Reviewer No.1 check list for application for addition: 25 mg medroxyprogesterone acetate (DMPA) + 5 mg estradiol-cypionate (E2C) combined injectable contraceptive

(1) Have all important studies that you are aware of been included?

[ ] Yes  [ ] No

Note: One Cochrane systematic review of 10 randomized controlled trials evaluated monthly combined injectable contraceptives compared to their progestin-only counterparts. DMPA + E2C was compared to DMPA in 2 trials. The trials were either open or did not describe any method of blinding. None of the trials reported a method of concealing the allocation process.

(2) Is there adequate evidence of efficacy for the proposed use?

[ ] Yes  [ ] No

(3) Is there evidence of efficacy in diverse settings and/or populations?

[ ] Yes  [ ] No

(4) Are there adverse effects of concern?

[ ] Yes  [ ] No

(5) Are there special requirements or training needed for safe/effective use?

[ ] Yes  [ ] No

(6) Is this product needed to meet the majority health needs of the population?

[ ] Yes  [ ] No

If "No", is there a special reason why this should be on the Model List?

Monthly injections seem to be acceptable and accessible to women who are concerned about daily pill taking, who prefer regular cycles to amenorrhea and who are concerned with a delay in the return of fertility. It serves as an alternative for women who wish to use injectable formulations that cause less disruption in vaginal bleeding and minimal side effects.

(7) Is the proposed dosage form registered by a stringent regulatory authority?

[ ] Yes  [ ] No

(8) What action do you propose for the Committee to take?

Despite the current inclusion of two long-acting injectable only-progestin contraceptives in the WHO Model List, and the similar contraceptive effectiveness between them and the combined injectable contraceptives, the differences in safety profile and convenience may serve to increase tolerance and continuation rates in women with different organic conditions and preferences. So, I recommend the addition of medroxyprogesterone acetate + estradiol-cypionate in the 15th WHO Model List.
Expert Committee Member Comment on Application for Inclusion of Combined Injectable Contraceptive in the 15th WHO Model List of Essential Medicines

Background: There are different reversible injectable hormonal contraceptives, providing effective contraception for 1, 2 or 3 months. They include progestogen-only contraceptives and combined contraceptives, the last ones containing both an estrogen and a progestin, in multiple formulations. In the first category, medroxyprogesterone acetate and norethisterone enantate are found. Currently combined injectable contraceptives include medroxyprogesterone acetate + estradiol-cypionate, medroxyprogesterone acetate + estradiol, norethisterone enanthate + estradiol valerate, dihydroxyprogesterone acetophenide + estradiol enanthate, dihydroxyprogesterone acetophenide + estradiol benzoate, dihydroxyprogesterone caproate + estradiol valerate and megestrol acetate + estradiol.

All of them are highly effective methods of contraception and they are mainly indicated for women with contraindications for oral contraceptive method, including those who have nonadherence to consistent use of oral contraceptives, HIV, learning disabilities or physical disabilities, or are younger than 16 years. Only-progestogen injectable contraceptives are mainly indicated for women with contraindications for estrogen-progestin combinations. Combined injectable contraception is indicated for women desiring the benefits of an injectable method while minimizing some side effects of progestin-only formulations.

The 14th WHO Model List already includes two injectable progestogen-only contraceptives: medroxyprogesterone acetate (DMPA) and norethisterone enantate (NET-EN). The first may be used as a short-term or long-term contraceptive for women, repeated every 12 weeks. The second provides contraception for 8 weeks. This difference in frequency of administration can have implications on patient uptake. They also differ in cost that may significantly affect budgeting in the health system. A Cochrane systematic review that included two trials indicated little difference between the effects of these contraceptives (frequency of discontinuation, duration of bleeding and spotting events, mean changes in body weight, systolic and diastolic blood pressure at 12 months) except that women on DMPA are more likely to develop amenorrhoea (21%). DMPA use over 12 months and 24 months is associated with significant and linear loss of bone mineral density in comparison to oral contraception (pills) and nonhormonal contraception (controls), with no evidence of increased risk of fracture. However, the DMPA-associated bone loss over 2 years can be arrested by estrogen replacement therapy. Given that the relative dosing is lower, and that the progestin is combined with estrogen, the medroxyprogesterone acetate + estradiol-cypionate (DMPA+ E2C) combination injectable contraceptive has less effects on bone mineral density.

