

A.23	Letrozole – infertility – EML
<b>Draft recommendation</b>	<input checked="" type="checkbox"/> Recommended <input type="checkbox"/> Not recommended  Justification: Current evidences shows that the proposed medicine is superior than and as safe as the current available option in the EML.
Does the proposed medicine address a relevant public health need?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable  Comments: Infertility is affecting a large number of people globally. A significant proportion of it is caused by ovulatory disorders/dysfunction or unexplained causes which could get benefit from the proposed medicine.
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication?  <small>(this may be evidence included in the application, and/or additional evidence identified during the review process)</small>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable  Comments: Letrozole has been included in several guidelines on the conditions. The evidence is based on a Cochrane systematic review (PCOS) and another yet to be published SR (unexplained infertility). For PCOS, letrozole is superior than clomiphene (already in EML) while for unexplained fertility it is similar to clomiphene. However, the certainty of the evidence of the recommendations are moderate to low
Does adequate evidence exist for the safety/harms associated with the proposed medicine?  <small>(this may be evidence included in the application, and/or additional evidence identified during the review process)</small>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable  Comments: The evidence is based on a Cochrane systematic review (PCOS) and another yet to be published SR (unexplained infertility). However, the certainty of the evidence of the recommendations are moderate to low
Are there any adverse effects of concern, or that may require special monitoring?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable  Comments: might cause congenital malformation of fetus when administered during pregnancy.

24<sup>th</sup> WHO Expert Committee on Selection and Use of Essential Medicines  
Expert review

<p>Are there any special requirements for the safe, effective and appropriate use of the medicines?</p> <p>(e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments: As required in the whole process of infertility treatment (as stated in the application p.5).</p>
<p>Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?</p>	<p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments: The cost is higher than the existing available medicine in the EML, but it is already used for the indication and still affordable in LMICs.</p>
<p>Are there any issues regarding the registration of the medicine by national regulatory authorities?</p> <p>(e.g. accelerated approval, lack of regulatory approval, off-label indication)</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments: Neither letrozole nor anastrozole are approved for the treatment of infertility by the US Food and Drugs Administration (FDA) or by the European Medicines Agency (EMA); their use for this indication is off label (application p.13). However, 40 countries already included it in their EML.<sup>1</sup></p>
<p>Is the proposed medicine recommended for use in a current WHO guideline?</p> <p>(refer to: <a href="https://www.who.int/publications/who-guidelines">https://www.who.int/publications/who-guidelines</a>)</p>	<p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input checked="" type="checkbox"/> Not applicable</p> <p>Comments: WHO guidelines on the prevention, diagnosis, and treatment of infertility are currently in development.</p> <p>Besides the guidelines mentioned in the application, several guidelines still didn't include aromatase inhibitors (letrozole and anastrozole) as the 1<sup>st</sup> line of treatment, such as: NICE (2013 updated 2017)<sup>2</sup>: Clomiphene citrate for WHO Group 2 anovulatory infertility; Do not offer oral ovarian stimulation agents (such as clomiphene citrate, anastrozole or letrozole) to women with unexplained infertility. [new 2013]</p>

<sup>1</sup> <https://global.essentialmeds.org/dashboard/medicines/1044>

<sup>2</sup> <https://www.nice.org.uk/guidance/cg156/chapter/recommendations>