A.25	Pertuzumab – HER2+ metastatic breast cancer
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments:
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.	Pertuzumab is used in treatment of Her2+ breast cancer in combination with trastuzumab and a taxane in previously untreated MBC. it is more effective when a taxanes combination is used.
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:
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). CLEOPATRA: phase 3 randomised trial (n=808) ORR: 80% vs 69% PFS: Median 19 vs 12 months; HR 0.62, 95% CI 0.51-0.75. AT 8 YEARS OS: 57 vs 41 months OS: 37% vs 23% HR; for death 0.6, 95% CI 0.58-0.82.9 PERUSE MEDIAN PFS 21 months PUFFIN randomised phase 3 trail (n=243) Median PFS was 14.5 months in the pertuzumab arm (95% confidence interval [CI] 12.5, 18.6) and 12.4 months in the placebo arm (95% CI 10.4, 12.7) in the intention-to-treat population (HR: 0.69 [95% CI 0.49, 0.99]). CI overlapping.

	Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? N/A
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments:
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: CLEOPATRA trial 1. Diarrhea (67 vs 46%) 2. Neutropenia (53 vs 50%) 3. Rash (34 vs 24%) 4. Mucositis (27 vs 20%) 5. Dry skin (10 vs 4%) 6. Febrile neutropenia (Grade ¾) (14 vs 8%) 7. Neuropathy (31 vs 16%)
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	In the CLEOPATRA Trial only 10% patients received trastuzumab in adjuvant settings. At 8 years follow-up of CLEOPATRA trial in metastatic breast cancer improvement in overall- survival 57 vs 41 months. 8 years survival rates 0.69, 95% CI 0.58-0.82.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Moderate
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: HER 2positive BC by IHC3+ HER2 positive BC by FISH if IHC 2+
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.	The combination of trastuzumab and pertuzumab both highly expensive medicines presents a significant financial challenge to both patients and health systems in low middle income and some setting in high income countries too. The access in these settings is limited. Already the affordability and access to trastuzumab (Listed in EML model 2015) remains very limited in resource constraints settings. The addition of pertuzumab to trastuzumab will compound the problem in LMICs. Financial considerations preclude support for inclusion of pertuzumab on the EML list. Availability of biosimilar's is critical to improve affordability and access. Currently there is no data on optimal duration of pertuzumab in patients with HER2+ metastatic breast cancer. This is the research priority in order for pertuzumab to b accessible.
Any additional comments	
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.	NOT APPROVED The updated data from CLEOPATRA and other trails PERUSE, PUFFIN demonstrated relevant benefit in OS of pertuzumab + trastuzumab and a taxane in HER2 positive MBC could be supported from a clinical perspective. The survival data from PUFFIN and & PERUSE trial do not show the same benefit as CLEOPATRA. However, the combination therapy with trastuzumab + pertuzumab, both highly priced medicines would present significant financial challenges to patients and health systems and access in many settings would be limited. The number of cycles to provide the survival benefit is 24. Already access and affordability to trastuzumab (already listed in EML since 2015) remains very limited in resource constrained settings and addition of another highly priced biologic medicine will compound the problem. Availability of biosimilars is critical to improve affordability and access. Consideration needs to be given to determine optimal duration of therapy with pertuzumab as there is no current clinical data. We should reassess pertuzumab once biosimilars are available and financial toxicity decreases at both patient and government level.
References (if required)	