Because of the possible effect on bone mineral density, benefits of using DMPA beyond 2 years should be evaluated against risks in all women. Care should be taken in recommending DMPA to adolescents in whom it should be used only when other methods of contraception are inappropriate. In women older than 40 years with risk factors for osteoporosis DMPA should not be considered.
An earlier application for inclusion of this combined injectable contraceptive into the 14th WHO Essential Medicines Model List was rejected by the WHO Expert Committee that expressed concerns over the lack of safety information presented.

The current application is for inclusion of 25 mg medroxyprogesterone acetate (DMPA) + 5 mg estradiol-cypionate (E2C) combined injectable contraceptive into the 15th WHO Essential Medicines Model List.

Combined injectable contraceptives primarily prevent ovulation, supplemented mainly by contraceptive actions at the endometrial and cervical mucus level. The contraceptive effectiveness of DMPA, when given at the recommended intervals, corresponds to pregnancy rates fewer than 4 in 1000 over 2 years, and is lower than that with norethisterone enantate. The annual pregnancy rates are below 0.4% for norethisterone enanthate/estradiol valerate and below 0.2% for medroxyprogesterone acetate/estradiol cypionate.

The contraceptive effect may remain for nine to ten months after the last injection of DMPA. This is a disadvantage for women who experience unpleasant side effects or want to discontinue DMPA to become pregnant. Compared to the progestin-only formulations, the hormonal injectable combination has a faster return to fertility after discontinuation. Median time to conception (5.5 months) is shorter than after discontinuation of progestin-only injectables (8.5 months) and slightly longer than after discontinuation of an IUD (4.5 months) or an oral contraceptive (3 months).

Compared to the progestin-only formulations, the combined injectable contraceptive is more likely to provide women with a normal bleeding pattern, although a temporary change in menstrual patterns could be the most common side effect (14.6% to 39.6%). More than two-thirds of women had predictable, regular cycles, and discontinuation due to bleeding-related problems occurred less than half as often as with progestogen-only injectables. Combination injectable contraceptives have a lower occurrence (0.1% to 2%) of amenorrhea than progestin-only injectable contraceptives. Less common side effects include weight gain, headaches and dizziness. Complications of the DMPA + E2C injectable combination are rare. In few cases abdominal pain, acne, alopecia, asthenia, breast tenderness, decreased libido, depression, enlarged abdomen, nausea, nervousness and vulvovaginal disorder were reported. In systematic reviews, randomized controlled trials generally do not have enough power for studying the risk of major events.

Combination injectable contraceptives do not require special facilities or skills, other than the ability to give an intramuscular injection using aseptic technique, with adequate supply of contraceptives, needles and syringes. However, the injections are usually provided in a clinical site or medical office. DMPA + E2C are given by deep intramuscular injection once every 30 days, with a grace period of ±3 days. DMPA is given by deep intramuscular injection once every 90 days, with a grace period of ±14 days.

The monthly injectables came to be more widely used because monthly withdrawal bleeding gives users the reassurance that they are not pregnant.
The DMPA+E2C combination injectable contraceptive is registered in 20 countries throughout Latin America, as well as Indonesia and Thailand and is available in both public and private sectors. An estimated 1.2 million women currently use the DMPA+ E2C combination injectable contraceptive. About 8 million women use the long acting injectable contraceptive depot medroxyprogesterone acetate (DMPA) and norethisterone enanthate (NET-EN). 

In South Africa, the commodity cost of DMPA is considerably lower than that of NET-EN. Public sector cost for DMPA (progestin-only) injections is USD 3.5 per year. The costs for DMPA+ E2C use are between USD 15 to USD 42 per year. Public sector cost is USD 10.2 per year. Those costs are for the injections only; costs of the health care services, medical fees etc. vary largely per region.

In summary, MPA/E2C has high efficacy, safety and convenience. Monthly injections seem to be acceptable and accessible to women who are concerned about daily pill taking, who prefer regular cycles to amenorrhea and who are concerned with a delay in the return of fertility. Its cost is higher than those of DMPA and NET-EN. It serves as an alternative for women who wish to use injectable formulations that cause less disruption in vaginal bleeding and minimal side effects.

