Application for inclusion of
a combined injectable contraceptive
in the WHO List of Essential Medicines

1. Summary statement of the proposal for inclusion, change or deletion

Combined injectable contraceptives, which contain both an estrogen and a progestin, were developed as a method choice for women desiring the benefits of injectable contraception while minimizing some side effects of progestin-only formulations. Combined injectable contraceptives are as effective as sterilization, with a 0 to 0.2% pregnancy rate at one year of use (1), reversible, discrete, independent of coitus, and offer the convenience of once-monthly dosing. Compared to the progestin-only formulations, they are more likely to provide women with a normal bleeding pattern and a faster return to fertility after discontinuation.

Currently marketed combination injectables include medroxyprogesterone acetate (DMPA) 25 mg plus estradiol-cypionate (E_2C) 5 mg (Cyclofem®) and the combination of norethisterone enanthate (NET-EN) 50 mg plus estradiol valerate (E_2V) 5 mg (Mesigyna®). Locally available in Latin American markets, the dihydroxyprogesterone acetophenide plus E_2 enanthate combination drug (Deladroxate, Perlutal) is used commonly, and in China, an older formulation containing hydroxyprogesterone caproate plus E_2V (Injectable No. 1) is still used. Of these combination injectables, DMPA+ E_2C and NET-EN + E_2V are the most thoroughly studied by toxicological, pharmacokinetic, and clinical comparative trials. In fact, the WHO supported both their research and development, in response to country requests for a safe and effective monthly injectable, over two decades ago. Since their entry into the market, the DMPA+ E_2C combination - which is the focus of this application - is the only combined injectable that has sought and been approved for use by the USFDA.

Complications of the DMPA+ E_2C combination injectable are rare. The most common side effect is a change in menstrual patterns, which is often temporary. The safety of this product is considered in the WHO Medical Eligibility Criteria for Contraceptive Use (2) where it is determined to be similar to or safer than the combined oral formulations. Less common side effects include weight gain, headaches and dizziness.

The DMPA+ E_2C combination injectable contraceptive is registered in 20 countries throughout Latin America, as well as Indonesia, Thailand and Hong Kong.
An application for this contraceptive was submitted to a prior WHO Expert Committee on the Selection and Use of Essential Medicines. The comments of the Committee at that time reflected concerns over the lack of safety information presented. In response to these concerns, this application includes a review of the spectrum of metabolic studies that demonstrate DMPA+E₂C's minimal or non-existent effect on metabolism, particularly when compared to oral contraceptives. Additionally, this application includes the assessments of the drug's safety as determined by the thorough review of published research in combination with an expert understanding of hormonal contraception and its risks by the WHO Expert Working Group for Contraceptive Use. This working group is responsible for the creation and maintenance of the recommendations in the WHO Medical Eligibility Criteria for Contraceptive Use (2). Since the last application, a Cochrane review of the drug, as well as continued, recent metabolic studies have been published and are considered in this document.

2. Name of the focal point in WHO submitting application

3. Name of the organization consulted and supporting the application
The Geneva Foundation for Medical Education and Research (GFMER; http://www.gfmer.ch/) is submitting the application. GFMER is a WHO Collaborating Centre in Education and Research in Human Reproduction. Staff at GFMER has extensive experience in conducting systematic reviews, critically appraising the literature and developing recommendations.

4. International Nonproprietary Name (INN, generic name) of the medicine
Medroxyprogesterone acetate (DMPA) plus estradiol-cypionate (E₂C): Cyclofem (Cyclofemina, Novafem®).

5. Whether listing is requested as an individual medicine or as an example of a therapeutic group
Individual medicine.
6. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

An estimated thirty-five million women worldwide use injectable steroids for contraception, including injectables with efficacy for 1, 2 or 3 months (3).

An estimated 1.2 million women currently use the DMPA+ E$_2$C combination injectable contraceptive, mainly in Latin America, Indonesia and Thailand (4).

7. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)

- **Dosage regimen**: Medroxyprogesterone acetate (DMPA) 25 mg plus estradiol cypionate (E$_2$C) 5 mg.
- **Duration**: one dose of the combination injectable contraceptive is effective for the duration of one month.
- **Existing WHO guidelines**: Combined injectables are listed as a separate category in the WHO's *Medical Eligibility for Contraceptive Use*, where they are fully considered and recommended for use separate from other methods of contraception. Additionally, two out of 33 questions in the WHO *Selected Practice Recommendations for Contraceptive Use* (5) are dedicated to combined injectables, where strict recommendations for initiating their use and contraindications to their use are delineated. Finally, their appropriate use in practice is covered in detail in a dedicated section of the WHO *Decision Making Tool for Family Planning Providers* (6), as well as in a dedicated chapter of the *Family Planning Handbook*, which is soon to be published.
- **Diagnostic facilities and skills**: The diagnosis of pregnancy should be excluded prior to administration of hormonal contraception. This clinical diagnosis may be made by adhering to the specific recommendations outlined in the section titled, 'How can a provider be reasonably sure that a woman is not pregnant?' in the WHO *Selected Practice Recommendations for Contraceptive Use* (5).
  
