Estradiol

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 18. Medicines for endocrine disorders > 18.3. Estrogens

ATC codes: G03CA03

Indication	Gonadotropin deficiency ICD11 code: 5A61.2
INN	Estradiol
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid > tablet:** 0.5 mg ; 1 mg ; 2 mg
EML status history	Application rejected in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Estradiol
DrugBank	Estradiol

Expert Committee recommendation

The Expert Committee noted that management of delayed pubertal development with estradiol aims to mimic normal puberty to allow achievement of final adult height and healthy bone mass accrual, and to avoid adverse physical and metabolic consequences in adolescents with primary or secondary ovarian failure. The Committee noted that the global prevalence of primary or secondary ovarian failure and primary ovarian insufficiency varies in different ethnic populations but was generally low. The Committee considered that the application reported insufficient information on the evidence supporting the efficacy and safety of estradiol for the proposed indications. The Committee also considered that information on the optimal dosage and formulations for use in the proposed population was inadequate. The Committee advised that any future consideration of estradiol therapy for inclusion on the Model Lists should also address its use in the management of other indications for which it is commonly used, such as hormone replacement therapy in menopause or after hysterectomy. The Expert Committee therefore did not recommend the inclusion of 17-β estradiol on the complementary list of the EML for the management of pubertal development in adolescents with primary or secondary ovarian failure.

Background

17-β-estradiol has not previously been considered for inclusion on the EML for management of pubertal development. Ethinylestradiol as hormone replacement therapy was included on the EML from 1977 until 2011, when it, and progestogens medroxyprogesterone acetate and norethisterone, were recommended for deletion. At that time, after consideration of a review of the available evidence, the Committee noted that long-term hormone

replacement treatment of menopause was no longer considered appropriate, notwithstanding possible individual need for the treatment of symptoms. The Committee recommended deletion of these medicines and signalled the need for a review of the short-term symptomatic management of menopause and the development of guidelines in this regard (1).

Public health relevance

The global prevalence of primary ovarian failure or primary ovarian insufficiency varies in different ethnic populations (2,3). It is characterized by elevated levels of gonadotropins and low levels of estradiol, and lack of spontaneous pubertal development and pubertal growth spurt, accompanied by symptoms including reduction in ovarian function and primary amenorrhoea/oligomenorrhoea. The prevalence of primary ovarian failure according to etiology is 5/10 000 females for Turner syndrome (4), 5/10 000 for oncological treatments (5), 6/100 000 for 46,XY dysgenetic disorders of sex development (6) and 1/10 000 for other etiologies of primary ovarian failure in females younger than 20 years (7). Long-term consequences of primary ovarian failure include increased lifetime risk of cardiovascular disease, osteoporosis, earlier mortality, and neurocognitive disorders (8) Secondary ovarian insufficiency (hypogonadotropic hypogonadism) is caused by multiple pituitary hormone deficiency in 1/10 000 newborns (9) or isolated gonadotropin hormone-releasing hormone deficiency in 1/125 000 females (10). It can also occur as a result of structural abnormalities, such as pituitary tumours or craniopharyngiomas and their treatments. The application defined absent pubertal development in girls as the absence of breast development by 13 years or the absence of menarche by 15 years. Accumulating data show that initiation of puberty at an age comparable with peers is essential for normal physiological development, including secondary sex characteristics, bone and muscle, and social, sexual and psychologic development. Delayed pubertal induction, which is often the case in individuals without pubertal development, may have longstanding consequences (11).