**Aims of the search:** To assess the contraceptive effectiveness, safety, convenience and comparative cost of an injectable contraceptive combination containing 25 mg medroxyprogesterone acetate + 5 mg estradiol-cypionate, in order to decide on its inclusion in the 15th edition of WHO Model List of Essential Medicines.

**Search strategy:** A Medline search, using PubMed (“combined injectable contraceptives”) for systematic reviews and randomized controlled trials (RCTs), from 2000 to 2007, yielded one systematic review, no meta-analyses, three RCTs and 12 non-systematic reviews.

The selected studies have compared the medroxyprogesterone acetate + estradiol-cypionate to depot medroxiprogesterone acetate and to norethisterone enanthate + estradiol valerate. A review on Cochrane Controlled Trials Register yielded two complete systematic reviews. Additionally, some older studies mentioned in the application report were reviewed. Health economic studies were not found. The studies were mainly published before 2000, and non-systematic reviews, observational studies and open trials predominate. In general, the studies did not yield robust evidence to answer some important clinical questions, such as the influence of injectable reversible contraceptive methods on bone metabolism.

**Comments:**

**COMPARATIVE CONTRACEPTIVE EFFECTIVENESS**

One Cochrane systematic review of 10 randomized controlled trials evaluated monthly combined injectable contraceptives compared to their progestin-only counterparts.
DMPA + E2C was compared to DMPA (2 trials) and to NET-EN + E2V (5 trials). Three of the trials were large (2252 to 2707 randomized women) and 12 treatment months in duration. The remaining trials randomized fewer women (100 to 600) and followed them for 6, 9 or 12 treatment months. The trials were either open or did not describe any method of blinding. None of the trials reported a method of concealing the allocation process. Six trials excluded randomized women from the analysis for protocol violations, a practice that can lead to biased estimates. One trial excluded women from two centers (n=222) from the analysis since the centers had poor follow-up rates. No differences were found in contraceptive effectiveness rates between the comparisons. Pregnancy rates for DMPA only, NET-EN only and combined injections were respectively: 0-0.1%, 0.4% and 0.0-0.12% after one year of use. Although injectable contraceptives are a highly effective method, the studies had insufficient power to study this outcome.

The return to fertility after method discontinuation was faster for ex- DMPA + E 2C -users, with a median time to conception of 5.5 months, when compared to ex-DMPA-users, which had a median time to conception of 8.5 months.8,12.

A cohort study15 of 70 DMPA + E 2C-users showed that the return to fertility rate after the discontinuation of the injectable contraceptive was 1.4 per 100 women at the end of the first month and reached 82.9 at one year. More than 50% were pregnant at 6 months.

COMPARATIVE EVIDENCE ON SAFETY

Menstrual disturbances
The comparison between DMPA + E2C and DMPA showed that the combination injectable contraceptive resulted in less amenorrhea and discontinuation due to amenorrhea or all bleeding problems than the progestin-only contraceptive. The comparison between DMPA + E2C and NET-EN + E2V found that the NET-EN + E2V group had more regular (cyclical) bleeding and fewer prolonged bleeding reference periods than the DMPA + E2C group. The two groups did not differ in their amenorrhea rates. However, the statistical significance of almost all of these findings was dependent on one trial conducted in China and the differences generally were not detected in the other populations studied.14

In a randomized controlled trial16 360 Kenyan women were randomly assigned to receive DMPA or DMPA + E 2C for a one year study. More women reported amenorrhea while using DMPA (70.6%) than those using DMPA + E2C (20.8%).

Bone mineral density changes
A 7-year prospective matched-cohort clinical study17 compared bone mineral density changes in new DMPA-IM users (n=248) and in women using nonhormonal contraception (n=360) for up to 240 weeks of treatment and 96 weeks of posttreatment follow-up. The results show BMD declines during DMPA-IM use; following discontinuation, significant increases in BMD occur through 96 weeks posttreatment.
A systematic review\textsuperscript{18} evaluated the association between depot medroxyprogesterone acetate and fracture risk or bone mineral density change. One study reported that DMPA users were more likely to experience stress fractures than nonusers; this association was not statistically significant after controlling for baseline bone density. In cross-sectional studies, the mean BMD in DMPA users was usually below that of nonusers, but within 1 SD. In longitudinal studies, BMD generally decreased more over time among DMPA users than among nonusers, but women gained BMD upon discontinuation of DMPA.

