National Essential Medicine List
Tertiary Medication Review Process
Component: Antiandrogens

MEDICINE MOTIVATION:

1. **Executive Summary**

Date: January 2019
Medicine (INN): Cyproterone Acetate (CPA) OR Medroxyprogesterone Acetate (MPA)
Medicine (ATC): G03HA01 OR G03AC06
Indication (ICD10 code): F65.4, F65.8, F65.9, F52.7
Patient population: Patients with hypersexual behaviour including paraphilias
Prevalence of condition: In 2017/18, a total of 50,108 sexual offences were recorded by the police in South Africa.[1] Note however that there is an underreporting rate of sexual offenses.
Level of Care: Tertiary
Prescriber Level: Specialist (Psychiatrist)
Current standard of Care: None
Efficacy estimates: (preferably NNT): *No good data on hard endpoints*
Evidence of no recidivism at 2 years for MPA[4] , no data on recidivism for CPA

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

3. **Author affiliation and conflict of interest details:** No applicable conflicts

4. **Introduction/ Background**

Cyproterone acetate (CPA) and medroxyprogesterone acetate (MPA) are anti-androgens that inhibit hypersexual behaviour in those patients for whom adequate control of their libidos is lacking with or without associated mental illness. This may be accompanied by poor judgement and impulsivity. Such lack of control can be associated with various diagnoses, including mental retardation, organic brain damage syndromes and severe psychotic disorders such as schizophrenia. The manic phase of bipolar disorder includes hyper-sexuality as one of the core features of the illness.

Paraphilias are sexual fantasies or acts that are deviations from the socially accepted sexual behaviour, but may be necessary and, in some cases, sufficient for some people to experience sexual arousal and/or orgasm. Paraphilias are not uncommonly encountered as co-morbid with certain disorders found in sexual offenders referred for observation (in terms of the Criminal procedures act to determine fitness to stand trial and criminal responsibility) and later treatment at specialised psychiatric hospitals (as state patients in terms of the Mental Healthcare Act(MHCA)). In most cases sex offenders are convicted for child sexual abuse, rape, or sexual assault. However, in certain instances they may be referred by the courts when they are found not fit and/or not responsible for their offences by virtue of psychiatric illnesses.

Adequate treatment of paraphilic behaviour may be effective to prevent acting out and increased victimization, thereby reducing the individual and social burden of paraphilias. Understandably, hyper-sexuality and inadequate control of sexual drives can lead to problematic consequences,

for both the patient and the community. This is particularly relevant in light of HIV/AIDS and other sexually transmitted infections.

One difficult aspect of rendering psychiatric treatments is that oral compliance on medication is often poor. A major contributory factor to this problem is due to the nature of severe mental conditions, where patients often have a complete loss of insight and judgement. In light of this, one can understand that injectable depot preparations of medication are useful. Oral therapy is not suitable due to the lack of insight into mental illness, as well as the fact that many patients are on leave of absence (LOA) often leads to non-compliance.

Forensic services

Psychiatric hospitals provide forensic services. State Patients are those patients admitted via the courts in terms of section 42 of the MHCA, who have committed serious criminal offences. A high proportion of these State Patients are sexual offenders with backgrounds of rape and other severe sexual offences. These patients are then managed by psychiatric hospitals, with the aim of rehabilitation back into the community.

5. **Purpose/Objective i.e. PICO question** [comparison to current standard of care for a specific indication]:

-P *(patient/population): Patients with paraphilias and/or inappropriate sexual behaviour*
-I *(intervention): Cyproterone acetate or medroxyprogesterone acetate*
-C *(comparator): no medical intervention or oral medical intervention*
-O *(outcome): re-offense (not good data); self-report/nurse report; phallometry.*

6. **Methods:**
   a. **Data sources** *e.g. Pubmed, Cochrane, review of references from guidelines/reviews.*
   b. **Search strategy**
   (("Paraphilic Disorders"[Mesh] AND "Libido"[Mesh]) AND "Cyproterone Acetate"[Mesh]) AND ("Medroxyprogesterone"[Mesh] OR "Medroxyprogesterone Acetate"[Mesh]) AND (Randomized Controlled Trial [ptyp] OR Meta-Analysis [ptyp] OR systematic[sb])
   2 studies retrieved:
      - Review of literature – androgen deprivation therapy[2]
      - Double-blind, placebo controlled trial (that failed to recruit an appropriate sample for statistical analysis). [3]

   Cochrane Library: 1 review:
      - Pharmacological interventions for those who have sexually offended or are at risk of offending, 2015[4] *(meta-analysis could not be done due to heterogeneity among studies).*

   c. **Excluded studies:**
   Studies evaluating psychological interventions, GnRH analogues (too costly).

d. Evidence synthesis

Author, date	*Type of study*	n	Population	Comparators	Outcomes and effect size	Comments
Cooper AJ, et.al. 1992[3]	Double-blind placebo controlled trial	10 (only 7 completed) (intention was for 25 patients)	Hospitalised Paedophiles	CPA MPA placebo	Findings similar for CPA and MPA in terms of: • Self-report • Nurse observation • Phallometry • Hormone levels • Side effects	• High drop-out rate. • Hard outcomes such as re-offense not evaluated.

