A.12	Cyclin-dependent kinase 4/6 inhibitors – HR-positive/ HER2-negative advanced breast cancer – EML
Draft recommendation	☐ Recommended ☒ Not recommended Justification: Breast cancer is a huge public health priority and cause of morbidity, disability, and mortality in women worldwide. Incidence rates are increasing in low and middle-income countries. CDK 4/6i are new medicines and a recent pharmacologic approach to treat ER-positive and HER2- negative advanced breast cancer. There is some evidence of clinical benefit, mainly with ribociclib, including cost-effectiveness in some jurisdictions. However, all three CDK 4/6i are on patent and very expensive. Not all countries have market approved them. Although they are oral medicines, with evident gains in respect to administration issues and indirect cost, all require intense clinical follow-up and monitoring of outcomes and of AEs, and of toxicities, specifically neutropenia and cardiotoxicity (especially ribociclib). This safety profile results in need to continuous monitoring that may not be feasible to implement in less resourced countries. Moreover, although there is some RWE on effectiveness and safety in different ethnicities (Caucasian and Asian populations) there are yet no studies for black women, due to a characteristic low baseline neutrophil count, which restricts trial enrolment for these women. I do not recommend inclusion of CDK 4/6is in the EML.

Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Breast cancer is the leading cause of morbidity, disability, and mortality in women worldwide. In 110 countries it is the main cause of mortality among women. According to International Agency for the Research on Cancer (IARC), in 2020 there were 2.3 million new breast cancer diagnoses, accounting for 25% of all malignancies in women and nearly 20% of all cancer deaths. Evolving epidemiological conditions, linked to increase of risk factors, mainly in low- and middle- income countries (in South America, Asia and Africa), have contributed to an increase of the incidence rates of breast cancer in the last decades, accounting for 60% of incident cases in 2018. Barriers related to access to care and services result in a large proportion of women – from low and middle-income settings - presenting with stage III or IV TNM. Investment in comprehensive and evidence-based cancer control planning, including cancer treatments, has demonstrated to positively impact on population health. More than half of women with breast cancer present with a disease that is ER-positive and HER2- negative, both in the early and advanced setting. CDK4/6 inhibitors are oral medicines, used for are used for the treatment of adult patients with hormone receptor positive/ HER2-negative advanced (metastatic) breast cancer. Palbociclib and ribociclib are a 3 ON/ 1 OFF schemes and abemaciclib on a continuous schedule, in combination with hormone agents. Aromatase inhibitors, already included in the WHO EML (i.e., anastrozole, letrozole and exemestane) or tamoxifen are used continuously, with no pause. Fulvestrant, not in the WHO-EML, is also proposed, used with at a high-dose schedule, as an IM injection on days 1, 15, and 29, then once monthly at doses of 500 mg (2 syringe of 250 mg/5 ml). Fulvestrant is commonly administered by nurses or doctors. Palbociclib is described as a highly selective, reversible inhibitor of CDK4 and 6, available as hard capsules, at the formulations of 75mg, 100mg and 125mg. It is indicated as a first-line therapy in combination with an aromatase inhibitor or in second-line fulvestrant in women (and men) who have received prior endocrine therapy, both pre- and post-menopausal women, both endocrine sensitive and endocrine resistant disease (ESMO definition). The recommended dose is 125 mg of palbociclib once daily for 21 consecutive days followed by 7 days off treatment (Schedule 3 weeks ON/ 1 week OFF) to comprise a complete cycle of 28 days. Maintenance dose may be tapered as clinically appropriate with 100mg or 75 mg daily. Ribociclib is described as a selective inhibitor of CDK 4 and 6 and is available in the market as film-coated tablets, at the formulation of 200mg. It is indicated in combination with an aromatase inhibitor, tamoxifen or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy, with fulvestrant. The recommended dose is 600 mg (3 X 200 mg tablets) once daily for 21 consecutive days followed by 7 days off treatment. Abemaciclib is described as a potent and selective inhibitor of CDK 4 and 6 .It is available in the market as film-coated tablets in the formulations of 50mg, 100mg and 150mg. Abemaciclib is indicated in combination with an aromatase inhibitor, tamoxifen or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy. The recommended dose of abemaciclib is 150 mg twice daily continuously when used in combination with endocrine therapy.