Benefits

The application presented a narrative summary of the benefits of estrogen therapy for induction of puberty in girls with hypogonadism. Estrogens are recommended as first-line treatment for inducing puberty in girls with hypogonadism (12,13), with the aim of mimicking normal puberty and allowing girls to achieve normal final adult height and healthy bone mass accrual, and avoiding adverse physical and metabolic consequences of hypogonadism (e.g. lack of breast development, infertility, cardiovascular disease, bone loss/osteoporosis) (14,15). The 2022 guidelines of the European Reference Network on rare endocrine conditions (11) recommend the use of bioidentical human estrogens (estradiol/17-□-estradiol E2) for pubertal induction or to sustain puberty in girls (low-quality evidence). The optimal type, route and administration, however, are not well established, and no advantage was observed for one type over another. From studies evaluated in the guideline development process, it was noted that transdermal forms were associated with estradiol, estrone and bioestrogen concentrations closer to normal in the high-dose transdermal group compared with oral forms, and normalization of gonadotropins was comparable between treatments when high-dose transdermal treatment was used (16). Oral 17-β-estradiol at a dose of 4 mg daily for 5 years immediately after pubertal induction was associated with more girls with Turner syndrome achieving a normal uterine size than those receiving a dose of 2 mg daily (17). For metabolic endpoints, including effects on bone mineralization, body composition, body mass index, lipids, glucose, insulin tolerance, protein turnover and lipolysis, there was very low-quality evidence that transdermal and oral routes of estrogen delivery had similar effects (18–20). The application acknowledged that the use of transdermal formulations was promising. However it did not propose inclusion of transdermal formulations for a number of reasons including: the need to change patches regularly which may not be acceptable to adolescents; the need to cut/manipulate adult patches; the limited availability in resource-constrained settings; stability concerns at different temperatures; and lack of comparative studies.

Harms

There is no evidence of liver toxicity (21) or increased risk of cancer before the age of natural menopause in women with primary ovarian failure (22) given estrogen replacement therapy. The evidence of potential harm related to estrogen therapy in girls with hypogonadism is dose related: high-dose estrogen treatment early in

puberty or rapid dose escalation may result in reduced final height and poor breast development, such as prominent nipple development with poor supporting breast tissue. This effect can be minimized by a gradual start with low-dose estrogen regimens. There are also concerns that supraphysiological supplementation may adversely affect uterine development and bone mass accrual (23). Non-specific adverse events that have been reported include nausea, vomiting, fluid retention, hypertension, ankle oedema, headache, depression, nervousness, insomnia, leg cramps, decreased high-density lipoprotein cholesterol, acne, itching, dry skin, dysmenorrhoea and irregular vaginal bleeding.

Cost / cost effectiveness

The application reported the monthly cost of treatment with 17-β-estradiol to be US$ 2.70 and US$ 4.50 for doses of 1 mg and 2 mg a day, respectively. Individual tablet costs were reported as US$ 0.15 for 2 mg tablets in Argentina, US$ 0.11 for 1 mg tablets in India and US$ 0.09 for both 1 mg and 2 mg tablets in New Zealand. No cost–effectiveness data were presented in the application.

WHO guidelines

WHO guidelines for management of pubertal development in adolescents with primary or secondary ovarian failure are not currently available.

Availability

Estradiol tablets are available globally in branded and generic formulations. Child-appropriate formulations are lacking for younger children, with the available formulations requiring manipulation to obtain appropriate doses.

Other considerations

The sexual health and reproductive cancers unit within the WHO Department of Sexual and Reproductive Health and Research reviewed the application. The technical unit supported the inclusion of 17-β-estradiol on the EML as an option to enable induction of puberty in: adolescents with certain relevant differences in sex development, including Turner syndrome; adolescent females who have undergone certain oncology treatments resulting in primary failure; and other adolescent females with primary ovarian failure. The technical unit highlighted that use of the medicine could support the prevention of bone loss, and noted the potential harm related to estrogen therapy delivered to adolescents at too high a dose and expressed concern about the current availability of adolescent-appropriate dosage forms in tablets or as transdermal patches. The technical unit noted the importance of holistic care for individuals with differences of sex development throughout the life course, including during adolescence. This care includes interdisciplinary support for mental and emotional well-being and development in addition to physical health and development. The technical unit highlighted that WHO did not currently have clinical guidelines on induction of puberty in adolescents and advised that the comments provided in relation to this application should be taken as a WHO recommendation. The technical unit also advised that it would welcome external appraisal of the current evidence about estrogen-only and combined estrogen–progestogen hormone replacement therapy for menopause to determine whether it warranted inclusion in the EML for relief of menopausal symptoms.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2011 (including the 17th WHO Model List of Essential Medicines and the 3rd WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2012 (WHO Technical Report Series, No. 965; https://apps.who.int/iris/handle/10665/44771, accessed 6 October 2023).
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