A.23	Letrozole – infertility – EML
Draft recommendation	☒ Recommended ☐ Not recommended Justification: Infertility is a prevalent health problem and female infertility may surpass male infertility. In around 40% of infertility cases, the source is polycystic ovarian syndrome or unexplained infertility. There is some evidence in SR&MA that letrozole likely provides greater benefits than clomiphene citrate among patients with infertility due to PCOS and similar benefits in patients with unexplained infertility. Although there is moderate certainty evidence for benefits and some harms, there is still low certainty evidence for the harm outcomes. Therefore, the overall certainty of evidence is LOW. In this case, the balance probably favors the intervention. Clomiphene citrate is the only drug listed for ovarian stimulation (complementary list). The addition of one more, for the same purpose and in the same list may seem unnecessary, despite the moderately favourable evidence. Clomiphene citrate is also much cheaper. There are price and cost-of-treatment comparisons, but no studies on comparative cost-effectiveness. However, in terms of provision possibilities, adding this drug may be a correct decision, as markets differ and drug shortages are ever more present around the world, mainly for low-cost and very low-cost drugs, which the pharmaceutical industry may choose not to manufacture any longer. An issue is the possible off label indication for ovulation induction in many jurisdictions. Additionally, the application is being submitted by the Sexual and Reproductive Health and Research Department of the WHO. Whilst there are no present WHO guidelines for the treatment of infertility they are being developed, with planned publication in late 2023. That guideline will recommend the use of letrozole as more effective and safer ovulation induction agent than clomiphene citrate. It is important that the EML and the WHO department recommendations coincide. I recommend the inclusion of letrozole as an ovulation stimulant with addition to (or in substitution of) clomiphene citrate in the complementary list. Reforming this section in the near future may be an adequate approach, as new evidence will be produced after the guideline, and there is thus an opportunity not to lengthen the list.

Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Infertility is an important health problem worldwide, with an estimate average of 48.5 million infertile couples worldwide[1]. Nearly one in six couples are infertile (infertility is defined as a condition of the reproductive system characterised by the failure to achieve a clinical pregnancy after 12 months of regular unprotected sexual intercourse). A 2019 study showed that female factors for infertility surpass male factors[2]. The public health relevance for the application is that a large portion of infertility, up to 25%, may be due to ovulatory disorders, which in turn, are 70% due to PCOS. Another 15% of couples have 'unexplained infertility'[1]. This application proposes an approach for 40% of infertility cases, or 19 million couples around the world. Founding a family is a Universal Health Right. Two Sustainable Development Goals (3 and 5) also indirectly address infertility. It is noteworthy that fertility services are perhaps unavailable or unaffordable in several countries, mainly low-resourced countries.

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: This application is for the use of aromatase inhibitors (letrozole and anastrozole) to be included as "Ovulation inducers" (section 22.2 in the 2021 WHO EML) and proposes the addition of letrozole to the complementary list as an ovulation inducer. Clomiphene citrate is the only medicine included in the EML as an ovulation inducer (complementary list). This REVIEW will focus on letrozole only. The subtypes of infertility deemed to be treated with letrozole are unexplained infertility and infertility due to Polycystic Ovarian Syndrome (PCOS). PCOS affects 8-13% of women of reproductive age. Clinical features are irregular menstrual cycles, hirsutism, infertility, and pregnancy complications. It is typically diagnosed based on the Rotterdam criteria with two of three features: anovulation or oligo-ovulation, polycystic ovarian morphology on ultrasound and hyperandrogenism, with the exclusion of other diagnoses. Clomiphene citrate (CC) is a selective oestrogen receptor modulator. Letrozole blocks oestrogen synthesis, stimulating ovarian follicle development and maturation. Both are administered orally. Letrozole is used for ovulation induction at a dose range of 2.5-7.5mg once daily for 5 days at the beginning of the follicular phase of the menstrual cycle. As to comparative effectiveness with clomiphene as the comparator and letrozole, there are several RCT and SR and MA available in the literature. Because of suspicion in a series of studies, resulting in retraction, some were not included in the analysis promoted by applicant. An independent search produced other references that made mention to the suspicious studies and were not used in this template[3,4]. Three SR&MA were included (Franik et al, 2022; Pundir et al.2021; Eskew et al, 2019). For effectiveness, live births (1646 patients in 8 RCTs; moderate certainty of evidence RR 1.52 (1.29 to 1.80)) and clinical pregnancies (2516 participants in 17 RCTs; moderate certainty of evidence; RR 1.41 (1.25 to 1.58) were the outcomes of choice. Evidence from meta-analyses found that letrozole likely provides greater benefits than clomiphene citrate among patients with infertility due to PCOS and similar benefits in patients with unexplained infertility. To add another view, a SR on agents for ovarian stimulation in ovulatory women with infertility, but for the purpose of intrauterine insemination (IUI), there was no certainty regarding the superiority of aromatase inhibitors (AI) in improving live birth rate compared with anti-oestrogens (OR 0.75, CI 95% 0.51 to 1.11; 1 study, 599 participants; low-certainty evidence). The chance of a live birth following anti-oestrogens is 23.4% versus 13.5% and 25.3% for AI[5]. Another study compared gonadotrophins with oral agents for unexplained infertility and found that gonadotrophins are more effective in producing live births[6].

