A.8	CYCLIN -DEPENDENT KINASE (CDK 4/6 inhibitors) - HR+/HER2+ breast cancer
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Explicitly discuss, the burden , greater than 50% of diagnosed with HR+ disease and the high proportion with advanced disease.
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.	CDK 4/6 inhibitors are indicated in primary or subsequent lines of managing HR + breast cancer . Their initial role was for the management of endocrine resistant breast cancer following treatment with hormonal agents Aromatase inhibitors, Tamoxifen and Fulvestrant which are the only hormonal agents listed in the current list except for fulvestrant . Prior to their development this subgroup of patients having failed several lines hormone therapies are subject to chemotherapy with poor outcome and AE. The benefit of these drugs compared to existing drugs is a proposed additional PFS , OS, QOL in all pre, post menopausal women, and men .The application is to endorse as an essential set of drugs the combination of these drugs with existing drugs for this purpose with the likely improvement in outcomes over existing medications in the metastatic setting.
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☒ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included: Desnoyers A, Nadler MB, Kumar V, Saleh R, Amir E. Comparison of treatment-related adverse events of different Cyclin-dependent kinase 4/6 inhibitors in metastatic breast cancer: A network meta-analysis. Cancer Treat Rev. 2020 Nov;90:102086. doi: 10.1016/j.ctrv.2020.102086. Epub 2020 Aug 17. PMID: 32861975.
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). PFS advantage undisputed across major phase 3 trials for all three drugs, MBCS V 1.1 at least 3 for first or second line with either ET or fulvestrant . Ribociclib scored the highest rating of 5. PFS gain > 5 months for ribociclib and abemaciclib, 4.9 for Palbociclib with fulvestrant In women with DFI<12 MONTHS MONOLESSA 3

	In pre menopausal women PALOMA 3, MONOLESSA 7, MONARCH 2 OS Gains reported in first line setting only for Ribociclib (MONOLESSA 3 and 7) Palbociclib in Paloma 3 , NS gain of 6.9 months in 2nd line setting. A 25% improvement in OS demonstrated for abemaciclib and ribocliclib considerably significant for a drug that is oral with minimal AE compared to chemotherapy indirectly suggesting minimal impact in QOL . Ribociclib is the only drug with patient reported outcomes extensively studied. A review of a recent metanalysis by Piezo m et al highlighted results but were not extensively discussed in the application. . Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients) Yes , stated categorically it has not been studied in children under 18 yrs There were document differences in AE type and severity in Blacks vrs Caucasian American and in Asians but not efficacy
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Afebrile neutropenia is the most common AE for all drugs and guidelines for monitoring and discontinuation described
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: . A causation statement for palbociclib with the highest discontinuation rate of 8-11% secondary to neutropenia worse in blacks. ECG changes occur with prolonged QT interval for Ribociclib and guidelines provided
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Favourable in the first line setting for ribociclib in the metastatic setting in combination with ET and fulvestrant in both pre and post menopausal setting , benefits out weigh risk of AE. Amebaciclib is of intermediate benefit in the first line setting but scores favourable in terms of low incidence of AE neutropenia. Uncertain is the role of Palbociclib in the first line setting due to borderline OS benefit and relatively higher incidence of drug discontinuation especially amongst certain ethnic groups such as blacks. In the second line setting , all drugs show a favourable benefit for patients with or without visceral metastases
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	The quality if the evidence provided is high. Very few phase 2 studies were analyzed in the application and shortcomings of the studies in discussion were elaborated.

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)	☒ Yes ☐ No ☐ Not applicable Comments: A base line EKG for patients on Ribociclib Hematological indices day 1 and 15 for first 2 cycles and based on physician discretion based on risk assessment intervals are increased. Guidelines are provided for dose reductions and drug discontinuation were necessary.
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)	☐ Yes ☒ No ☐ Not applicable Comments:
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)	☐ Yes ☒ No ☐ Not applicable Comments:
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	A cost effectiveness analysis indicates none of the medications were considered cost effective , worse in transitioning economies and LMIC. All of these drugs are currently patented and could account for the high price. The burden of women with metastatic breast cancer is higher in sub-Saharan Africa and yet many patients cannot access the drug further widening the global disparities In breast cancer outcomes.
Any additional comments	From my review of the application, I recommend these drugs should be assessed individually .
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.	Even though there is currently no data comparing the 3 types of CDK 4/6 I, on review of this document and other evidence , my assessment is as follows, Considering the impact on the MSCB v1.1, QOL scales, and definitive OS my view will be to support the application specific for Ribociclib in the first line setting in pre and post menopausal women in combination with ET or fulvestrant. In the second line setting and beyond all CDK4/6 i be recommended for patients with metastatic breast cancer in combination with ET or fulvestrant. A major concern is the injectable fulvestrant requiring regular hospital visits and inadvertently erode QOL . In the economic analysis , High cost of these drugs are likely to erode health spending budgets for LMIC.

References	