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☐ Yes ☒ No ☐ Not applicable Comments: This issue should be discussed. There is some evidence, and what exists is 'adequate', but in my view, not enough to substantiate a robust evidence base for entry. For palbociclib two Phase III trials are reported in detail. 1) PALOMA-3 (with fulvestrant). The setting was patients with hormone receptor-positive, HER2- negative locally advanced or advanced breast cancer who had received prior ET. The trial used as controls fulvestrant–placebo. Median of progression-free survival was 4.6 months, with a 4.9-month gain (HR: 0.46 (0.36-0.59)), and Median Overall Survival: 28.0 months with a 6.9 -month gain (HR: 0.81 (0.64-1.03) NS). The results included delayed deterioration of Quality-of-Life. 2) PALOMA-2 (with letrozole). Setting was patients with hormone receptor-positive, HER2- negative locally advanced or advanced breast cancer, in combination with an aromatase inhibitor. It used letrozole-placebo as control. Median of progression-free survival was 14.5months, with a 10.3-month gain (HR: 0.58 (0.46-0.72)), and no difference for Median Overall Survival. There were no Quality-of-Life benefits. For ribociclib three Phase III trials are reported in detail. 1) MONALEESA-7 (with ET). Setting was first-line premenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer patient. Control was placebo–ET. Median of progression-free survival was 13.0 months, with a 10.8-month gain (HR: 0.55 (0.44-0.69)), and Median Overall Survival: 48.0 months with a 10.7-month gain (HR: 0.76 (0.61-0.96)). The results included delayed deterioration of Quality-of-Life. This was considered the best evidence, according to ESMO. 2) MONALEESA-3 (with fulvestrant). Setting was First- or second-line postmenopausal, hormone receptor-positive, HER2-negative advanced breast cancer. Control was placebo–fulvestrant. Median of progression-free survival was 12.8 months, with a 7.7-month gain (HR: 0.59 (0.48-0.73)), and Median Overall Survival: 41.5 months with a 12.2-month gain (HR: 0.73 (0.59-0.90)). There were no Quality-of-Life benefits. 3) MONALEESA-2 (with letrozole). Setting was first-line postmenopausal, hormone receptor-positive, HER2-negative advanced breast cancer. It used letrozole-placebo as control. Median of progression-free survival was : 16.0 months, with a 9.3-month gain (HR: 0.57 (0.46-0.70)), and Median Overall Survival: 51.4 months with a 12.5-month gain (HR: 0.76 (0.63-0.93)). There were no Quality-of-Life benefits. For abemaciclib two Phase III trials are reported in detail. 1) MONARCH 3 (with aromatase inhibitor). Setting was first-line treatment of hormone receptor-positive, HER2-negative locally advanced or advanced breast cancer. Control was placebo-aromatase inhibitor. Median of progression-free survival was 14.8 months, with a 13.4-month gain (HR: 0.54 (0.42-0.70)), and Median Overall Survival: 54.5 months with a 12.6 -month gain (HR: 0.75 (0.58-0.97) – interim was NS). There were no Quality-of-Life benefits. 2) MONARCH 2 (with fulvestrant). Setting was second-line treatment of hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer having received prior ET. Control was placebo-fulvestrant. Median of progression-free survival was 9.3 months, with a 7.1-month gain (HR: 0.55 (0.45-0.68)), and Median Overall Survival: 37.3 months with a 9.4 -month gain (HR: 0.76 (0.61-0.95)). There were no Quality-of-Life benefits. The pooled analysis from trial- based metanalysis of clinical trials confirmed the findings. The best evidence was for adding a CDK4/6 inhibitor to endocrine therapy, with relative benefits in terms of PFS and OS (irrespective of the presence or not of visceral metastases, the number of metastatic sites, the breast cancer histology, and the length of the treatment-free interval from the adjuvant treatments). Additionally, adding CDK4/6 inhibitors to aromatase inhibitor sensitive and resistant patients may significantly improve overall survival. While some are of the view that a combination of CDK 4/6 inhibitors with AI is recommended as a first-line treatment for HR+, HER2-, metastatic breast cancer and that ribociclib plus letrozole might be a cost-effective options[1], according to moderate-quality evidence, it is likely that CDK4/6 inhibitors provide superior efficacy when compared to ET monotherapies, increasing progression-free survival and overall survival, but would also lead to an increase in the incidence of severe AEs (such as neutropenia) and in the percentage of patients to discontinue treatment due to toxicity[2,3]. However, there is little evidence of where CDK4/6inhibitors will yield more benefits, if in first-line or in second line. In case of disease progression there must be cessation of use. Moreover, they have not been compared to each other in trials. Some RWE evidence of has tried to corroborated trial results. Studies in Europe (n=1017), USA (n=878), Argentina (n=128), S. Korea (n=169), and a phase II in Japan (n=42). There are no studies for black women, who characteristically present with a baseline neutrophil count lower than enrollment criterium of 1500 mm3).

Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: The principal class effect of CDK4/6i is hematological toxicity, presented by predictable, reversible, and generally not infection- prone neutropenia. Because there is no comparative effectiveness evidence, toxicities may inform treatment decision-making, as the safety profile is a defining characteristic in first or second line of therapy. Higher rates of treatment-related diarrhea caused more treatment discontinuation for abemaciclib; ribociclib has been associated with a prolongation of the QT interval. For palbociclib there were 74% of G3 and 4 AEs (grading from 1-5 according to the e CTCAE, the Common Terminology Criteria for Adverse Events), 65% of G3 and G4 neutropenia, with <1% neutropenic fever, 24% (5.5% G3/4) anemia, All grade <10% increased AST or ALT and 25% diarrhea, 35% nausea. For ribociclib there were 79% of G3 and 4 AEs, 58% of G3 and G4 neutropenia, with <1% neutropenic fever, 19% anemia, 25% (G3/4/ in 9%) increased AST or ALT and 35% diarrhea, 52% nausea. For abemaciclib there were 58% of G3 and 4 AEs, 26% of G3 and G4 neutropenia, with <1% neutropenic fever, 30% (7% G3) anemia, All grade <10% increased AST or ALT and 87% diarrhea (13% G3) 45% nausea (3% G3).
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Neutropenia is the main AE associated to the CDK4/6i. For abemaciclib and palbociclib no cardiotoxicity has been reported; however, ECG monitoring for is required for patients receiving ribociclib.

Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: All CDK4/6 inhibitors oblige an intense succession of CBC, liver function and cardiac tests. Monitoring and follow-up may not be possible in resource-restricted settings. For palbociclib complete count blood (CBC) should be offered on day 1 of every cycle and for the first 2 cycles, and an adjunctive CBC is recommended on day 15, to assess tolerability and hematological toxicity. If the medicines is well- tolerated, CBC can be offered every 3 months, in the absence of concerning or major toxicities and good tolerability for at least 6 continuous cycles. At the recommended dose, no ECG monitoring is required. For ribociclib CBC should be ordered before the initiation of the treatment, and then used for clinical monitoring every 2 weeks for the first 2 cycles, then at day 1 for 4 cycles; eventually, if the therapy is tolerated, in the absence of concerning or major toxicities, CBC is requested at the clinician's discretion. Liver function tests should be done at day 1 of every cycle, following the same schedule of CBC. Ribociclib also requires cardiac monitoring, to ensure no elongation of the QT tract. An ECG is required before the treatment start and repeated at 2 weeks of treatment, during cycle 1 and at the beginning of cycle 2; then, as clinically appropriate. For abemaciclib patients should be monitored with CBC at day 1 of every cycle and at day 15, for the first 2 cycles. Thereafter, CBC should be ordered at day 1 for other 2 cycles, and eventually as clinically appropriate. Liver function tests are required before the treatment start, then every 2 weeks for the first 2 months, monthly for other 2 months and then as clinically appropriate. At the recommended dose, no ECG monitoring is requested.

Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: <u>First line – with tamoxifen</u> Palbociclib – cost effectiveness analyses have ben done in Japan, US (2), Switzerland and Canada. In Canada and the US, it not considered cost effective. In Japan: cost-effectiveness ratio per month: JPY 391,551.3/PFS (3400 USD) and in Switzerland, ICER: CHF 301,227/QALY Ribociclib – studies were made in the UK, US (3), Singapore and Canada. In Singapore and Canada it was not considered cost-effective. In the US two studies considered it cost-effective: ICER: $282,996/QALY; Effectiveness: 5.28 QALYs Total cost: $385,112 (cost effective). In the UK, ribociclib was found more cost effective and cost-saving than Palbociclib. Abemaciclib – no cost effectiveness evidence <u>Second line – with fulvestrant</u> Palbociclib – two studies in the US did not consider Palbociclib cost-effective. Ribociclib – two studies in the US; one acknowledged cost-effectiveness (Gain:1.19 life-years 0.96 QALYs ICER $157,343 per QALY), while one study in China did not. Abemaciclib – no cost effectiveness evidence
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☒ Yes ☐ No ☐ Not applicable Comments: There are no pediatric formulations available, since effectiveness and safety have not been established in those aged less than 18 yrs (The application submitted is for adult and pediatric use “if considered appropriate”; however the application states that pediatric use is not proposed). Cyclin-dependent kinase 4/6 inhibitors (palbociclib, ribociclib, abemaciclib) have been approved by the FDA and the EMA. Palbociclib is first-in-class, followed by ribociclib and abemaciclib. They are all on-patent, and expiry dates are January 2023 for Palbociclib in the US and Europe, but patents are surely to be extended up to 5 years. For ribociclib, the expiry is November 2031 and for abemaciclib, December 2029.

Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☐ No ☐ Not applicable Comments: No WHO guidelines are available. (According to the WHO, inclusion of cancer medicines on the WHO Model list must be done based on meaningful clinical benefit associated with treatment, which should be patient-centric and of public health relevance, with a threshold for benefit of at least 4-6 months survival gain).

Additional References

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