A Cochrane review,\textsuperscript{19} evaluating the effect of using hormonal contraceptives before menopause on the risk of fracture in women, found no trial had fracture as an outcome. Combination contraceptives did not appear to affect bone health. However, DMPA was associated with decreased bone mineral density. The two placebo-controlled trials showed BMD increases for DMPA plus estrogen supplement and decreases for DMPA plus placebo.

A randomized clinical trial\textsuperscript{20} evaluated 123 adolescents who began receiving depot medroxyprogesterone acetate injections every 12 weeks, and were assigned randomly to receive monthly injections of estradiol cypionate or placebo. Participants, technicians, and physicians were blinded to estrogen treatment. Over a 24-month period, the percentage of change from baseline bone mineral density at the lumbar spine was 2.8% in the estradiol cypionate group versus -1.8% in the placebo group ($P < .001$). At the femoral neck, the percentage of change from baseline bone mineral density was 4.7% in the estradiol cypionate group versus -5.1% in the placebo group ($P < .001$). These results suggest that estrogen supplementation is protective of bone in adolescent girls who receive depot medroxyprogesterone acetate injections.

A cross-sectional descriptive study\textsuperscript{6} evaluated the effects of DMPA + E2C and NET-EN + E2V on the bone mineral density (BMD) of women in comparison to those using TCu 380A IUDs as control subjects, paired by age and body mass index. There was no difference in BMD between users of either injectable contraceptives and nonusers at either section of the forearm studied, nor did the duration of use influence the BMD values. The study did not evaluate the risk of fracture.

**Metabolic changes**

One-year longitudinal study\textsuperscript{21} evaluating lipid metabolism demonstrated very minor changes in lipid profiles, with less than a 10% change from baseline (for all parameters) for DMPA + E2C users. Such small variations in lipid metabolism for users of DMPA + E2C are unlikely to modify cardiovascular risk. This is in contrast to a historic control, users of progestin-only injectables, whose change in serum lipids is noted in multiple studies to be 10-40% from baseline.

One study compared effects of DMPA + E2C and NET-EN upon lipoprotein parameters after 12 months of use. Total cholesterol, high-density, low-density and very low-density lipoprotein cholesterol and triglyceride levels decreased at 12 months in both groups and these changes were statistically significant.\textsuperscript{22}

Another study evaluated DMPA + E2C effects on both glucose metabolism and liver function. Users of DMPA + E2C were found to have slight elevations of glucose levels and bilirubin; however, these values remained within the normal range. This is in contrast to DMPA which, in
small studies, describe up to 63% of women experiencing borderline abnormal or abnormal glucose tolerance after one year of treatment.\textsuperscript{23}

\textit{Coagulation and fibrinolysis changes}

A randomized controlled multicenter study\textsuperscript{24} was undertaken to monitor the effects on hemostasis of norethisterone enanthate + estradiol valerate and medroxyprogesterone acetate + estradiol cypionate in comparison with oral contraceptive (norethisterone + ethinyl estradiol) users. Overall, the injectable preparations may be more beneficial than the oral preparation in not enhancing a hypercoagulable state because of the reduced synthesis of fibrinogen, factors VII and X; however, decreases in antithrombin and protein C, which are potent coagulation inhibitors, may raise some concern.

\textit{Weight gain}

A cohort of users of depot-medroxyprogesterone acetate (DMPA) showed a weight increase of 8.2 kg at the end of the fifth year. An increase of the final BMI (from 25.5 ± 0.4 to 28.7 ± 1.3) was also observed in DMPA users.\textsuperscript{25}

A cohort study\textsuperscript{26} evaluated weight variation in 3183 women using the injectable medroxyprogesterone acetate + estradiol cypionate. The weight gain was inversely proportional to the weight at admission. The groups of women weighing less than 50 kg at admission, experienced a higher increase, 2.8% in four months, and they continued gaining weight, reaching 7.7% in 13 months. Women weighing more than 64 kg at admission did not present any weight change in 4 months and increased only 1.7% at 13 months. Discontinuation rates due to weight increase were proportional to the weight at admission. This rate was almost three times higher in the group of women weighing more than 64 kg at admission than in the group weighing less than 55 kg (p<0.001).

