A.15	Estradiol – induction of puberty – EML
Draft recommendation	☒ Recommended ☐ Not recommended Justification: The reviewer supports the proposal for inclusion of **17-ß-estradiol tablets** as an individual medicine for the management of pubertal development in adolescents with primary or secondary ovarian failure to the **complementary list of EML**.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: The global prevalence of primary ovarian failure (POF) or primary ovarian insufficiency (POI) varies among different ethnic populations and depending of etiology: - Turner syndrome 5:10,000 females - Oncologic treatments 5:10,000 - 46,XY dysgenetic disorders of sex development (DSD) 6:100,000 - Other POF etiologies in females under 20 years of age 1:10,000. The long-term consequence of POF is an increased lifetime risk of cardiovascular disease, osteoporosis, earlier mortality, and neurocognitive disorders
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: Estrogens are the first line of inducing puberty in girls. Pubertal induction in girls with hypogonadism aims to mimic normal puberty. In a recent ENDO-ERN clinical practice guideline (Nordenstrom et al., 2022) recommends that 17-β-estradiol be used especially for pubertal induction. Indeed, 17-β-estradiol is bioidentical in contrast to non-bioidentical agent (e.g. ethinylestradiol, conjugated equine oestrogens, dienestrol and mestranol).
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:

Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments:
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: Diagnosis and management of absent pubertal development in girls are mostly performed by paediatric endocrinologists and, in some countries with limited capacity, by adult endocrinologists and general paediatricians. The cause of absence of pubertal development are suspected by history and physical examination. Hormonal investigations and imaging, if needed, are key to confirm the diagnosis and will be adapted on an individual basis and may include: - Serum levels of LH, FSH, estradiol, prolactin (all included in the EDL) - Karyotype (Turner syndrome) - Pelvic ultrasound - MRI of the brain Routine monitoring of serum LH or FSH levels is not recommended during estrogen treatment, because levels remain elevated in agonadal girls until higher levels of estrogen are given. Blood count, liver function tests and lipid profile are recommended to assess potential complications of estrogens. Bone age, pelvic ultrasound and bone densitometry are recommended on a case-by-case basis to assess the effect of the therapy but do not replace careful clinical follow up
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☒ No ☐ Not applicable Comments: Estradiol is globally available as a generic product and a variety of branded formulations and is affordable. Submission includes several examples for the cost of 1 tablet of 1 or 2mg: - Argentina: 2 mg: 0.15 USD - India: 1mg: 0.11 USD - Mexico: not available - New Zealand: 1 mg and 2 mg (same price): 0.14 NZD (= 0.09 USD) On average, the monthly cost is 2.7 to 4.5 USD
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: Estradiol is authorized worldwide in a range of branded and generic products. The submission has included a brief summary of marketing authorization status in stringent regulatory authorities such as US FDA, EMA, Health Canada and PMDA.

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: Currently there are no WHO guidelines for the management of adolescent girls with absent pubertal development. However, in the 3rd EDL Technical Report, in 2021 (TRS 1031, https://www.who.int/publications/i/item/9789240019102, pp 106-148), there is an extensive background and discussion on POF and the relevant laboratory tests.