South African National Essential Medicine List
Primary Health Care Medication Review Process
Component: Family planning

MEDICINE REVIEW:

1. Executive Summary

Date: 26 August 2020 (Update of August 2019 review)
Medicine (INN): Medroxyprogesterone (104 mg), SC injection
Medicine (ATC): G03AC06
Indication (ICD10 code): Z30.0/Z30.4/Z30.8
Patient population: Women of childbearing potential (WOCP)
Prevalence of condition: n/a - This is for prevention of pregnancy
Level of Care: Primary health care
Prescriber Level: Nurse prescriber
Current standard of Care: IM – DMPA, 150 mg
Efficacy estimates: (preferably NNT): n/a
Motivator/reviewer name(s): S Takuva, E Bera
PTC affiliation: n/a

2. **Name of author(s)/motivator(s):** Dr Simbarashe Takuva; Dr Ebrahim Bera; supported by Trudy D Leong for comparative costing analysis.

3. **Author affiliation and conflict of interest details:**
   Primary reviewer – S Takuva
   - **a.** Affiliation: Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand; School of Health Systems and Public Health, Faculty of Health Sciences, University of Pretoria; Adult Hospital Level Committee member (2017-2020).
   - **b.** No conflicts of interest to declare.

   Secondary reviewer – E Bera
   - a. Affiliation: Department of Obstetrics & Gynaecology, University of the Witwatersrand; Adult Hospital Level Committee member (2017-2020).
   - b. No conflicts of interest to declare.

   Support – TD Leong
   - a. Affiliation: Essential Drugs Programme, National Department of Health; Secretariat to the Primary Health Care and Adult Hospital Level Expert Review Committees.
   - b. No conflicts of interest to declare.

4. Introduction/ Background:

Contraception is one of the World Health Organization's four strategic prongs for the prevention of mother-to-child transmission of HIV. Contraception and planning for conception contribute to the reduction of HIV transmission, thereby supporting the National Strategic Plan on HIV, STIs and TB (2017-2022). (1) There has been increasing focus on LARC (long-acting reversible contraception), which are among the most effective contraceptive methods and have the greatest potential to reduce unintended pregnancies. There are two available and widely used progestogen-only injectables in South Africa: depot medroxyprogesterone acetate (DMPA), 150mg formulation once every 12 weeks, and norethisterone

enanthate (NET-EN), once every 8 weeks.(2) Injectables are popular among clients because they are highly effective, easy to comply with, require only periodic clinic visits, are private and no supplies need to be kept at home. (3)

DMPA works as a contraceptive by inhibiting the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation and results in endometrial thinning. DMPA at its current 150 mg IM dose has visible metabolic effects: Weight gain is common and may be a problem for some clients and tends to increase with duration of use. This is mainly mediated through increased appetite.(4) Also, glucose tolerance is impaired thereby reducing the threshold for diabetes onset among women with borderline glucose tolerance. Other common side-effects include changes in menstrual bleeding (irregular, prolonged or/and heavy bleeding, amenorrhoea), headaches, dizziness, acne, mood changes and decrease in sex drive These metabolic effects are postulated to be due to its initial very high peak levels after administration, these stay relatively high over 3 months. It has however been demonstrated that the current IM formulation when administered SC at lower doses achieves 5-6 times much lower initial peak levels and these levels remain much lower but still above the presumptive contraceptive threshold over 3 months than the IM formulation. This then points to alternative potential dosing and route of administration of DMPA. Studies indicate that the 100 mg/0.5 mL dose is the lowest subcutaneous DMPA dose that consistently suppressed ovulation for at least 3 months. See Figure 1 and Figure 2 (Source: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/076553_S000_Medroxyprogesterone_BIOPHARMR.pdf). The slower rate of absorption observed with DMPA-SC relative to the IM formulation allows for a lower peak serum concentration and a long duration of effect; thus, serum concentrations are maintained above the required minimum concentration for ovulation suppression over a targeted period of 3 months with a 30% lower subcutaneous dose.

