health
Department:
Health
REPUBLIC OF SOUTH AFRICA

National Essential Medicine List
Tertiary Medication Review Process
Component: Gender Dysphoria

MEDICINE MOTIVATION:

1. Executive Summary

Date: August 2019
Medicine (INN): Estrogen
Medicine (ATC): G03CA
Indication (ICD10 code): *F64.0*
Patient population: Patients with gender dysphoria - Feminising
Prevalence of condition: no accurate figures in SA. Recent population based surveys in the United States suggest that the number of self-identified trans people represent approximately 0.1-0.5% of the population.[1,2]
Level of Care: Tertiary (initiation), can be down referred are required
Prescriber Level: Multidisciplinary Specialist Team
Current standard of Care: Psychosocial/hormone/surgery therapy
Efficacy estimates: (preferably NNT)

2. Name of author(s)/motivator(s): Tertiary Committee

3. Author affiliation and conflict of interest details:

Dr Grobler – Part of Gender Clinic at Steve Biko Hospital.

No other applicable conflicts declared.

4. Introduction/ Background

Gender dysphoria is defined as the distress and unease experienced if gender identity and designated gender are not completely congruent. In 2013, the American Psychiatric Association released the fifth edition of the DSM-5, which replaced “gender identity disorder” with “gender dysphoria” and changed the criteria for diagnosis.

Gender incongruence is an umbrella term used when the gender identity and/or gender expression differs from what is typically associated with the designated gender. Not all individuals with gender incongruence have gender dysphoria or seek treatment.

5. Purpose/Objective i.e. PICO question:

-P *(patient/population): Gender Dysphoria - Feminising*
-I *(intervention): Estrogen*
-C *(comparator): No therapy*
-O *(outcome): Quality of life*

6. **Methods:**
   a. **Data sources:** Pubmed, Cochrane Library, Google Scholar.
   b. **Search strategy**

   ("Gender Dysphoria"[Mesh]) AND ("Hormone Replacement Therapy"[Mesh] OR "Estrogen Replacement Therapy"[Mesh])

c. **Excluded studies:** n/a

d. **Evidence synthesis**

Author, date	***Type of study***	**n**	**Population**	**Comparators**	**Primary outcome**	**Effect sizes**	**Comments**
Murad MH, et.al. 2010[3]	Systematic review and Meta-analysis	28 studies, 1833 participants (1093 male-to-female; 801 female-to-male)	Health user with gender identity disorder (GID) receiving hormonal therapy	No control	• Improvement in gender dysphoria • Improvement in psychological symptoms • Improvement in quality of life • Improvement in sexual function.	• 80% of individuals with GID reported significant improvement in gender dysphoria (95% CI = 68–89%; 8 studies; I2 = 82%); • 78% reported significant improvement in psychological symptoms (95% CI = 56–94%; 7 studies; I2 = 86%); • 80% reported significant improvement in quality of life (95% CI = 72–88%; 16 studies; I2 = 78%); • 72% reported significant improvement in sexual function (95% CI = 60–81%; 15 studies; I2 = 78%).	Subjective outcome measures only

Evidence quality: Level II evidence

Cross-sectional study

Author, date	***Type of study***	**n**	**Population**	**Comparators**	**Primary outcome**	**Effect sizes**	**Comments**
Gorin-Lazard A, et.al. 2012[4]	Cross-sectional study	61 participants (44 received hormonal therapy)	GID individuals	No hormonal therapy	Quality of life (Short Form 36)	• Hormonal therapy was significantly associated with a higher QoL • Depression was significantly associated with a lower QoL.	

e. **Evidence quality:** The outcomes reported are subjective and include measures such as improvement of psychological symptoms, improvements of quality of life, improvement in gender dysphoria, and improvement in sexual function. Since there are no hard clinical outcomes, a value judgement is required.

Adverse effects: risk of thromboembolic events associated with estrogens in general seems most concerning with ethinyl estradiol specifically, which is why it is suggested that it not be used in any transgender treatment plan.[5, 6, 7]

Alternative agents: Alternative treatment includes changes in gender expression, surgery, and psychotherapy. The treatment interventions are individualized on a patient basis, with interventions applied in different orders.

