/6 inhibitors in early/adjuvant breast cancer would be important and may inform future decisions on their listing.</p> <p>Although metastatic breast cancer is unlikely to be cured, there have been meaningful improvements in survival due to the availability of more effective systemic therapies, including ET in the treatment of hormone-sensitive disease. Hormone receptor-positive patients usually begin treatment with ET, reserving chemotherapy for patients whose cancers appear to be either refractory to ET or to have extensive symptomatic visceral involvement.</p> <p>Patients with estrogen receptor-positive metastatic breast cancer often respond to ET alone or in combination with targeted agents, including CDK4/6 inhibitors. Dysregulation of the cyclin dependent-CDK4/6-pRb pathway is frequent in hormonal</p>

	<p>receptor (HR) positive breast cancer and represents a key mediator of endocrine resistance. Although there are no randomized trials addressing the optimal sequencing of various targeted agents or their combination in patients receiving ET, indirect comparisons suggest improved outcomes with CDK 4/6 inhibitors and aromatase inhibitors (AIs) relative to other combinations of ET and targeted agents (Giuliano 2019).</p> <p>CDK4/6 inhibitors have been extensively studied in various clinical trials for patients with HR+/HER2-negative metastatic breast cancer. Population in these trials may be classified as follows:</p> <p>(a) sensitive to aromatase inhibitors (AI-sensitive), which includes patients that are either naïve to AI or late relapsers (>12 months) since the stopping of the AI-based adjuvant treatment; or</p> <p>(b) resistant to AI (AI-resistant), which includes patients that are either pretreated with an AI in a metastatic setting or those that relapsed during or early after (less 12 months) the AI-based adjuvant treatment.</p> <p>Clinical guidelines for the management of breast cancer all acknowledge the role of CDK4/6 inhibitors in the metastatic setting, both for the pre- and post- menopausal women. The inclusion of CDK4/6 inhibitors in combination with ET in international treatment guidelines, both for AI-sensitive and AI-resistant patients, represents the most relevant advance in the management of HR-positive/HER2-negative advanced or metastatic breast cancer over the last years.</p> <p>In terms of progression-free survival or time to progression, no standard treatment schedule of chemotherapy with or without targeted therapy was significantly better than CDK4/6 inhibitors plus hormone therapies, which, in turn, showed a favorable and manageable toxicity profile. No significant differences in efficacy and overall activity were observed among the three CDK4/6 inhibitors (Giuliano 2019). Decisions are driven by cost and side-effect profile.</p> <p>Anastrozole and tamoxifene are already included in the Model List for hormone receptor-positive early stage or metastatic breast cancer.</p> <p>Other targeted therapies such as mTOR inhibitors (everolimus) and PI3Kα-selective inhibitor (alpelisib) are not included in the Model List.</p>
<p>Have all important studies and all relevant evidence been included in the application?</p>	<p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>If no, please provide brief comments on any relevant studies or evidence that have not been included:</p> <p>The Application mentions the main studies and evidence relevant in this setting. Phase 2 studies are not mentioned but this is considered acceptable, given the availability of phase 3 trials.</p> <p>The Application does not mention the MONARCH plus study, a multinational, randomized, placebo controlled, double-blind phase III study conducted at 45 medical institutions in four countries (China, India, Brazil, and South Africa) (Zhang QY et al., 2019).</p>

Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?

- ☒ Yes
☐ No
☐ Not applicable

Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s).

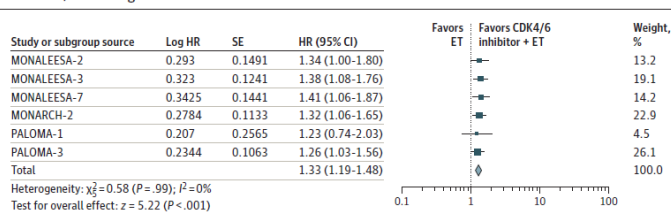
The evidence included in the Application regards the use of CDK4/6 in first and second lines of treatment in both pre- and post-menopausal women. Overall, seven phase 3 trials are included.

At least two recent systematic reviews with meta-analysis were published (Piezzo 2019, Li 2020). We summarize the results of the most recent one that included one phase II trial and 8 phase III trials assessing the efficacy and safety of treatment with CDK4/6 inhibitors plus ET vs ET alone (Li 2020)

Overall survival

OS was reported by 6 studies (5 phase III: MONALEESA-7, MONALEESA-3, MONALEESA-2, PALOMA-3, MONARCH 2; 1 phase II: PALOMA-1). The meta-analysis showed that the addition of CDK4/6 inhibitors was associated with significant benefit to OS vs ET alone (HR: 1.33; 95%CI, 1.19-1.48, low heterogeneity, see figure below from Li 2020).