Evidence quality: poor quality, hard to deduce anything conclusive.

Cochrane Review[4]:
Six studies that evaluated the effectiveness of testosterone-suppressing agents were evaluated (CPA, MPA, ethinyl oestradiol). Meta-analysis was not possible due to heterogeneity of interventions, comparators, designs etc.

Two studies evaluated the outcome of recidivism. One study[5] evaluating MPA IM plus imaginal desensitisation found no recidivism at 2 years. The other study[6] evaluated assertiveness training versus MPA plus Assertiveness training, where there was a significant drop in the MPA group, however there is a high risk of bias due to significant dropout rate. Recidivism not assessed in any of the CPA studies.

e. General evidence quality: General lack of randomized controlled data. Only one study found comparing MPA to CPA (sample did not allow for statistical analysis). Evidence quality is poor with limitations associated with sample sizes, lack of blinding, allocation concealment, high treatment drop-out rates.

7. Alternative agents: GnRH analogues

8. Cost

Based on dosing of:

- CPA: 300mg monthly
- MPA 300mg weekly

Product	Branded product	Strength/vial		Price	*Source**	Price per mg	Dose	Frequency	Cost per dose	Cost per month	Cost per year
Cyproterone Acetate 100mg/mL 3 mL	Androcur Depot	300	mg	R118.65	*Contract*	R0.40	300	Monthly	R118.65	R237.30	R2,847.60
Medroxyprogesterone Acetate 150 mg/ml, 10ml	Petogen	1500	mg	R293.87	*SEP*	R0.20	300	weekly	R58.77	R235.10	R2,821.16
Medroxyprogesterone Acetate 150mg/ml, 100ml	Petogen	15000	mg	R2,938.76	*SEP*	R0.20	300	weekly	R58.78	R235.10	R2,821.21
Medroxyprogesterone 150mg/ml, 1ml	Depo-provera 150mg	150	mg	R44.88	*SEP*	R0.30	300	weekly	R89.77	R359.08	R4,308.91

**prices based on November 2018 contract and SEP prices*

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></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>Both CPA and MPA have similar side effect profiles. The benefits of treating these patients would outweigh the risk to the patient and the community.</td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:
Yes [X] No [ ]

List the members of the group.

List specific exclusion from the group:</td><td>Rationale for therapeutic alternatives included:
Either CPA or MPA can be used.

References:

Rationale for exclusion from the group:

References:</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></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [ ] Less intensive [ ] Uncertain [X]</td><td>Cost of medicines/ month:
<table><tr><th>Medicine</th><th>Cost (ZAR)</th></tr><tr><td>CPA</td><td>R2,847.60 (contract)</td></tr><tr><td>MPA</td><td>R2,821.16 (SEP)</td></tr></table></td></tr>
</table>

EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [ ] Uncertain [X]	
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

It is recommended that either cyproterone acetate or medroxyprogesterone acetate be available on the Essential Medicines List from the management of hypersexuality, to be prescribed by a psychiatrist. If there is price parity between the two agents, cyproterone is preferred due to monthly dosing.

Review indicator:

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

VEN status:

Vital	Essential	Necessary
[ ]	[X]	[ ]

References:

[1] https://africacheck.org/factsheets/factsheet-south-africas-crime-statistics-for-2017-18/

[2]Silvani M, et. al. Androgen deprivation therapy (castration therapy) and pedophilia: What's new. Archivio Italiano di Urologia e Andrologia. 2015, 87(3): 222-226.

[3] Cooper AJ, et.al. A double-blind placebo controlled trial of medroxyprogesterone acetate and cyproterone acetate with seven pedophiles. Can J Psychiatry. 1992, 37(10):687-693.

[4] Khan O, et.al. Pharmacological interventions for those who have sexually offended or are at risk of offending. Cochrane Database of Systematic Reviews. 2015, Issue 2.

[5] McConaghy NBA, et.al. Treatment of sex offenders with imaginal desensitization and/or medroxyprogesterone. Acta Psychiatrica Scandinavica 1988; 77(2):199–206.

[6] Langevin R, et al. The effect of assertiveness training, Provera and sex of therapist in the treatment of genital exhibitionism. Journal of Behavior Therapy and Experimental Psychiatry 1979;10(4):275–82.