**South African National Essential Medicine List**
**Adult Hospital Level Medication Review Process**
**Component: Gynaecology**

**MEDICINE REVIEW:**

## 1. Executive Summary

**Date:** 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:** Regional level of care
**Prescriber Level: Specialist -** Obstetrician and gynaecologist
**Current standard of Care:** Clomifene
*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). (13)
**Efficacy estimates:** 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)[7]
**Motivator/reviewer name(s):** GS Gebhardt, supported by TD Leong
**PTC affiliation:** Tygerburg Hospital PTC

## 2. Name of author(s)/motivator(s): GS Gebhardt

## 3. Author affiliation and conflict of interest details:

*GS Gebhardt:* Stellenbosch University, National Committee of Confidential Enquiries into Maternal Deaths (NCCEMD); Adult Hospital Level Committee (2017-2020); 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.

## 4. 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(2). 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 (3). 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 metaanalysis from 2012, metformin on its own cannot regarded as a primary ovulation induction agent (4).

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 (5). Aromatase inhibitors have been used successfully to induce ovulation in women with PCOS. In addition, 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 (from (6)).

**5. Purpose/Objective i.e. PICO**

In women with WHO type II anovulation/PCOS, does the use of Letrozole as first line ovulation induction agent, leads to better pregnancy outcome and less side effects (multiple pregnancy, ovarian hyperstimulation) than the current gold standard treatment (clomifene citrate)?

**6. Methods:**

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

**b. 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(7). 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(8).

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) (9) and one of letrozole vs. acupuncture pre-treatment and letrozole

(10). 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(7):

- 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 (8):

- 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 (12)

**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 (11) 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 (8) 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.

**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?**<br>Confident [X] Not confident [ ] Uncertain [ ] | |
| **BENEFITS & HARMS** | **Do the desirable effects outweigh the undesirable effects?**<br>Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ] | |
| **THERAPEUTIC INTERCHANGE** | Therapeutic alternatives available:<br>Yes [ ] No [X]<br>List the members of the group: n/a | Rationale for therapeutic alternatives included: n/a<br>References: n/a |

**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 | No | Uncertain |
|---|---|---|
| X | | |

**RESOURCE USE**

**How large are the resource requirements?**

| More intensive | Less intensive | Uncertain |
|---|---|---|
| X | | |

Cost of medicines/ month:

| Medicine | Cost (ZAR) |
|---|---|
| Letrozole 2.5 mg tabs (5) | R 49.69* |
| Clomifene 50 mg tabs (5) | R 21.83** |

*60% of the average SEP (R82.81), SEP database 27 May 2017

** Contract circular, HP03-2015CHM

Estimated annual budget impact:

- Using StatSA population statistics for females age group i)20-49 ; ii)25-49 years and iii) 15-49 years of age (assuming 80% want children; 14% are infertile of which 25% women have PCOS).
- Respective estimated annual expenditure based on the afore-mentioned assumptions:

*A: Letrozole*

i) 18,243,713; ii) 14,727,935 and iii) 10,878,136.

*B: Clomifene*

i) R 8,014,897; ii) R 6,470,332 and iii) R 4,779,024.

| Age group | A: Letrozole | B: Clomifene |
|---|---|---|
| 20-49 yrs | R 18 mil | R 8 mil |
| 25-49 yrs | R 15 mil | R 6 mil |
| 15-49 yrs | R 11 mil | R 5 mil |

*C: If it is assumed that 20% of clomifene failures would require letrozole (expert opinion),* the total estimated annual budget impact for clomifene, followed by letrozole for clomifene treatment failures:

| Age group | Clomifene, followed by letrozole for clomifene failures |
|---|---|
| 20-49 yrs | R 11,663,640 |
| 25-49 yrs | R 9,415,919 |
| 15-49 yrs | R 6,954,651 |

**Additional resources: n/a**

**EQUITY**

**Would there be an impact on health inequity?**

| Yes | No | Uncertain |
|---|---|---|
| | X | |

| FEASIBILITY | **Is the implementation of this recommendation feasible?**<br>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] | [ ] | [ ] | [ ] | [ ] |

**Recommendation**

The Adult Hospital Level Committee recommends that letrozole not be considered for inclusion on the EML, unless there is a price reduction of this agent. The Committee is of the opinion that consideration be made for possible use at Tertiary and Quaternary level where there has been no response to clomifene. It is noted that letrozole is currently not regstered with the Medicines Control Council for induction of ovulation.

*Rationale:* Evidence showed a higher clincal pregnancy rate and live birth rate of letrozole vs. clomifene or clomifene+metformin. However, letrozole is currently considered too expensive as an alternative to clomifene.

**Level of Evidence: II Meta-analysis of low to moderate quality RCTs**

**Review indicator:**

| Evidence of efficacy | Evidence of harm | Price reduction |
|---|---|---|
| [ ] | [ ] | [X] |

**Ven status:**

| Vital | Essential | Necessary |
|---|---|---|
| [ ] | [ ] | [X] |

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Following review of the evidence review, NEMLC recommended at the meeting of 12 April 2018, that the evidence for a class effect (aromatase inhibitors) be reviewed for use in infertility, as anastrozole was more reasonably priced.

*Evidence review:*

Ovulation induction success rates with clomifene are poor (±30%). However, no available RCT evidence could be retrieved for anastrozole – studies have mostly been done with letrozole. As the management of infertility cases resistant to clomifene would take place at tertiary level of care – the Adult Hospital Level Expert Review Committee (ERC) recommended that medicine review be forwarded to Tertiary and Quaternary (T&Q) Committee for consideration for inclusion on the T& Q EML.

**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.

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*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.**

## Monitoring and evaluation considerations

## Research priorities

## References:


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