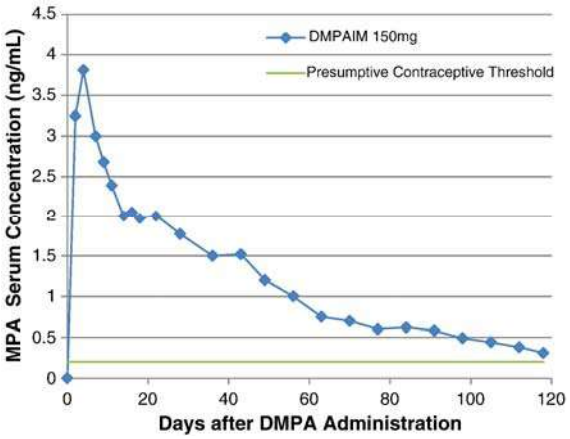

Figure 1: MPA blood levels after a single injection of DMPA IM 150 mg.

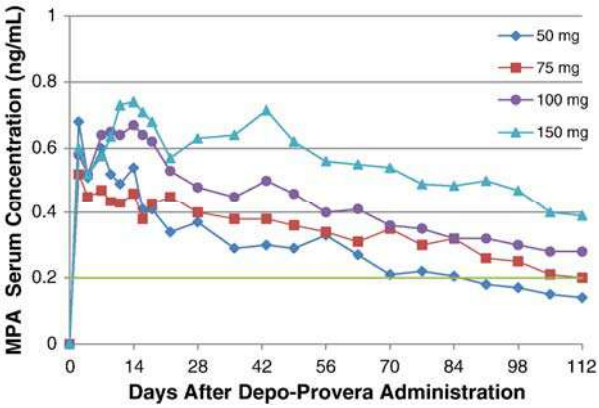

Figure 2: MPA blood levels after single injection SC of various doses of current DMPA IM formulation.

As the dose ally lower muscular ewer side a small but growing evidence base provides consistent evidence to suggest that self-administration of depot medroxyprogesterone acetate subcutaneous injectable contraception can lead to improved contraceptive continuation rates and equivalent pregnancy prevention compared with healthcare provider administration.(5) . Therefore DMPA-SC potentially offers women a new, highly effective and convenient long-acting contraceptive option.

5. Purpose/Objective

The objective of this medicine review is to appraise the efficacy and safety of low dose subcutaneous DMPA formulations compared to the current intramuscular 150mg dose. This review followed the PICO (population, intervention, comparison and outcomes) question: Is DMPA-SC of similar therapeutic efficacy and safety profile as DMPA-IM? Additionally, the evidence on acceptability of self-administration of low dose SC DMPA was reviewed.

Population	Individuals of reproductive age
Intervention	Low dose DMPA subcutaneous formulations (class) — DMPA S.C. 104mg every 3 months
Comparison	DMPA 150 mg intramuscular formulation given every 3 months
Outcomes	Efficacy – prevention of pregnancy Safety – weight gain, bleeding patterns, endometriosis, HIV acquisition, other adverse events

6. Methods:

a. Data sources: PubMed and EMBASE

b. Search strategy Search strategy adapted from Drogoman et al, 2016 (6). PubMed database searched to identify all relevant evidence published in peer-reviewed journals in any language from inception through June 2019 regarding the safety and efficacy of DMPA-SC in women of reproductive age: ("contraceptive agents, female"[MeSH] AND ("injections"[MeSH] OR ("injections"[MeSH] OR "injections"[All Fields] OR "injection"[All Fields])) AND (subcutaneous[All Fields] OR ("sc"[All Fields]) OR SQ[All Fields])) OR ("dmpa"[All Fields] OR (depot[All Fields] AND ("medroxyprogesterone"[MeSH] OR "medroxyprogesterone"[All Fields])) OR ("medroxyprogesterone acetate"[MeSH] OR ("medroxyprogesterone"[All Fields] AND "acetate"[All Fields]) OR "medroxyprogesterone acetate"[All Fields] OR ("depo"[All Fields] AND "provera"[All Fields]) OR "depo provera"[All Fields])) AND (subcutaneous[All Fields] OR ("sc"[All Fields]) OR "SQ"[All Fields] OR "subQ"[All Fields]")). We also searched the Cochrane Library database for any existing systematic reviews on the method using the search terms "depot medroxyprogesterone SC or SQ or subcutaneous." Additionally, we hand-searched reference lists of identified articles for further citations of interest. For efficacy only studies designed with efficacy as the outcome/primary outcome were considered.

