A.15	Fulvestrant
Does the application adequately address the issue of the public health need for the medicine?	☐ Yes ☒ No ☐ Not applicable This application proposes to add fulvestrant to the list of WHO Essential Medicine as treatment for Women with Metastatic Breast Cancer
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.	The association of fulvestrant plus aromatase inhibitors has been studied in women hormone receptor-positive metastatic breast cancer as a first or second line of treatment : this association doesn't exist in guidelines Therapeutic agent currently used (recommendations of the European society of medical oncology) First line : inhibitors CDK4/6 (Ribociclib/Palbociclib/Abemaciclib) + Aromatase Inhibitors anastrozole or letrozole (AI) Second line : Inhibitors CDK4 6 +Fulvestrant Ou Exemestane + Everolimus (trial BOLERO)
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). It is difficult to draw a robust conclusion about the superiority of fulvestrant in association with aromatase inhibitors, in comparison to aromatase inhibitors alone considering the heterogeneity of the studies included in the systemic review. Moreover the results of the metanalysis showed that the use of fulvestrant in association with aromatase inhibitors, in comparison to aromatase inhibitors alone, increase the overall survival in approximately 7 months (HR 0.85, 95% CI 0.62 - 1.15; low certainty evidence) and the progression free survival in one month (HR 0.89, 95% 0.73 - 1.08; low certainty evidence). As described, there was substantial heterogeneity on the meta-analysis, with the FACT trial suggesting no effect and the SWOG0226 trial showing a benefit of

	fulvestrant plus aromatase inhibitors. There were many differences between these two trials beyond the type of patients included. Without having access to the individual patient data Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?
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.)	Uncertain
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	LOW Heteregenous methodology between clinical trials : The first trial conducted in postmenopausal women and premenopausal women receiving a gonadotropin-releasing hormone agonist, at first relapse after primary treatment. Investigators randomized participants to fulvestrant loading dose regimen followed by monthly injection plus 1 mg of anastrozole daily or to 1 mg of anastrozole daily alone. The second trial identified included postmenopausal women with previously untreated hormone-receptors-positive metastatic breast cancer. Participants were randomized to fulvestrant (intramuscularly at a dose of 500 mg on day 1 and 250 mg on days 14 and 28 and monthly thereafter) plus 1 mg of anastrozole daily or to 1 mg of anastrozole daily alone The third trial evaluated postmenopausal women with hormone-receptor-positive breast cancer who had relapsed or progressed with locally advanced or metastatic disease during treatment with aromatase inhibitors. Participants were randomized to fulvestrant (500 mg intramuscular injection on day 1, followed by 250 mg doses on days 15 and 29, and then every 28 days) plus daily oral anastrozole (1 mg); fulvestrant plus anastrozole-matched placebo; or daily oral exemestane (25 mg).

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: hormone receptor-positive metastatic breast cancer
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.	Only two studies of pharmacoeconomics were retained The Chinese study, post menopausal women with hormone receptor-positive metastatic breast cancer using a Markov model, showed that fulvestrant is cost effective with 15665/Qaly. The willingness to pay 29.383 /qaly.(which is very high) in this study the dose was 250 mg and not 500 mg as recommended in CONFIRM, on the other hand they only considered the direct costs and considered Chinese healthcare system perspective only. The second American study, which also used the Markov model, showed that fulvestrant is not cost effective yet it considered the dose of 500mg and direct costs only. The addition of fulvestrant to anastrozole cost 194.450 par Qaly gained with a threshold of 150.000 par qaly in US
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.	Unfavorable: there was a trend in favour of fulvestrant +IA but it didn't reach statistical significance. This association is not recommended in recommendations Very expensive.
References (if required)	