Figure 1. Association of Cyclin-Dependent Kinases 4 and 6 (CDK4/6) Inhibitors Plus Endocrine Therapy (ET) vs ET Alone With Overall Survival Among Women With Hormone Receptor-Positive, *ERBB2*-Negative Metastatic Breast Cancer



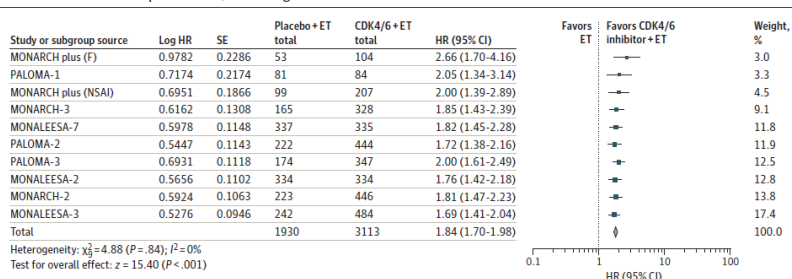
A significant OS improvement was observed with ribociclib plus fulvestrant, ribociclib plus ET, abemaciclib + fulvestrant (MONALEESA-3, MONALEESA-7 and MONARCH-2 trials) but not with palbociclib plus letrozole, palbociclib plus fulvestrant, and ribociclib plus letrozole (PALOMA-1, PALOMA-3 and MONALEESA-2 trials).

The median OS gains were estimated in range of 9.4 (ademaciclib + fulvestrant vs fulvestrant) to 16 (ribociclin plus ET vs ET alone) months.

Progression free survival

A meta-analysis of nine trials (8 phase III: MONALEESA-7, MONALEESA-3, MONALEESA-2, PALOMA-2, PALOMA-3, MONARCH 2, MONARCH 3; MONARCHPlus; 1 phase II: PALOMA-1) showed that the addition of CDK4/6 inhibitors was associated with significant benefit in PFS vs ET alone (HR, 1.84; 95%CI, 1.70-1.98; low heterogeneity). This effect is maintained irrespective of the presence of visceral metastases, the number of metastatic sites, and the time from the end of the adjuvant therapy.

Figure 2. Association of Cyclin-Dependent Kinases 4 and 6 (CDK4/6) Inhibitors Plus Endocrine Therapy (ET) vs ET Alone With Progression-Free Survival Among Women With Hormone Receptor-Positive, *ERBB2*-Negative Metastatic Breast Cancer



The median PFS values were about 11 months in the first line and 6 months in the second line setting.

Quality of life

Although most phase III trials did report on quality of life (QoL), conclusive data are not available.

Palbociclib

In the PALOMA-2 trial, the addition of palbociclib to letrozole maintained health-related QoL. In the PALOMA-3 trial: overall, global QoL scores significantly favored the palbociclib plus fulvestrant group as compared with fulvestrant.

Ribociclib

In the MONALEESA-2 trial, on-treatment HRQoL scores were similar between the two arms (ribociclib+letrozolo vs letrozolo). Similar results were reported in the MONALEESA-3 trial whereby the combination of ribociclib and fulvestrant maintains QoL compared with fulvestrant plus placebo. Moreover, in the MONALEESA-7 trials median time to definitive deterioration of QoL was longer in the ribociclib plus standard therapy (non-steroidal aromatase inhibitor/tamoxifene + goserelin) vs standard therapy alone.

Abemaciclib

The MONARCH-2 study showed no significant differences in HRQoL but diarrhea, appetite loss, nausea, and vomiting were worse in the abemaciclib plus fulvestrant than fulvestrant group.

Since the average duration of use of CDK4/6 inhibitors is substantially longer in first compared to second or subsequent lines, patients are subjected to potential side effects and more frequent hospital visits for a longer period of time when these drugs are used as first line treatment. This might be part of the reason why adding a CDK4/6 inhibitor to ET does not clearly result in improved QoL, not even in first line treatment.

Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?