To extract studies comparing self-administration versus provider administration of injectable contraception on outcomes of pregnancy, side effects/adverse events, contraceptive uptake, contraceptive continuation, self-efficacy/empowerment and social harms, we adapted the search strategy from the systematic review and meta-analysis by Kennedy et al (2019).
("Sayana Press" [tiab] OR "depot medroxyprogesterone acetate" [tiab] OR "depo-medroxyprogesterone acetate" [tiab] OR "Depo Medroxyprogesterone Acetate" [tiab]
OR "Medroxyprogesterone" [tiab] OR "Medroxyprogesterone Acetate" [tiab] OR DMPA [tiab] OR DMPA-SC[tiab] OR Uniject [tiab] OR Depo-Provera [tiab] OR "Depo Provera" [tiab] OR "Depo-Subq Provera" [tiab] OR "Long-Acting Reversible Contraception" [Mesh])
AND (self-administration [tiab] OR self-administer [tiab] OR self-administered [tiab] OR self-injection [tiab] OR self-inject [tiab] OR self-injected [tiab] OR "home use" [tiab] OR "home administration" [tiab] OR "home injection" [tiab] OR "self- vs provider-administered" [tiab] OR "self- and provider-administered" [tiab] OR "self- vs physician- administered" [tiab] OR "self- and physician-administered" [tiab] OR "self and clinical administration" [tiab] OR "self- vs clinician-administered" [tiab] OR "self and clinician administered" [tiab] OR "self-care" [Mesh] OR self-administration [Mesh] OR self-assessment [Mesh]).

c. Evidence synthesis

- **EFFICACY**

Author: Jain et al, 2004 (6)
Type of study: 2 Phase 3, open label multi-center trials
Population and N: 722 for North and South American popn (total 7,209 woman-cycles of exposure). 44% were overweight or obese at baseline.
1,065 for European and Asian popn (total 11,472 woman-cycles of exposure). 27% were overweight or obese at baseline.
Comparators: DMPA-SC (104 mg/0.65 mL) every 3 months was the intervention. Non-comparator trial
Outcomes:

Contraceptive efficacy at 1 year: No pregnancies observed. Also, No pregnancies across all BMIs. DMPA-SC provides highly reliable (99.9%) contraceptive efficacy that is uncompromised by BMI
Patient satisfaction: Very high level of satisfaction. In both trials, subjects reported a very high level of satisfaction with DMPA-SC in three of the PSQ and EOTQ measures: preferring it with respect to other contraceptive methods, being willing to continue treatment and willingness to recommend it to a friend.
Safety: DMPA-SC tolerability profile was similar to or better than that of DMPA-IM. See safety section of this review.

Comments:
- These were industry sponsored studies (funding, statistical expertise, etc.).
- Study drop-out rates were high (>20%) especially in the Americas study. 489 (67.7%) completed the study and in the Europe and Asia study, 856 (80.4%) completed the study.
- While these studies do include women from study sites around the world, supporting some generalizability of the results, most studies did not include women from sub-Saharan Africa.
- The open-label, non-comparator study design (rather than placebo-controlled) was considered suitable and ethical for these trials because Depo-Provera IM® is used as a contraceptive in many countries and has proven efficacy.
- Efficacy outcome: Pearl Index (number of pregnancies per 100 woman-years of use) was 0, as was the cumulative pregnancy rate at 1 year (the primary efficacy endpoint), based on the life-table method (percentage of women whose method of contraception failed within the specified time period) in each study.
    - Excluding months during which barrier contraception was used at least sometimes or no intercourse occurred, DMPA-SC was a highly effective (99.9%) contraceptive in these studies, as evidenced by the absence of pregnancies in the 720 women in the Americas trial or the 1059 women in the European/Asian trial for whom data were available.
- Participant satisfaction with treatment results was evaluated using a patient satisfaction questionnaire (PSQ) and end-of-treatment questionnaire (EOTQ). It collected data regarding the respondent's experience with the study, the aspects of treatment that were liked and disliked and the likelihood of selecting that method for future contraceptive purposes.

