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

MEDICINE REVIEW:

1. Executive Summary

Date: 29 April 2020, Update of June 2017 review
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 1.68, 95% CI 1.42 to 1.99, n=2954, I^2=0%; number needed to treat for an additional beneficial outcome (NNTB) = 10; moderate-quality evidence).
Motivator/reviewer name(s): GS Gebhardt, TD Leong
PTC affiliation: GS Gebhardt - Tygerburg Hospital PTC

2. Name of author(s)/motivator(s): GS Gebhardt, TD Leong

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 randomised, 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). The NICE clinical guideline recommends use of ovarian stimulation agents for anovulation (clomifene or letrozole) as monotherapy or in combination with metformin (clomifene with metformin). As there is a paucity of long-term research on ovarian stimulation and ovulation induction for women, NICE recommends further research to determine an association between ovulation induction or ovarian stimulation and adverse long-term (over 20 years) effects.

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 randomised trials published after April 2016 and not included in the above review yielded no new trials. There are two published protocols for randomised trials that include letrozole in the one arm: a randomised 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.

An additional search of the Cochrane database was performed on the 29 April 2020, and an update of the 2014 review of aromatase inhibitors for subfertile women with polycystic ovary syndrome was identified (24/08/2018). The Cochrane review was updated in to include 16 new RCTs in the quantitative synthesis analysis (meta-analysis).

c. Evidence synthesis

i) Letrozole vs clomifene

The updated Cochrane review(14):

- Thirteen 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 1.68, 95% CI 1.42 to 1.99, n=2954, I^2=0%; number needed to treat for an additional beneficial outcome (NNTB) = 10; moderate-quality evidence).

- There was no evidence of a difference in ovarian hyperstimulation syndrome rates when letrozole (with or without adjuncts) was compared with clomifene citrate (with or without adjuncts) (12 RCTs, n=2536, I^2=0%; high-quality evidence).
- Twenty-five 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 1.56, 95% CI 1.37 to 1.78, n=4629, I^2=1%; NNTB = 10; moderate-quality evidence).
- Rate of miscarriage by pregnancy of clomifene citrate vs letrozole was comparable (20% vs 19%; OR 0.94, 95% CI 0.70 to 1.26; n=1210 participants; 18 RCTs; I^2 = 0%; high-quality evidence) as well as multiple pregnancy rate (1.7% vs 1.3%; OR 0.69, 95% CI 0.41 to 1.16; n=3579 participants; 17 RCTs; I^2 = 0%; high-quality evidence).

Evidence quality: The quality of the evidence was rated as moderate 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). However, the updated Cochrane included additional studies of low risk of bias, and as the update has a large number of participants, the authors stated that it is unlikely that additional studies would affect the estimates. Funnel plot showed mild asymmetry, indicating that some studies in favour of clomiphene might be missing.

ii) Ranking of ovarian stimulation agents [including letrozole, clomifene (with/without metformin) and metformin]

2017 network meta-analysis (8):

- Analysis compared the most common pharmacological ovarian stimulation therapies directly or indirectly.
- All pharmacological agents were superior to placebo or no treatment in terms of ovulation and pregnancy in anovulation.
- However, for the primary outcomes of pregnancy rates combined clomifene with metformin ranked the highest. The surface under the cumulative ranking curve provided a hierarchical ranking: 90%, 82%, 80%, 50%, 46%, 27%, 22%, and 3%, for combined clomifene and metformin, follicle stimulating hormone (FSH), letrozole, metformin, clomiphene, tamoxifen, laparoscopic ovarian drilling, and placebo or no treatment, respectively.
- For the secondary outcome of live birth, 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.

Evidence quality: Network meta-analysis (8) had a number of limitations:

- Comparison of side effects for interventions was not included as these were either not reported in some primary RCTs or reporting varied between studies.
- Pregnancy rather than live births (secondary outcome) was the primary outcome, as most studies reported on pregnancy.
- 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.
- 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.

iii) Adverse events

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).

iv) 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 randomised 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.

7. Alternative agents:

Clomifene; Clomifene with metformin; Laparoscopic ovarian drilling.

