National Essential Medicine List
Tertiary Medication Review Process
Component:

Review updated and adapted form Adult Hospital Level Expert Review Committee (ERC) – June 2017

MEDICINE MOTIVATION:

1. Executive Summary

Date: March 2020 (Initial Adult review: June 2017)
Medicine (INN): Letrozole
Medicine (ATC): L02BG04
Indication (ICD10 code): Female infertility associated with anovulation (N97.0)
Patient population: Females with infertility due to anovulation (WHO classification of ovulation disorders Group II: hypothalamic-pituitary-ovarian dysfunction (predominately polycystic ovary syndrome)[1].
Prevalence of condition: 25% of all infertile couples; 1 out of 7 couples have infertility
Level of Care: Tertiary
Prescriber Level: Specialist - Obstetrician and gynaecologist
Current standard of Care: Clomifene (adult hospital level)
Note: Letrozole can be used as a second line option when there is failure or resistance to clomifene, which occurs in 20% of cases. (Clomifene resistance is defined as failure to ovulate after receiving 150 mg of clomifene daily for 5 days per cycle, for at least three cycles).[2]
Efficacy estimates:
Randomised controlled trial:[3]

- Pregnancy rate: Letrozole 61%, clomifene 43%, rate ratio =1.4 (95% CI 1.1 to 2.0), absolute difference = 18% (3 to 33%), p = 0.022. NNT = 6
- Live birth rate: Letrozole 48.8%, clomifene 35.4%, rate ratio = 1.4 (95% CI 0.95 to 2.0), absolute difference = 13% (-2 to 28%), p = 0.089. NNT = 7
- Time to pregnancy: shorter with letrozole (4 versus 6 cycles with clomifene)

Cochrane[4]
Letrozole vs. clomifene with or without adjuncts - OR 1.64, 95% CI 1.32 to 2.04, n=1783, I^2=3%); NNT=12 (i.e. need to treat 12 women with letrozole for an additional live birth compared to clomifene).
Motivator/reviewer name(s): Initial reviewers: GS Gebhardt, supported by TD Leong. Updated by Tertiary ERC.

2. Name of author(s)/motivator(s)

Initial Review: GS Gebhardt, Trudy Leong
Review Update: Tertiary Committee

Author affiliation and conflict of interest details

GS Gebhardt: Stellenbosch University, National Committee of Confidential Enquiries into Maternal Deaths (NCCEMD); no conflict of interest declared.
T D Leong: National Department of Health, Essential Drugs Programme; Secretariat to the Adult Hospital Level Technical Sub-Committee of NEMLC; no conflicts of interest.
Tertiary Committee: No conflicts of interest declared

3. Introduction/ Background

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women and yet remains enigmatic. Despite its high prevalence in the population, much controversy remains regarding its diagnosis, its aetiology and the most appropriate treatment strategy.[5] Anovulation may be due to PCOS, obesity, hypothalamic dysfunction related to eating disorders, extremes of weight loss, exercise or other stress, hyperprolactinemia, pituitary tumours, or thyroid disease in some cases, but often the immediate cause cannot be determined. Clomifene citrate (CC) was the initial treatment of choice for most anovulatory or oligo-ovulatory infertile women.[6] Due to the high rate of insulin resistance in women with PCOS, metformin is often given as pre-treatment before or in combination with CC. Several small randomized, controlled studies have shown that pre-treatment with metformin in doses of 1,500 to 1,700 mg daily significantly improved ovulation rates and pregnancy rates in response to CC in women who had previously failed to ovulate with CC alone (summarized in(3)). Based on a systematic review and meta-analysis from 2012, metformin on its own cannot regarded as a primary ovulation induction agent.[7]

Letrozole is a non-steroidal aromatase inhibitor and is registered for use in post-menopausal women with breast cancer. Letrozole has excellent pregnancy rates compared to clomifene citrate and can be considered at par with CC as first line drug for ovulation induction in infertile women with PCOS.[8] Aromatase inhibitors have been used successfully to induce ovulation in women with PCOS. Aromatase inhibitors block the conversion of androgens to oestrogens in the ovarian follicles, peripheral tissues and in the brain, which results in firstly the fall in circulating and local oestrogens and secondaly a rise in intraovarian androgens. The fall in oestrogen levels releases the hypothalamopituitary axis from the negative feedback of oestrogens, thus there is a surge in follicle stimulating hormone release resulting in follicular growth. [9]

Multiple reports suggest that aromatase inhibitors may be effective alternative agents for ovarian stimulation in couples with unexplained infertility. Their administration is reported to be associated with monofollicular development in most cases which may result in enhanced fertility and a reduced risk of ovarian hyperstimulation and multiple births as compared with current standard therapies such as gonadotropin and clomifene. Use of an aromatase inhibitor to promote conception has not been associated with a significantly increased risk of congenital anomalies.[10]

4. Purpose/Objective i.e. PICO question

-P *(patient/population):* women with WHO type II anovulation/PCOS (failed on clomifene)
-I *(intervention):* letrozole
-C *(comparator):* clomifene
-O *(outcome):* better pregnancy outcome (live births) and less side effects (multiple pregnancy, ovarian hyperstimulation)

5. Methods:

a. Data sources Pubmed, Cochrane database of systematic reviews, Sciencedirect, NICE, Google scholar and SUNSearch.