The trials mentioned above were conducted mainly in the United States and United Kingdom. The Application mentions the issue of possible ethnical differences in the safety and response. Study conducted specifically in the Black ethnicity are lacking. PFS was shorter in Asian than white patients enrolled in pivotal trials, but this difference should be interpreted with caution given the post-hoc nature of this exploratory analysis and the small sample size of the Asian subgroup.

The lack of data for CDK4/6 inhibitors in population from China, Brazil, India, and South Africa triggered the conduction of the MONARCHPlus trial (Zhang 2019). Post-menopausal women with HR-positive, HER2-negative advanced breast cancer with no prior systemic therapy in an advanced setting (cohort A) or progression on prior ET

	<p>(cohort B) received abemaciclib or placebo plus anastrozole or letrozole (cohort A) or fulvestrant (cohort B). This study confirmed that the addition of abemaciclib to ET led to a significant and clinically meaningful improvement in PFS. OS data were immature at the cut-off date.</p> <p>No evidence in pregnant women is available.</p>
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>In general, the CDK4/6 inhibitors are well tolerated. The risk of developing all grades of fatigue and any-grade alopecia and rash was significantly higher with CDK 4/6 inhibitors than with ET alone. Hematological toxicities, primarily neutropenia, is common. However, in clinical trials the proportion of permanent discontinuations were lower than that of temporary discontinuations. Thus, it may be assumed that neutropenia can be managed with measures like dose reductions and dose interruptions.</p> <p>For all three agents, the FDA has issued a warning about rare, but serious, cases of pneumonitis.</p> <p>Distinct side-effects associated with the different CDK4/6 inhibitors:</p> <ul style="list-style-type: none"> - ribociclib: hepatotoxicity; reversible, concentration-dependent prolongation of the QT interval. - abemaciclib: diarrhoea; fatigue; hepatotoxicity; venous thromboembolic events <p>These differences in the safety profile could possibly drive the choice of one drug over the others.</p>
Are there any adverse effects of concern, or that may require special monitoring?	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>All drugs: need for close monitoring of the haematological toxicity (cell blood count)</p> <p>Ribociclib: ECG monitoring before starting the treatment to assess the risk of QT prolongation</p>
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	<p>This reviewer considers that the benefit/risk is favourable, mainly because adding CDK4/6 inhibitors to ET improves PFS, with a magnitude of the effect of about 11 months for the first line treatment and 6 months in the second line. However, OS data are relatively immature; so far, only ribociclib and abemaciclib have demonstrated a statistically significant improvement of OS in at least one trial. Data on QoL suggests not a benefit nor a deterioration. The drug-related toxicities appear to be manageable.</p> <p>Moreover, no chemotherapy regimen with or without targeted therapy is significantly better than CDK4/6 inhibitors plus hormone therapies in terms of PFS.</p>

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<p>Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)</p>	<p>Overall, the risk of bias of the phase III trials was low (adequate randomisation, double-blind design, adequate completeness of follow up). Estimates of PFS appears to be sufficiently precise while data on OS and QoL are immature.</p> <p>The lack of head-to-head data comparing the three agents limits the ability to select one product over another. Similarly, the comparison against placebo precludes any conclusions about the comparative efficacy over other targeted therapies.</p> <p>All the trials were sponsored by the products manufactures.</p>
<p>Are there any special requirements for the safe, effective and appropriate use of the medicine(s)? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>But those listed above, i.e., need for cell blood count monitoring for the whole class and for ECG monitoring before starting the treatment with ribociclib.</p>
<p>Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>The three CDK4/6 inhibitors were approved by the main regulatory agencies, including:</p> <ul style="list-style-type: none"> • European Medical Agency (European Union) • Food and Drug Administration (United States) • Health Canada • Therapeutic Goods Administration (Australia) • Medsafe (New Zealand) with the exception of abemaciclib <p>Palbociclib is also approved in China and Japan.</p>
<p>Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p>
<p>Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.</p>	<p>Although the price of CDK4/6 inhibitors varies for each drug and among countries, it is sure that they are much more expensive than ET. High prices could be a potential barrier to access these treatments.</p> <p>Ribociclib 200mg 21 tablets (Novartis Pharmaceuticals UK Ltd) €2730.00 /\$3262.35</p> <p>Palbociclib 21 capsules of 75 mg (Pfizer Limited) €2,689.18/\$3213.57</p> <p>Abemaciclib 28 tablets of 50 mg (Lilly): €1,366.68/\$1633.18</p> <p>(source: https://thesocialmedwork.com/)</p> <p>In the USA, the monthly wholesale price of all three CDK inhibitors is over US\$ 13,500, compared with less than US\$ 50 for ET monotherapy.</p> <p>The average cost for a course of one month of treatment with palbociclib in Europe</p>