EVIDENCE TO DECISION FRAMEWORK

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the overall confidence in the evidence of effectiveness?
Confident [X] Not confident [ ] Uncertain [ ]</td><td>Cochrane review by Franik et al (2018) reported a live birth rate of clomifene (with/without adjuncts) compared to letrozole (with/without adjuncts) as 214/1000 vs 314/1000 (95% CI 279 to 352); moderate quality evidence.</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?
Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]</td><td>Miscarriage rate and multiple pregnancies rate shown to be lower with letrozole compared to clomifene (with/without adjuncts) in the Cochrane review by Franik et al (2018).</td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:
Yes [ ] No [X]
(See page 6 of this review for the rationale concerning the non-recommendation of aromatase inhibitors as a therapeutic class)</td><td>Rationale for therapeutic alternatives included: n/a</td></tr>
<tr><td>VALUES & PREFERENCES / ACCEPTABILITY</td><td>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 [ ]</td><td>No specific research surveying patients' value of this therapeutic agent is currently available.

The NEMLC and Adult Hospital Level Committee were of the opinion that healthcare providers possibly consider this option to be acceptable.</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [ ] Less intensive [X] Uncertain [ ]</td><td><u>Cost of medicines/ month:</u>
<table><tr><th>Medicine</th><th>Cost (ZAR)</th></tr><tr><td>Letrozole 2.5 mg tabs (5)</td><td>R 6.77*</td></tr><tr><td>Clomifene 50 mg tabs (5)</td><td>R 20.18**</td></tr></table>*Contract circular RT290-2018: letrozole 2.5mg, 28 tabs = R37.90
** Contract circular, RT283-20017: clomifene 50 mg, 10 tabs = R40.35
<u>Estimated annual budget impact:</u>
• 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) R 2,564,797; ii) R 2,102,646 and iii) R3,003,684
B: Clomifene
i) R 7,645,666; ii) R 6,267,993 and iii) R 8,953,989
<table><tr><th>Age group</th><th>A: Letrozole</th><th>B: Clomifene</th></tr><tr><td>20-49 yrs</td><td>R 2.6mil</td><td>R 7,65 mil</td></tr><tr><td>25-49 yrs</td><td>R 2.1 mil</td><td>R 6,3 mil</td></tr><tr><td>15-49 yrs</td><td>R 3 mil</td><td>R 9 mil</td></tr></table></td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes [ ] No [X] Uncertain [ ]</td><td></td></tr>
</table>

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]	[ ]	[ ]	[ ]	[ ]

Recommendation

The Adult Hospital Level Committee recommends that letrozole be considered for inclusion on the Adult Hospital Level EML, as first-line therapy for anovulation (clomifene may be considered as second-line option, where letrozole cannot be used). It is noted that letrozole is currently not registered with the South African Health Products Regulatory Authority for induction of ovulation.

Rationale: Updated Cochrane review (n=2954) showed a higher clincal pregnancy rate and live birth rate of letrozole compared to clomifene or clomifene+metformin; number needed to treat for an additional beneficial outcome=10; moderate quality evidence. The rate of miscarriage by pregnancy and multiple pregnancy rate between treatment groups showed little or no difference, but the funnel plot showed mild assymetry suggesting publication bias.

The recent decrease in price of letrozole makes it a cheaper alternative to clomifene.

Level of Evidence: II Meta-analysis of low to moderate quality RCTs [14]

Review indicator:

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

Ven status:

Vital	Essential	Necessary
[ ]	[X]	[ ]

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:

No available RCT evidence could be retrieved for anastrozole – studies have mostly been done with letrozole.

Recommendation: The Adult Hospital Level Committee recommends that aromatase inhibitors not be considered for inclusion on the Adult Hospital level EML as a therapeutic class, and that consideration be made for possible use of letrozole.

Rationale: Evidence showed a higher clinical pregnancy rate and live birth rate for letrozole compared to clomifene or clomifene+metformin.

Furthermore, as there is a paucity of RCT evidence for anastrozole; aromatase inhibitors cannot be considered as a therapeutic class for use in infertility.

Infertility cases that are resistant to clomifene or letrozole would require further management at sub specialist facilities.