Author: Kaunitz et al, 2009 (7)
Type of study: Randomized, evaluator-blinded study
Population and N: DMPA-SC (n=266) or DMPA-IM (n=268) for 2 years with an option to continue for a third year.
Comparators: Subcutaneous injection (104 mg/0.65 mL; DMPA-SC) vs. intramuscular DMPA (150 mg/mL; DMPA-IM).
Outcomes:

Contraceptive efficacy at 2 years: The 2-year treatment-failure cumulative pregnancy rate was 0% in the DMPA-SC group and 0.8% (95% CI, 0.00–2.37%) in the DMPA-IM group (life-table method). The Pearl Index was 0 for DMPA-SC and 0.24 (95% CI, 0.00–0.70) for DMPA-IM at 3 years.
Bone mineral density (BMD) changes: There were no statistically significant differences in BMD loss between DMPA-SC and DMPA-IM groups at the end of Year 3.
Patient satisfaction: In both study groups, participants reported being very satisfied with their contraceptives; no statistically significant differences were noted between the two study groups with regard to treatment satisfaction.

Comments:
- This industry sponsored study was an extension of the studies published by *Jain et al*.
- A total of 225 women completed the first 2 years of this study (DMPA-SC, n=116; DMPA-IM, n=109).

- **SAFETY**

Dragoman et al published a systematic review in 2016 that evaluated the published peer-reviewed literature regarding the safety of DMPA-SC among women with various characteristics or medical conditions. Results of this review informed the decision-making of a WHO Guideline Development Group. The search strategy for this technical review was adopted from this SR. Post the 2016 review, the ECHO trial was published, and their findings are added to the summaries below.(8,9)

  - Due to heterogeneity of study designs, study populations, and outcome measures collected, the authors did not compute summary measures of associations.
  - No clinical safety concerns unique to DMPA-SC have been reported in any of these studies. The safety profiles of the SC and IM are largely similar.
- **Weight change in obese women:** Data suggests that the safety of DMPA-SC use among obese women is like nonobese women; and, obese users of DMPA-SC and DMPA-IM experience similar adverse effects. No studies reported on adverse outcomes among adolescents.
- **Weight change in non-obese women across different age-groups**: All women experienced weight gain during use of either method over time that was similar, there were no consistent differences in the distribution of weight change across age groups (< 25, 25–35, > 35 years). There was a trend toward higher weight gains among women > 35 years in the North/South American noncomparative Phase 3 trial (not statistically significant, p = .076). However, in the DMPA-SC/IM Phase 3 trial including among women aged 18–35 years, weight gain was significantly higher among women < 25 years using DMPA-SC compared to women ages 25 to 35 years at month 9 (p = .025) and 12 (p = .003).
- **Changes in bone mineral density**: Over two and three years, the median percent changes in BMD among DMPA-SC compared to DMPA-IM users were not statistically different.
- **Endometriosis:** There was no evidence that DMPA-SC contributed to a worsening of their condition or an increased frequency of any other serious adverse events.
- **HIV acquisition risk:** The ECHO trial was a randomized, multicenter, open-label trial across 12 research sites in eSwatini, Kenya, South Africa, and Zambia. It included 7829 HIV-seronegative women aged 16–35 years who were seeking effective contraception and were randomly assigned to receive an injection of 150 mg/mL **DMPA-IM** every 3 months, a copper IUD, or an LNG implant. In the modified intention-to-treat analysis, the hazard ratios for HIV acquisition were 1·04 (96% CI 0·82–1·33, p=0·72) for DMPA-IM compared with copper IUD, 1·23 (0·95–1·59, p=0·097) for DMPA-IM compared with LNG implant, and 1·18 (0·91–1·53, p=0·19) for copper IUD compared with LNG implant. Depo-Provera appeared to pose a marginally higher risk of H.I.V. infection than contraceptive implants? Overall, there was no substantial difference in HIV risk among the methods evaluated, and all methods were safe and highly effective. (10)
- **Injection site reactions:** Users of DMPA-SC may experience injection site reactions more frequently, but these are rare, typically mild to moderate in severity and generally resolve without further intervention.