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: As to comparative effectiveness with clomiphene as the comparator and letrozole, there are several RCT and SR and MA available in the literature. Because of suspicion in a series of studies, resulting in retraction, some were not included in the analysis promoted by applicant. An independent search produced other references that made mention to the suspicious studies and were not used in this template[3,4]. Three SR&MA were included (Franik et al, 2022; Pundir et al.2021; Eskew et al, 2019). For safety, miscarriages (1752 patients in 10 RCTs, moderate certainty of evidence; RR 1.36 (0.98 to 1.89)), multiple pregnancy (1971 in 12 RCTs; low certainty of evidence; RR 0.69 (0.34 to 1.41), ovarian hyperstimulation syndrome (1572 in 8 RCTs; low certainty of evidence; 4 cases in 1000) and congenital foetal malformations (776 in 13 RCTs; low certainty of evidence; 18 cases per 1000), were the outcomes of choice. Overall certainty of evidence of safety is low. In another SR on agents for ovarian stimulation in ovulatory women with infertility, but for the purpose of intrauterine insemination (IUI), there was no certainty regarding the safety of AI as compared with anti-oestrogens in leading to a higher multiple pregnancy rate (OR 1.28, CI 95% 0.61 to 2.68; I 2 = 0%; 4 studies, 1000 participants; low-certainty evidence)[5]. Another study compared gonadotrophins with oral agents in unexplained infertility and found that even if gonadotrophins are more effective in producing live births, there is a greater risk of adverse outcomes, namely multiple pregnancies[6].
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Side effects of clomiphene citrate (include changes to the endometrium and cervical mucus, and hot flashes) are likely to be more relevant that for letrozole due to a shorter half-life of the latter. However, common side effects of letrozole are several: headaches, depression, somnolence , Carpal Tunnel Syndrome, sensory disturbances (including paraesthesia, taste loss and taste perversion), palpitations, hot flushes, hypertension, nausea, dyspepsia, constipation, abdominal pain, diarrhoea, vomiting, anorexia, hypercholesterolaemia, increased levels of alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase, hyperhidrosis, alopecia, rash, dry skin, arthralgia, myalgia, bone pain, osteoporosis, bone fractures, arthritis, vaginal bleeding, vaginal dryness fatigue (including asthenia, malaise) , weight increase, peripheral oedema, chest pain. More serious side effects such as hepatitis, Stevens-Johnson syndrome, angioedema, urticaria, hypercalcaemia, tendon rupture, hyperbilirubinemia, jaundice, ischaemic cardiac events, thrombophlebitis, pulmonary embolism, arterial thrombosis, cerebral infarction are uncommon or rare. Safety outcomes of choice that must be carefully monitored are miscarriages, multiple pregnancies, ovarian hyperstimulation syndrome and foetal malformations.

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: Given the profile of common side effects, treatment with letrozole requires monitoring as well as access to specialist care. Monitoring of follicular growth by transvaginal ultrasound during a stimulation cycle for effectiveness and to reduce the occurrence of adverse events is recommended.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: Costs of both letrozole and clomiphene citrate are low; however, clomiphene citrate is very low-cost in comparison to letrozole (average 10x lower). Costs could vary depending on context, and differences in availability of funding or health insurance for fertility services. However, overall letrozole is probably more expensive. Although the costs of letrozole may be higher this is outweighed by the moderate sized benefits related to an increase in live births (as compared with clomiphene citrate). There are no cost-effectiveness analyses.
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: Letrozole is available as a 2.5mg tablet or capsule. Provision is esteemed feasible. It was patented in 1986 and approved for medical use in 1996. Prices are relatively low around the world, except for the US. However, in many jurisdictions it is approved for indications in cancer and would be off label for ovulation induction.
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: There are no present WHO guidelines for the treatment of infertility but they are being developed, with planned publication in late 2023. This guideline will recommend the use of letrozole as more effective and safer ovulation induction agent than clomiphene citrate (presently on the WHO EML complementary list).

Additional References

1. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS Med. 2012;9:e1001356 Available from: https://dx.plos.org/10.1371/journal.pmed.1001356.

2. Elhussein, O.G., Ahmed, M.A., Suliman, S.O. et al. Epidemiology of infertility and characteristics of infertile couples requesting assisted reproduction in a low-resource setting in Africa, Sudan. Fertil Res and Pract 5, 7 (2019). https://doi.org/10.1186/s40738-019-0060-1

3. Qin F, Zhou Y, Huan L, Gui W. Comparison of clomiphene and letrozole for superovulation in patients with unexplained infertility undergoing intrauterine insemination: A systematic review and meta-analysis. Medicine (Baltimore). 2020 Jul 31;99(31):e21006. doi: 10.1097/MD.0000000000021006.

4. Yu Q, Hu S, Wang Y, Cheng G, Xia W, Zhu C. Letrozole versus laparoscopic ovarian drilling in clomiphene citrate-resistant women with polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. Reprod Biol Endocrinol. 2019 Feb 6;17(1):17. doi: 10.1186/s12958-019-0461-3.

5. Cantineau AE, Rutten AG, Cohlen BJ. Agents for ovarian stimulation for intrauterine insemination (IUI) in ovulatory women with infertility. Cochrane Database Syst Rev. 2021 Nov 5;11(11):CD005356. doi: 10.1002/14651858.CD005356.pub3

6. Zolton JR, Lindner PG, Terry N, DeCherney AH, Hill MJ. Gonadotropins versus oral ovarian stimulation agents for unexplained infertility: a systematic review and meta-analysis. Fertil Steril. 2020 Feb;113(2):417-425.e1. doi: 10.1016/j.fertnstert.2019.09.042.