A.15	Fulvestrant – 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.	Fulvestrant: an ER antagonist that blocks ER dimerization and DNA binding, increases ER turnover, and inhibits nuclear uptake of the receptor. It is administered as an intramuscular injection (500 mg loading dose on days 1, 14, and 29 of the first month, then maintenance dosing monthly at day 28, ±3 days). Available for use 1st line and 2nd line use. In earlier studies, often lower doses were used, which may have hampered results. Up to Date states: Currently 1st line therapy hormone receptor positive metastatic breast cancer is an aromatase inhibitors plus CDK 4/6 inhibitors. Fulvestrant can be used with a CDK 4/6 inhibitor in those with prior aromatase inhibitor therapy. Single-agent treatment with fulvestrant or an aromatase inhibitor alone may also be appropriate for those with low disease burden or those who are less likely to tolerate combination with CDK 4/6 inhibitors. Fulvestrant versus aromatase inhibitor: The 1st line FALCON trial, randomised patients with histologically confirmed estrogen receptor-positive or progesterone receptor-positive, or both, locally advanced or metastatic breast cancer and received to fulvestrant (500 mg intramuscular injection; on days 0, 14, 28, then every 28 days thereafter) or anastrozole (1 mg orally daily). Median PFS was 16.6 months in the fulvestrant group vs 13·8 months (11·99–16·59) in the anastrozole group. The OS did not differ, but only 31% of events collected and quality of life was similar. ESMO-MCBS score 2. There has not been a head to head comparison between fulvestrant and an aromatase inhibitor plus a CDK 4/6 inhibitor. In combination with fulvestrant, the CDK4/6 inhibitors palbociclib, ribociclib and abemaciclib have each been approved for HR+/HER2- MBC following the results of randomized Phase III studies (PALOMA-3 (ESMO-MCBS 4, MONALEESA-3 ESMO-MCBS 4, MONARCH-2 ESMO-MCBS 3) and shown PFS advantage The addition of fulvestrant to aromatase inhibitor did affect OS in 1 of 2 trials: In the FACT trial, PFS and OS were similar for the combination of fulvestrant (500 mg loading dose, 250 mg on days 14 and 28, then 250 mg every 28 days) and anastrozole and anastrozole alone (11 vs 10 months; HR 0.99, 95% CI 0.81-1.20) and OS (38 months in both arms; HR 1.0, 95% CI 0.76-1.32). The SWOG S0226 trial compared anastrozole or fulvestrant plus anastrozole. The combination-therapy group had 247 deaths among 349 women (71%) and a median OS of 49.8 months, as compared with 261 deaths among 345 women (76%) and a median OS of 42.0

	months in the anastrozole-alone group, (HR for death, 0.82; 95% confidence interval [CI], 0.69 to 0.98; P=0.03 by the log-rank test). Differences between the 2 studies may be partly because there were more cases of endocrine-naïve patients in the SWOG S0226 trial than the FACT trial, and many patients with non-metastatic locally advanced cancers in the FACT trial (all patients in S0226 must have had distant metastases).
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 Meta-analysis included in the application showed low-certainty evidence of a median OS gain of 5.8 months and median PFS gain of 1 month for fulvestrant. There was substantial heterogeneity between individual trials (one showing no effect, one showing benefit). Fulvestrant has a score of 2 on the ESMO-MCBS for use in the 1st- and 2nd-line settings based on the FALCON trial: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards?filterType=agent&mcbs_score_cards_form%5Btested-agent%5D=Fulvestrant
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:

Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	• Monotherapy versus aromatase inhibitor only PFS effect known • Fulvestrant plus aromatase inhibitor: Meets threshold of 4-6 months based on meta-analysis and in, 1 study positive and in 1 study no effect on OS • No major side effect issues • Of advantage for patients when they do not tolerate aromatase inhibitor • Backbone in several studies with CDK4/6 inhibitors that show PFS effect of CDK4/6 inhibitors
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:
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.	• Is a highly-priced medicine • Eligible patient population is likely to be large • Cost-effectiveness studies had different conclusions, as did national medicine reimbursement agencies • It is unlikely to be used in LMICs
Any additional comments	Generic version approved by FDA 2019

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.	High-priced medicine, im administration, large numbers of potential patients, low ESMO-MCBS. ADVICE not to be on the EML list, unless CDK4/6 inhibitor data would require so. Moreover, medicine of interest for patients that do not tolerate Aromatase inhibitor. Propose not to list the medicine.
References (if required)	