Level of Evidence: II Meta-analysis of low to moderate quality RCTs[14], Expert opinion

NEMLC MEETING OF 11 JUNE 2020:

NEMLC accepted the inclusion of letrozole as first-line therapy for anovulation to the Adult Hospital Level EML. Where letrozole cannot be used, clomifene may be considered.

NEMLC recommended that the referral criteria be deleted in the Standard Treatment Guideline, as management of this condition is by specialists, and other interventions such as in vitro fertilisation is not available at tertiary level of care in the public sector.

Monitoring and evaluation considerations: Uptake of technology at secondary and tertiary level of care.

Research priorities: n/a

References:

1. Fertility problems: assessment and treatment | Guidance and guidelines | NICE [Internet]. [cited 2017 Jun 10]. Available from: https://www.nice.org.uk/guidance/cg156
2. Cedars MI. PCOS: key issues and remaining questions. Fertil Steril. 2012 Jan 1;97(1):1.
3. Use of clomiphene citrate in infertile women: a committee opinion. Fertil Steril. 2013 Aug 1;100(2):341–8.
4. Is Metformin Indicated as Primary Ovulation Induction Agent in Women with PCOS? A Systematic Review and Meta-Analysis - FullText - Gynecologic and Obstetric Investigation 2012, Vol. 73, No. 4 - Karger Publishers [Internet]. [cited 2017 Jun 10]. Available from: https://www.karger.com/Article/FullText/335253
5. Kar S. Clomiphene citrate or letrozole as first line ovulation induction drug in infertile PCOS women: a prospective randomised trial. Fertil Steril. 2012 Sep 1;98(3):S86.
6. Diamond MP, Legro RS, Coutifaris C, Alvero R, Robinson RD, Casson P, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. N Engl J Med. 2015 Sep 24;373(13):1230–40.
7. Franik S, Kremer JAM, Nelen WLDM, Farquhar C. Aromatase inhibitors for subfertile women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2014 Feb 24;(2):CD010287.
8. Wang R, Kim BV, van Wely M, Johnson NP, Costello MF, Zhang H, et al. Treatment strategies for women with WHO group II anovulation: systematic review and network meta-analysis. The BMJ [Internet]. 2017 Jan 31;356. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5421445/
9. Li Y, Kuang H, Shen W, Ma H, Zhang Y, Stener-Victorin E, et al. Letrozole, berberine, or their combination for anovulatory infertility in women with polycystic ovary syndrome: study design of a double-blind randomised controlled trial. BMJ Open. 2013 Nov 25;3(11):e003934.
10. Li J, Ng EHY, Stener-Victorin E, Hu Z, Wu W, Lai M, et al. Comparison of acupuncture pretreatment followed by letrozole versus letrozole alone on live birth in anovulatory infertile women with polycystic ovary syndrome: a study protocol for a randomised controlled trial. BMJ Open. 2016 Oct 7;6(10):e010955.
11. Ibrahim MH, Tawfic M, Hassan MM, Sedky OH. Letrozole versus laparoscopic ovarian drilling in infertile women with PCOS resistant to clomiphene citrate. Middle East Fertil Soc J [Internet]. 2017 Feb 28; Available from: http://www.sciencedirect.com/science/article/pii/S1110569016301443
12. Tatsumi T, Jwa SC, Kuwahara A, Irahara M, Kubota T, Saito H. No increased risk of major congenital anomalies or adverse pregnancy or neonatal outcomes following letrozole use in assisted reproductive technology. Hum Reprod Oxf Engl. 2017 Jan;32(1):125–32.
13. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, Christman GM, Huang H, Yan Q, Alvero R, Haisenleder DJ, Barnhart KT, Bates GW, Usadi R, Lucidi S, Baker V, Trussell JC, Krawetz SA, Snyder P, Ohl D, Santoro N, Eisenberg E, Zhang H; NICHD Reproductive Medicine Network. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. N Engl J Med. 2014 Jul 10;371(2):119-29. doi: 10.1056/NEJMoa1313517. Erratum in: N Engl J Med. 2014 Oct 9;317(15):1465. https://www.ncbi.nlm.nih.gov/pubmed/25006718
14. Franik S, Eltrop SM, Kremer JA, Kiesel L, Farquhar C. Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2018 May 24;5:CD010287.https://www.ncbi.nlm.nih.gov/pubmed/29797697