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 [ ]	Although evidence does not evaluate hard outcomes, there is support for quality of life outcomes for these patients.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [ ] Harms outweigh benefits [ ] Benefits = harms or Uncertain [X]	Risk of thromboembolic events. Monitoring for this must be included in the treatment plan.
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:

<table>
<tr>
<td>VALUES & PREFERENCES / ACCEPTABILITY</td>
<td>Is there important uncertainty or variability about how much people value the options?
Minor [X] Major [ ] Uncertain [ ]

Is the option acceptable to key stakeholders?
Yes [X] No [ ] Uncertain [ ]</td>
<td></td>
</tr>
<tr>
<td>RESOURCE USE</td>
<td>How large are the resource requirements?

More intensive [ ] Less intensive [ ] Uncertain [ ]</td>
<td>Cost of medicines/ month:
<table><tr><th>Medicine</th><th>Cost (ZAR)</th></tr><tr><td>Estradiol</td><td>Starting dose (1mg): R34.58/month
Maximum dose (6mg): R207.48</td></tr><tr><td>Conjugated estrogen</td><td>Starting dose (0.3mg): R62.37/month
Maximum dose (2.5mg): R498.92</td></tr></table>
Additional resources:
Patients will need to be managed by a multidisciplinary team including endocrinologists, psychiatrists, surgery, psychologist etc.</td>
</tr>
<tr>
<td>EQUITY</td>
<td>Would there be an impact on health inequity?

Yes [ ] No [ ] Uncertain [X]</td>
<td>With no formal EML recommendations, there is inequity with treatment only afforded at those facilities running a gender dysphoria clinic.</td>
</tr>
<tr>
<td>FEASIBILITY</td>
<td>Is the implementation of this recommendation feasible?
Yes [X] No [ ] Uncertain [ ]</td>
<td></td>
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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
	☐	☐	☐	☐	☒

Recommendation

Estrogen is recommended for inclusion on the Tertiary and Quaternary Essential Medicine List for patients with gender dysphoria for the feminising regimen, to be initiated by specialists in a multidisciplinary team.

Rationale:

Appropriate access will assist in enabling the proper and safe use, and avoid unsafe practices.

Level of Evidence:

II and III

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
☐	☒	☐

VEN status:

Vital	Essential	Necessary
☐	☒	☐

Monitoring and evaluation considerations

Individual patient monitoring required: ALT, fasting glucose, cholesterol, electrolytes, prolactin, risk of thromboembolic risk.

Research priorities

Patient outcomes, adverse effects of long term treatment.

References:

[1] Conron KJ, Scott G, Stowell GS, Landers SJ. Transgender Health in Massachusetts: results from a household probability sample of adults. Am J Pub H. 2012; 102:118-122.

[2] Gates GJ. How many people are lesbian, gay, bisexual, and transgender? UCLA: Williams Institute. 2011 Apr:1-8. https://escholarship.org/uc/item/09h684x2 (Accessed on 21 February 2016)

[3] Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, Erwin PJ, Montori VM. Hormonal therapy and sex reassignment: A systematic review and meta-analysis of quality of life and psychosocial outcomes. Clinical endocrinology. 2010 Feb 1;72(2):214-31.

[4] Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Gebleux S, Penochet J-C, Pringuey D, Albarel F, Morange I, Loundou A, Berbis J, Auquier P, Lançon C, and Bonierbale M. Is hormonal therapy associated with better quality of life in transsexuals? A cross-sectional study. J Sex Med 2012;9:531–541.

[5] Meriggiola MC, Gava G. Endocrine care of transpeople part I. A review of cross-sex hormonal treatments, outcomes and adverse effects in transmen. Clin Endocrinol (Oxf). 2015;83(5):597–606.

[6] Prior JC, Vigna YM, Watson D. Spironolactone with physiological female steroids for presurgical therapy of male-to-female transsexualism. Arch Sex Behav. 1989;18(1):49–57.

[7] Dittrich R, Binder H, Cupisti S, Hoffmann I, Beckmann MW, Mueller A. Endocrine treatment of male-to-female transsexuals using gonadotropin-releasing hormone agonist. Exp Clin Endocrinol Diabetes. 2005;113(10):586–592.