Letrozole

Essential medicine status

Section: 22. Medicines for reproductive health and perinatal care > 22.2. Ovulation inducers

ATC codes: L02BG04

Indication	Female infertility without specification whether primary or secondary ICD11 code: GB4Z
INN	Letrozole
Medicine type	Chemical agent
List type	Complementary
Formulations	Oral > Solid > dosage form: 2.5 mg
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	Medicines within the same pharmacological class can be used
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Letrozole
DrugBank	Letrozole

Expert Committee recommendation

The Expert Committee acknowledged that the availability of and access to effective treatments for infertility was important as part of sexual and reproductive health and for achieving targets of the SDGs. The Committee noted evidence that letrozole was associated with a moderate increase in live births and clinical pregnancies compared with clomifene (a medicine currently included in the EML) in patients with infertility due to polycystic ovary syndrome, and had similar efficacy to clomifene for live births or biochemically tested pregnancy in couples with unexplained infertility. The Committee considered the safety profile of letrozole to be acceptable and, on balance, the medicine to have a favourable benefit-to-harm profile. The Committee noted that WHO guidelines for the prevention, diagnosis and treatment of infertility were in development and were expected to include recommendations for use of letrozole for ovulation induction in women with infertility caused by polycystic ovary syndrome, and women with unexplained infertility undergoing intrauterine insemination. Based on these considerations, the Expert Committee therefore recommended inclusion of letrozole on the complementary list of the EML for the treatment of anovulatory infertility associated with polycystic ovary syndrome or unexplained infertility. Listing was recommended with anastrozole as a therapeutic alternative under a square box listing.

Background

Aromatase inhibitors for the treatment of anovulatory infertility have not previously been considered for inclusion in the EML. Anastrozole (with a square box specifying other aromatase inhibitors classified at the fourth level ATC chemical subgroup L02BG as therapeutic alternatives) is included on the EML for use in the treatment of early-stage and metastatic breast cancer.

Public health relevance

Infertility affects millions of people worldwide, often with serious consequences. In 2010, up to 48.5 million couples were estimated to be affected by infertility globally (1). Although a large proportion of adults express a desire for children (2,3), nearly one in six

experience infertility, which is defined as a disease of the reproductive system characterized by the failure to achieve a clinical pregnancy after 12 months of regular unprotected sexual intercourse (4). Fertility care is an important component of sexual and reproductive health and rights, but in most countries, infertility policies and services are inadequate. The Universal Declaration of Human Rights (Article 16) states that "men and women of full age, without any limitation due to race, nationality or religion, have the right to marry and found a family" (5). Treating infertility is part of realizing the human right to the enjoyment of the highest attainable standard of physical and mental health, as well as the right to decide the number, timing and spacing of children (6). Addressing infertility is also central to achieving Sustainable Development Goal (SDG) 3 (ensure healthy lives and promote well-being for all at all ages) and SDG 5 (achieve gender equality and empower all women and girls). However, fertility care services are unavailable or unaffordable in many countries, particularly in low- and middle-income countries (7). Although uncertainty exists, ovulatory disorders may account for up to 25% of infertility (8,9), with 70% of ovulatory dysfunction due to polycystic ovary syndrome. Similarly, although uncertainty exists, up to a further 15% of couples are thought to have so-called unexplained infertility (8). These are the two causes of infertility for which aromatase inhibitors can be used as part of treatment. Therefore, up to 40% of infertility cases, or 19 million couples globally, could benefit from fertility treatment with ovulation induction medicines, including aromatase inhibitors.

Benefits

Note on concerns about data integrity The application highlighted that some clinical evidence in this area has been affected by concerns of potential research fraud. Several manuscripts by Badawy and Abu Hashim have been retracted or are the subject of editorial expressions of concern (10–15). Some systematic reviews that provided data to support this application had included data from the above research group. To mitigate this issue, the applicants conducted a re-analysis excluding potentially fraudulent data, where these data had been included. Conclusions are based on analyses that excluded these studies. Infertility due to polycystic ovary syndrome A 2022 Cochrane systematic review and meta-analysis evaluated the effectiveness and safety of aromatase inhibitors compared with clomifene citrate (a selective oestrogen receptor modulator) for ovulation induction in infertile women with polycystic ovary syndrome (16). This review did not include studies by Badawy and Abu Hashim. The review found moderate-certainty evidence for a moderate increase in live births (risk ratio (RR) 1.52, 95% confidence interval (CI) 1.29 to 1.80; absolute difference 104 more live births per 1000 (95% CI 58 to 160 more); eight randomized controlled trials, 1646 participants) and clinical pregnancies (RR 1.41, 95% CI 1.25 to 1.58; absolute difference 94 more clinical pregnancies per 1000 (95% CI 58 to 133 more); 17 randomized controlled trials, 2516 participants) with letrozole compared with clomifene in patients with infertility due to polycystic ovary syndrome. Unexplained fertility As part of developing a new guideline for the treatment of infertility, WHO commissioned an analysis by a team at McMaster University, Canada, to adapt the 2019 systematic review by Eskew and colleagues (17) of letrozole use in unexplained infertility by excluding potentially fraudulent data from the analysis. The result of the as-of-yet unpublished analysis by McMaster University is presented in the application as the best available meta-analysis. Results of this analysis found no significant difference between letrozole and clomifene citrate when used for ovarian stimulation followed by intrauterine insemination for couples with unexplained infertility for: live births (RR 1.00, 95% CI 0.81 to 1.22; absolute difference 0 more live births per 1000 (95% CI 125 fewer to 145 more; one randomized controlled trial, 191 participants, low-certainty evidence); or pregnancy (RR 1.32, 95% CI 0.83 to 2.09; absolute difference 80 more pregnancies per 1000 (95% CI 43 fewer to 272 more; five randomized controlled trials, 1266 participants). Anastrozole The Cochrane systematic review (16) included one trial (40 participants) comparing letrozole and anastrozole (18). No data were available for live births and there was insufficient evidence of a difference between treatments for the outcome of clinical pregnancy rate (odds ratio (OR) 1.88, 95% CI 0.40 to 8.88).