- **Changes in bleeding patterns and other adverse effects:** No consistent differences reported in bleeding patterns across age groups (≤ 25, 25–35, > 35 years) among DMPA-SC users in Phase 3 trials. No differences in AEs, most mild or moderate in severity and SAEs rare.

Comments:
- These were industry sponsored studies (funding, statistical expertise, etc.).
- Study drop-out rates were high (>20%) in many of the trials
- While these studies do include women from study sites around the world, supporting some generalizability of the results, most studies did not include women from sub-Saharan Africa
- Safety outcomes measured – many used surrogate markers and many outcomes are heterogenous hence difficult to combine into single estimates.

- **ACCEPTABILITY OF SELF-ADMINISTRATION**

As no new studies focusing on sub-Saharan Africa were identified after publication of the Kennedy et al 2019 systematic review and meta-analysis (5) we review below this synopsis of published studies.

Summary of results (Kennedy et al, 2019): Six studies with 3851 total participants met the inclusion criteria: three RCTs and three controlled cohort studies. All studies examined self-injection of DMPA-SC;
comparison groups were either provider-administered DMPA-SC or provider-administered intramuscular DMPA. All studies followed women through 12 months of contraceptive coverage and measured (dis)continuation of injectable contraception.
Three studies were conducted in SSA:

- *Burke et al*(11) - Mangochi District, Malawi: Women aged 18–40 years old receiving family planning services. Mean age: 26.9 years (SD: 5.21). Randomised controlled trial, 731 participants (364 self administration, 367 provider administration) and 12-month follow-up;
- *Cover et al* (12)- 5 districts in Uganda: Women aged 18–45 years old attending participating health facilities for routine FP visits who expressed an interest in using injectable contraception, Mean age: (Intervention) 26.9 (SD: 6.4); (Control) 26.5 (SD: 6.2).Controlled cohort study. 1161 participants (561 self administration, 600 provider administration). 12-month follow-up;
- *Cover et al*(13) - Dakar and Thiés regions of Senegal: Women aged 18–45 years old attending participating health facilities for routine FP visits who expressed an interest in using injectable contraception, Mean age: (Intervention) 26.9 (SD: 6.4); (Control) 26.5 (SD: 6.2). Controlled cohort study. 1299 participants (650 self administration, 649 provider administration). 12-month follow-up.

Meta-analysis found higher rates of continuation with self-administration compared with provider administration in three RCTs (RR: 1.27, 95% CI 1.16 to 1.39) and three controlled cohort studies (RR: 1.18, 95% CI 1.10 to 1.26). Four studies reported pregnancies; all showed no difference across study arms. Four studies reported side effects/adverse events; while two controlled cohort studies showed increased injection site reactions with self-administration, no other side effects increased with self-administration. One study found no difference in social harms. No studies reported measuring uptake or self-efficacy/empowerment.

- In the meta-analysis, the relative risk of contraceptive continuation was higher with self-administration of injectable contraception compared with provider administration.
- There were no major differences in pregnancy or side effects/adverse events, except that the two controlled cohort studies showed increased injection site reactions with self-administration.

d. Evidence quality: Moderate quality. High rates of drop out.