\textbf{COMPARATIVE CONVENIENCE}

One study comparing DMPA + E2C and DMPA found no difference in overall early trial discontinuation between the two study groups.\textsuperscript{27} A smaller trial\textsuperscript{28} found statistically significantly higher odds of early discontinuation with the combination than the progestin-only group, but the effect estimate was imprecise (OR = 8.4; 95%CI: 1.8 -38.8). In contrast, the combination injectable users were more likely than the progestin-only contraceptive group to discontinue early for other medical reasons (e.g., headache, not feeling well, or weight change) or personal reasons. The comparison between DMPA + E2C and NET-EN + E2V found that NET-EN + E2V resulted in less overall early discontinuation and less discontinuation due to amenorrhea or prolonged bleeding than DMPA + E2C. However, life table estimates of the three trials that reported these estimates showed no difference in discontinuation rates between the two combination injectable groups. Therefore, the heterogeneity among these trials should be interpreted with caution since the discontinuation rates are dependent on many other factors.\textsuperscript{14} While discontinuation rates can be viewed as a measure of method acceptability, this acceptability is dependent on the population studied since perceptions of bleeding pattern changes and environmental conditions can vary. In the Kenian study\textsuperscript{16} the 1-year continuation rate was 75.4% for DMPA users versus 56.5% for DMPA + E2C users (p<.001). Main reasons for discontinuation included difficulty making clinic visits (45.1% for DMPA + E2C vs. 40% for
DMPA), menstrual changes (14.1% vs. 12.5%) and nonmenstrual problems (15.5% vs. 12.5%). None of the DMPA users and 8.5% of the DMPA + E2C users claimed frequency of visits as the main reason for discontinuation. So, there was no important difference in discontinuation rates because of menstrual or nonmenstrual problems; the difference mainly reflected the frequency of visits required.

**Comparative Cost and Cost-Effectiveness**

The net prices of different progestin-only injectable contraceptives are about: £ 5.01 for medroxyprogesterone acetate; £ 3.59 for norethisterone enantate.29The cost of a 1-month dose of DMPA + E2C is comparable to the retail price of a pack of oral contraceptives (about $30 per month).30

**Conclusions**

**Effectiveness**

- Injectable contraceptives provide effective, long-term birth control yet do not involve a daily regimen. Combined injectables were developed to provide better cycle control than progestin-only injectables. Progestin-only contraceptives are considered appropriate for women who should avoid estrogen due to medical conditions.
- Because progestin-only injectables are long acting, there may be a delay in the return of fertility. These factors can limit their acceptability, especially among young and low-parity women. This is a disadvantage for women who experience unpleasant side effects or want to discontinue DMPA to become pregnant. Compared to the progestin-only formulations, the hormonal injectable combination has a faster return to fertility after discontinuation.

**Safety**

- The safety of combined injectable contraceptives is considered to be similar to combined oral contraceptives.
- Given the results of metabolic studies and the fact that the parenteral administration avoids first-pass hepatic metabolism, the injectable contraceptive restriction for use in women with medical problems is more relaxed than those for oral contraceptive use.
- The more frequent side effects are changes in menstrual bleeding patterns in most users, including prolonged or irregular spotting/bleeding. However, combined injectable contraceptives yielded less amenorrhea than DMPA.
- Despite the literature controversy about reduction of bone mineral density (surrogate endpoint) and the absence of studies evaluating the risk of fracture, DMPA-IM decreases BMD during its use, a reversible effect following discontinuation or estrogen supplementation. Combination injectable contraceptives did not appear to affect bone health.

**Convenience**

- The continuation rates for DMPA (3 months duration of action) were substantially higher than those for DMPA + E2C, certainly a meaningful programmatic advantage. Substantially
more DMPA + E2C users discontinued the method because of the monthly clinic visits required to obtain the injections.

- The narrower window in which DMPA + E2C must be scheduled (±3 days) may be inconvenient for some users in comparison with a grace period of ±14 days for progestin-only injectables.
- The monthly injection seems more convenient for women who want predictable, regular cycles, similar to menses. The monthly withdrawal bleeding gives users the reassurance that they are not pregnant.

**Recommendation:**

Despite the previous inclusion of two long-acting injectable only-progestin contraceptives in the WHO Model List, and the similar contraceptive effectiveness between them and the combined injectable contraceptives, the differences in safety profile and convenience may serve to increase tolerance and continuation rates in women with different organic conditions and preferences. So, I recommend the addition of medroxyprogesterone acetate + estradiol-cypionate in the 15th WHO Model List.

**References:**