Search strategy

(("letrozole"[Supplementary Concept] OR "letrozole"[All Fields]) AND ("ovulation induction"[MeSH Terms] OR ("ovulation"[All Fields] AND "induction"[All Fields]) OR "ovulation induction"[All Fields]) AND ("anovulation"[MeSH Terms] OR "anovulation"[All Fields]) AND compared[All Fields] AND ("clomifene"[MeSH Terms] OR "clomifene"[All Fields])) OR ("metformin"[MeSH Terms] OR "metformin"[All Fields])

A review of the Cochrane Database identified one review (updated 18/09/2014) on Aromatase inhibitors for subfertile women with polycystic ovary syndrome.[4] This review included 26 randomised trials

reporting on 5560 women. In all studies the aromatase inhibitor was letrozole.

A review of the National Institute for Health and Care Excellence (NICE) revealed a clinical guideline for the assessment and treatment of fertility problems, updated in February 2013.[1]

An updated systematic review and meta-analysis was published in 2017 and included 57 randomised controlled trials reporting on 8082 women. All the trials included in the Cochrane review was included as well. The search included all articles up to 26 April 2016.[11]

A search for new randomized trials published after April 2016 and not included in the above review yielded no new trials. There are two published protocols for randomized trials that include letrozole in the one arm: a randomized trial of letrozole versus the Chinese herbal medicine (berberine)[12] and one of letrozole vs. acupuncture pre-treatment and letrozole.[13] As neither includes a comparison with clomifene citrate, future results will not influence the 2016 systematic review and meta-analysis.

c. Evidence synthesis

From the Cochrane review[4]:

- Nine RCTs compared letrozole with clomifene citrate (with or without adjuncts in one or both arms) followed by timed intercourse. The *birth rate* was higher in the letrozole group (OR 1.64, 95% CI 1.32 to 2.04, n=1783, I^2=3%).
- There was no evidence of a difference in ovarian hyperstimulation syndrome rates when letrozole (with or without adjuncts) was compared with placebo (one RCT, n=36), clomifene citrate (with or without adjuncts) (nine RCTs, n=2179).
- Fifteen RCTs compared letrozole versus clomifene citrate (with or without adjuncts in one or both arms) followed by timed intercourse. The *pregnancy rate* was higher in the letrozole group (OR 1.40, 95% CI 1.18 to 1.65, n=2816, I^2=26%).
- The quality of the evidence was rated as low for live birth and pregnancy outcomes.
- The reasons for downgrading the evidence were poor reporting of study methods, possible publication bias and the tendency for studies that reported live birth to report higher clinical pregnancy rates in the letrozole group than studies that failed to report live birth (suggesting that results might be somewhat less favourable to letrozole if all studies reported live birth).

From the 2017 meta-analysis[11]:

- Compared with clomifene alone, letrozole (odds ratio 1.58, 95% confidence interval 1.25 to 2.00) as well as the combination of clomifene and metformin (odds ratio 1.81, 95% confidence interval 1.35 to 2.42) led to significantly higher pregnancy rates (primary outcome).
- For the secondary outcome of live birth, 23 randomised controlled trials with 4206 women were included in the network meta-analysis. Letrozole resulted in a significantly higher live birth rate compared with clomifene (odds ratio 1.67, 95% confidence interval
- 1.11 to 2.49) and metformin led to lower live birth rate than letrozole (0.54; 0.29 to 0.98). The other comparisons showed no significant differences.
- Both letrozole (OR 0.46, 95% CI 0.23 to 0.92) and metformin (OR 0.22, 95% CI 0.05 to0.92) led to lower rates of multiple pregnancy compared with clomifene alone, but these differences were not significant.
- The superiority of letrozole over clomifene was stable in all sensitivity analyses including modifying the criteria of population (treatment naive), reporting strategies (reporting clinical pregnancy) and quality of included studies (low risk of randomization and allocation bias). Miscarriage is often discussed in the literature especially in women with PCOS, and data in relation to this are controversial. In this study, there were no significant differences in miscarriage rates indifferent comparisons; therefore, the superiority of letrozole over clomifene in terms of live birth does not seem to be related to a decreased miscarriage rate.