	<p>can range between 5000 and 13,000 US dollars, for ribociclib 8900 US dollars and for abemaciclib 3500- 12,000 US dollars.</p> <p>Cost-effectiveness analyses in Singapore (ribociclib) and Canada, the USA, and Switzerland (palbociclib) concluded that it is very unlikely that CDK4/6 inhibitors are cost-effective at current pricing.</p>
Any additional comments	<p><i>Use of CDK4/6 inhibitors in combination with fulvestrant</i></p> <p>While the Application regarding CDK4/6 inhibitors clearly reports that there is no intention to endorse the use of fulvestrant as a single agent, in the second-line setting, the evidence of efficacy of CDK4/6 inhibitors is related to their use in combination with fulvestrant. The three trials assessing the efficacy and safety of CDK4/6 inhibitors in patients that progressed during ET (PALOMA 3, MONALEESA 3, MONARCH 2) compared the CDK4/6 inhibitors in combination with fulvestrant to fulvestrant alone.</p> <p>Fulvestrant is not listed in the Model List. An Application for its inclusion as a treatment for women with metastatic breast cancer has been submitted. Based on this Application, the use of fulvestrant in association with AI increases OS of approximately 7 months (HR 0.85, 95% CI 0.62 - 1.15; low certainty evidence) and PFS of one month (HR 0.89, 95% 0.73 - 1.08; low certainty evidence) compared to AI alone. According to the ESMO scoring system, the use of fulvestrant in the first- and second-line settings is associated with a modest improvement of PFS. Data on cost effectiveness of fulvestrant over AI alone are limited and not conclusive.</p> <p>Therefore, the Expert Committee should take into consideration the possible impact of listing CDK4/6 inhibitors on the use of fulvestrant, as it cannot be ruled out that the inclusion of CDK4/6 inhibitors would fuel its clinical use, irrespective of the outcome of the Application as single agent.</p>
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	<p>Although the benefit risk ratio was judged positive, this Reviewer still have concerns in relation to the listing proposal:</p> <ol style="list-style-type: none"> 1) data on OS are promising but immature, particularly in the first line setting. Additional randomized trials with similar design as the pivotal studies are unlikely to be conducted, given the widespread endorsement of CDK4/6 inhibitors in the clinical practice. Marketing authorisation holders are currently conducting observational studies to complement the evaluation of these agents in real practice conditions. These studies might offer an estimate of the benefit of CDK4/6 inhibitors in terms of OS, an evidence, however, limited due to the lack of randomisation. These studies may also produce valuable data on patient reported outcomes. 2) high cost of treatments may pose serious hurdles to the affordability of these treatments, especially in disadvantage settings. To increase access, it would be interesting to explore the possibility of granting voluntary licensing through a request to the Medicines Patent Pool. 3) possible impact of listing CDK4/6 inhibitors on the use of fulvestrant. A better definition of the benefit risk profile of CDK4/6 inhibitors in early setting will overcome this issue.
References (if required)	<p>Cardoso F, Paluch-Shimon S, Seenkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-1649.</p> <p>Giuliano M, Schettini F, Rognoni C, et al. Endocrine treatment versus chemotherapy in postmenopausal women with hormone receptor-positive, HER2-negative, metastatic breast cancer: a systematic review and network meta-analysis. Lancet Oncol.</p> <p>Li J, Huo X, Zhao F, et al. Association of Cyclin-Dependent Kinases 4 and 6 Inhibitors With Survival in Patients With Hormone Receptor-Positive Metastatic Breast Cancer A</p>

	<p>Systematic Review and Meta-analysis. JAMA Network Open. 2020;3(10):e2020312.</p> <p>Piezzo M, Chiodine P, Riemma M, et al. Progression-Free Survival and Overall Survival of CDK 4/6 Inhibitors Plus Endocrine Therapy in Metastatic Breast Cancer: A ystematic Review and Meta-Analysis. Int. J. Mol. Sci. 2020, 21, 6400</p> <p>Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries CA CANCER J CLIN 2021;71:209–249.</p> <p>Zhang QY, Sun T, Yin YM, et al MONARCH plus: abemaciclib plus endocrine therapy in women with HR+/HER2- advanced breast cancer: the multinational randomized phase III study. Ther Adv Med Oncol. 2019;20(10):1360.</p>
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