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>Clinical trial data</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>Benefits outweigh potential harms</td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:

Yes [x] No [ ]
All other available contraceptive modalities, as women’s choice is a prerogative.
List the members of the group: see above
List specific exclusion from the group: n/a</td><td>Rationale for therapeutic alternatives included:
All other available contraceptive modalities, as women’s choice is a prerogative.
References: n/a

Rationale for exclusion from the group: n/a

References: 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 [x] Major [ ] Uncertain [ ]

Is the option acceptable to key stakeholders?
Yes [x] No [ ] Uncertain [ ]</td><td>-There is a possibility of self-administration which may even increase the way people value the option.

-Its very likely this option will be acceptable to stakeholders as it has non-inferior efficacy and safety profile.

Note: Please see evidence described in the narrative above.</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [ ] Less intensive [ ] Uncertain [X]</td><td>Price of medicines/3 months (84 days):
<table>
<tr><th>Medicine</th><th>Pack size Price (ZAR)*</th><th>Price/ 84 days (ZAR)</th></tr>
<tr><td>Medroxyprogesterone,104 mg/0.65 mL, SC – SAHPRA registered but no SEP available</td><td>n/a</td><td>n/a</td></tr>
<tr><td>Copper IUCD</td><td>159,99</td><td>7,36</td></tr>
<tr><td>Levonorgestrel/ethinyl estradiol, triphasic tablets</td><td>6,28</td><td>18,84</td></tr>
<tr><td>Levonorgestrel/ethinyl estradiol, monophasic tablets</td><td>2,90</td><td>8,70</td></tr>
<tr><td>Norethisterone enanthate injection</td><td>24,01</td><td>36,02</td></tr>
<tr><td>Etonogestrel implant</td><td>224,58</td><td>17,23</td></tr>
<tr><td>DMPA injection</td><td>15,40</td><td>15,40</td></tr>
</table>
* Contract circulars RT283-2017, HP03-2017CHM/01
Additional resources:
Could not source other international prices (including Canada; Australia; Netherlands; Spain; Turkey).</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?

Yes [ ] No [X] Uncertain [ ]</td><td></td></tr>
<tr><td>FEASIBILITY</td><td>Is the implementation of this recommendation feasible?

Yes [ ] No [ ] Uncertain [X]</td><td>While the product is now SAHPRA registered, the price to the market is not yet available.</td></tr>
</table>

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: Based on the evidence reviewed, the Adult Hospital Level Committee recomends that subcutaneous DMPA should be considered as a therapeutic alternative of the progestogen injectable therapeutic group. There is no preference for either formulation as they seem to have similar therapeutic efficacy and safety profile. The option of self-administration has been shown to be feasible and acceptable in Sub-Saharan Africa (Malawi, Uganda and Senegal); where training and support is available to women.

Rationale: Available evidence among healthy women suggests that DMPA-SC and DMPA-IM appears to be therapeutically equivalent interms of safety and efficacy. Satisfication rate for DMPA-SC is similar to that of the IM formulation. Data from other countries in sub-Saharan Africa supports the option of self administration of DMPA -SC. A local acceptability and feasibility study may be required to determine if the self-administration option is a viable option for South Africa.

Low dose DMPA- SC:

Level of Evidence: I Systematic review, RCT

Self administration of low dose DMPA-SC:

Level of Evidence: II Systematic Review (moderate quality RCTs); cohort studies

Review indicator: *Availability of SAHPRA registered product on the South African market, affordable price*

Evidence of efficacy	Evidence of harm	Price reduction
x		

VEN status:

Vital	Essential	Necessary
	X	

NEMLC MEETING OF 26 SEPTEMBER 2019:

NEMLC accepted the proposal as recommended by the Adult Hospital Level Committee, noting that SAHPRA registration and a reasonable price is required for consideration for inclusion in the national EML.

NEMLC MEETING OF 17 SEPTEMBER 2020:

NEMLC accepted the updated medicine review that now includes comparative pricing.

Monitoring and evaluation considerations

Research priorities

- Feasibility of self administration
- Long term safety profile
- Acceptability studies for self-administration of subcutaneous low-dose DMPA in South Africa

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