A recent large retrospective cohort study has indicated that letrozole stimulation reduces the risk of miscarriage, with no increase in the risk of major congenital anomalies or adverse pregnancy outcomes.[14]

Letrozole versus laparoscopic ovarian drilling

Laparoscopic ovarian drilling (LOD) has fallen out of favour as a method to induce ovulation in PCOS due to the risks of surgery and hospitalization as well as the risk of adhesion formation and loss of ovarian function. A 2017 randomized trial[15] included 80 women with clomifene resistant PCOS randomly allocated into groups A and B. Group A (n = 40) underwent LOD, and group B (n = 40) received 2.5 mg letrozole from days 3 to 7 of menses for up to six cycles. A 6-month follow-up was performed. Letrozole had a higher rate of ovulation (70 vs. 57.5%) and superior reproductive outcomes compared with LOD.

d. Evidence quality: Network meta-analysis[11] had a number of limitations:

i. Comparison of side effects for interventions was not included as these were either not reported in some primary RCTs or reporting varied between studies.
ii. Pregnancy rather than live births (secondary outcome) was the primary outcome, as most studies reported on pregnancy.
iii. Lifestyle interventions was not analysed as a confounder in the study, as there is conflicting data as to whether lifestyle modification with weight loss preceding infertility treatment results in improved ovulation and live births.
iv. WHO group II anovulation is a heterogeneous condition with various clinical manifestations and sub-analysis (body mass index and hyperandrogenaemia status) was not possible due to heterogeneity of studies.

Addition of new evidence

Author, date	***Type of study***	**n**	**Population**	**Comparators**	**Primary outcome**	**Effect sizes**	**Comments**
Amer et.al. 2017[3]	*Double blind randomised controlled trial*	159	Anovulatory women with polycystic ovarian syndrome	Clomifene citrate and letrozole – then cross over for those that failed to fall pregnant	Pregnancy rates Secondary: Live births, time to pregnancy	Pregnancy rate: Letrozole 61%, clomifene 43%, rate ratio =1.4 (95% CI 1.1 to 2.0), absolute difference = 18% (3 to 33%), p = 0.022. Live birth rate: Letrozole 48.8%, clomifene 35.4%, rate ratio = 1.4 (95% CI 0.95 to 2.0), absolute difference = 13% (-2 to 28%), p = 0.089. Time to pregnancy: shorter with letrozole (4 versus 6 cycles with clomifene)	After cross over: 45 women with clomifene resistance/failure were put on letrozole, and 31 women with letrozole resistance/failure were put on clomiphene. Pregnancy rates were not significantly different between the two groups: letrozole 28.9% and clomifene 22.6%, p = 0.539; Live births were also not significantly different: letrozole 24.4% and clomifene 19.4%, p = 0.601

Evidence quality: sufficiently powered RCT, participants fulfilled universally accepted Rotterdam diagnostic criteria for PCOS (generalizable for clinical practice), obese women excluded (may affect applicability of results in this sub-group). Pregnancy rates over live births was used as primary outcome, although authors argue this is still a clinically important outcome.

7. Alternative agents:
Clomifene; Clomifene with metformin; Laparoscopic ovarian drilling.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	**SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS**
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [X] Not confident [ ] Uncertain [ ]	
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [X] List the members of the group. List specific exclusion from the group:	Rationale for therapeutic alternatives included: References: Rationale for exclusion from the group: References:

VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [X] Uncertain [ ]	Cost of medicines/ month: **Medicine** | **Cost (ZAR)*** Letrozole 2.5 mg tablets (5) | R6.86 Clomifene 50 mg tablets (5) | R20.18 *Anastrozole 1mg tablets (5)* | *R5.03* **contract price as of: February 2020* **Notes:** Letrozole and anastrozole available on National Contract, and has a number of generics available in the market, resulting in a more favourable price than clomifene (first line option)
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	☐	**X**

Previous Adult ERC and NEMLC recommendation:

Adult recommendation

The Adult Hospital Level Committee recommends that aromatase inhibitors not be considered for inclusion on the Adult Hospital level EML, and that consideration be made for possible use of letrozole at Tertiary and Quaternary level where there has been no response to clomifene. Clomifene is included in the secondary level EML for infertility.

Rationale: Evidence showed a higher clinical pregnancy rate and live birth rate of letrozole vs. clomifene or clomifene+metformin. Furthermore, there is a paucity of RCT evidence for anastrozole and therefore aromatase inhibitors cannot be considered as a therapeutic class for use in infertility. Infertility cases that are resistant to clomifene would require further management at sub specialist facilities.

Level of Evidence: II Meta-analysis of low to moderate quality RCTs [7], Expert opinion.

NEMLC MEETING OF 7 SEPTEMBER 2018:

NEMLC accepted the proposal recommended by the Adult Hospital Level Committee (pertaining to letrozole), as described above

Updated Tertiary **Recommendation**	It is recommended that letrozole be included on the Essential Medicines List for female infertility associated with anovulation in patients who do not fall pregnant after 3 cycles with use of clomifene.
Rationale:	Letrozole is affordable, and found to be more effective than clomifene.
Level of Evidence:	Level I: Randomised Controlled Trial

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
X	X	X

VEN status:

Vital	Essential	Necessary
	X	

Monitoring and evaluation considerations

Research priorities

References:

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