Harms

In the context of using aromatase inhibitors for ovulation induction, the main serious adverse events are ovarian hyperstimulation syndrome, a rare but serious syndrome associated with treatments that stimulate ovulation, and multiple pregnancy. Less serious adverse effects that can occur with letrozole treatment include hot flashes, headache, fatigue, dizziness and irritability. Infertility due to polycystic ovary syndrome The above-mentioned Cochrane systematic review included data on miscarriage, ovarian hyperstimulation syndrome and multiple pregnancies in the meta-analysis (16). It found that compared with clomifene citrate, the risk of miscarriage was slightly increased with letrozole (RR 1.36, 95% CI 0.98 to 1.89; absolute difference 22 more miscarriages per 1000 (95% CI 1 fewer to 53 more); 10 randomized controlled trials, 1752 participants, moderate-certainty evidence), with no difference in the risk of multiple pregnancies (RR 0.69, 95% CI 0.34 to 1.41; absolute difference 6 fewer per 1000 (95% CI 13 fewer

to 8 more); 12 randomized controlled trials, 1971 participants, low-certainty evidence) and ovarian hyperstimulation syndrome (risk difference (RD) 0.00, 95% CI –0.01 to 0.00; absolute difference 0 fewer cases of ovarian hyperstimulation syndrome per 1000 (95% CI 10 fewer to 0); eight randomized controlled trials, 1572 participants, low-certainty evidence). Unexplained fertility For letrozole versus clomifene citrate followed by intrauterine insemination in unexplained infertility, the McMaster University re-analysis found a small reduction in miscarriage (RR 0.52, 95% CI 0.20 to 1.38; absolute difference 134 fewer miscarriages per 1000 (95% CI 224 fewer to 106 more); four randomized controlled trials, 324 participants, low-certainty evidence) and no differences in multiple pregnancies (RR 0.76, 95% CI 0.22 to 2.64; absolute difference 17 fewer multiple pregnancies per 1000 (95% CI 55 fewer to 116 more); four randomized controlled trials, 323 participants, low-certainty evidence) or ectopic pregnancies with letrozole compared with clomifene citrate. Another systematic review and meta-analysis of 45 studies (17 randomized controlled trials with 776 participants, 21 comparative cohorts with 2453 participants and seven non-comparative cohorts) analysed the risk of fetal harm after letrozole use for ovulation induction/ovarian stimulation in couples with infertility of different causes (19). Studies of concern were excluded from that analysis. The review found no difference in the risk of congenital malformations with letrozole versus clomifene citrate (RD from randomized controlled trials: 0.00, 95% CI –0.02 to 0.02; RD from cohort studies: –0.02, 95% CI –0.04 to –0.01). In the above-mentioned study comparing letrozole and anastrozole, no data were available for ovarian hyperstimulation syndrome. No multiple pregnancies were reported with either treatment (30,31).

Cost / cost effectiveness

The application presented comparative prices of aromatase inhibitors and clomifene citrate as shown in Table 27 (refer TRS 1049). In most comparisons, letrozole and anastrozole were more expensive than clomifene citrate. However, the absolute cost was not high, and the medicines were likely to only be used for 5 days per cycle, so their total cost, relative to the overall cost of treatment including stimulated intrauterine insemination, would also not be high. No relevant studies were identified in the application that assessed the cost–effectiveness of aromatase inhibitors for the proposed indications.

WHO guidelines

WHO guidelines on the prevention, diagnosis and treatment of infertility are currently being developed and are expected to be published by the end of 2023. Based on the evidence reviewed so far, the Guideline Development Group intends to suggest the use of letrozole as the preferred agent for ovulation induction in women with infertility caused by polycystic ovary syndrome, and the use of either letrozole or clomifene citrate in women with unexplained infertility undergoing intrauterine insemination.

Availability

Letrozole and anastrozole are available globally as originator and generic brands.

Other considerations

Neither letrozole nor anastrozole are approved for the treatment of infertility by the United States Food and Drug Administration or by the European Medicines Agency; their use for this indication is off label.

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