  Additional requirements are the technical capacity and skill to evaluate a woman's health and administer injections using aseptic technique, with adequate supply of contraceptives, needles and syringes.
- **Treatment facilities and skills**: combination injectable contraceptives are administered every 28 to 30 days (not to exceed 35 days). The first injection should be given during the
first 7 days of the cycle. It may be given at any other time during the cycle, if it is reasonably certain that the woman is not pregnant, in which case she will have to abstain from sex or use additional protection for 7 days following administration of the contraceptive (5). No special facilities or skills, other than the ability to give an IM injection, are required.

8. Summary of comparative effectiveness in a variety of clinical settings:

- Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

The Cochrane Controlled Trials Register, CENTRAL, MEDLINE, EMBASE, POPLINE, LILACS, AIM, IMSEAR and IMEMR from their inception to October 2006 were systematically searched. Reference lists of retrieved papers were also searched. No unpublished data was used, now were authors contacted for additional information.

One Cochrane systematic review (7), published in 2006 and last-updated in 2005, as well as a newly-published randomized clinical trial (8), not yet included in the Cochrane review, were identified and are considered in this application.

Studies selected for the Cochrane review were randomized controlled trials reported in any language comparing a combination injectable to any other contraceptive method (a second combination injectable contraceptive, progestin-only injectable contraceptive, other hormonal contraceptive or barrier method). The research was limited to currently marketed combination injectables. Trials were assessed and included if they had adequate concealment of allocation, randomization procedure and follow-up. Quality assessment and data extraction were conducted by two reviewers independently.

Participants were women of reproductive age without contraindications to combined injectable contraceptives. Meta-analysis was performed only when identical drugs, dosages and regimens were compared.

Results were presented as relative risk (RR) with 95% confidence intervals (CI) for dichotomous outcomes and weighted mean difference (WMD) with 95% CI for continuous outcomes.

The outcome measures included: contraceptive efficacy, bleeding patterns, method continuation, user preferences and side effects (reported medical or personal reasons). Bleeding patterns were reported for different reference periods depending on the study. For the purpose of this application, data from the first follow-up and after one year are presented.
Ten studies comparing combination injectable contraceptives to another contraceptive method were included in the Cochrane review. The data presented here concentrates on DMPA+ E₂C, but the Cochrane Review presents some data which compiles the results for DMPA + E₂C with another combined injectable, NET-EN + E₂V, and these results are presented as well.

Outcomes:

1. Combined injectable contraceptives (DMPA 25 mg + E₂C 5 mg, NET-EN 50 mg + E₂V 5 mg) compared to their progestin-only counterparts (DMPA 150 mg or NET-EN 200 mg) resulted in:
   - Higher rates of regular bleeding patterns with the combined methods (DMPA: one trial; RR 3.2, 95% CI 2.4-4.2 after the 1st follow-up and RR 2.8, 95% CI 2.2-3.6 after one year; NET-EN: one trial; RR 2.1, 95% CI 1.6-2.7 after the 1st follow-up and RR 1.6, 95% CI 1.1-2.3 after one year)
   - Lower rates of amenorrhea with the combined methods (DMPA: one trial, RR 0.3, 95% CI 0.12-0.65 after the 1st follow-up and RR 0.08, 95% CI 0.04-0.15 after one year; NET-EN: one trial, RR 0.3, 95% CI 0.1-0.9 after one year)
   - Less oligomenorrhea (infrequent bleeding patterns) with the combined methods (DMPA: one trial; RR 0.2, 95% CI 0.1-0.3 after the 1st follow-up and RR 0.5, 95% CI 0.3-0.9 after one year; NET-EN: RR 0.3, 95% CI 0.2-0.6 after the 1st follow-up and RR 0.7, 95% CI 0.5-0.9 after one year)
   - Higher rates of discontinuation for reasons other than amenorrhea with the combined methods (NET-EN: one trial, RR 2.2, 95% CI 1.2-4.1 for other medical reasons and RR 1.8, 95% CI 1.2-2.7 for personal reasons)
   - More women intending to continue to use the method after completion of the study in the combined-method group (DMPA: one trial, RR 2.65, 95% CI 1.78-3.94)

2. NET-EN 50 mg + E₂V 5 mg compared to DMPA 25 mg + E₂C 5 mg had the following results:
   - Discontinuation rates demonstrating heterogeneity between trials; however, life-table estimates of the three trials that reported these estimates showed no difference in discontinuation rates between the two combination injectable groups.
   - Amenorrhea occurred in a similar number of women in both of the combination injectable groups (three trials; RR 0.7, 95% CI 0.2-2.3 after the 1st follow-up and RR 0.9, 95% CI 0.5-1.6 after one year); other bleeding outcomes showed statistically
lower rates of discontinuation for 'all bleeding problems' in the DMPA + E₂C and no other statistically significant differences.

An additional randomized controlled trial (8), that meets eligibility for inclusion in the Cochrane review when it is updated, enrolled 360 women in Kenya who were randomized to use DMPA or DMPA + E₂C for a one year study to compare bleeding patterns and continuation rates. In this study setting, more women continued use of DMPA when compared to women who continued use of DMPA + E₂C, with 75% and 57% at one year, respectively (p<.001). In both groups, two-thirds of the women reported a positive experience with their method. More women reported amenorrhea while using DMPA (71%) than those using DMPA + E₂C (21%). Additionally, more DMPA + E₂C users reported difficulty making clinic appointments (29%) when compared to DMPA users (11%), and a higher proportion of DMPA + E₂C users reported that clinic appointments were too frequent (32% and 0%, respectively).

Reports from large cohort studies demonstrate that effectiveness, measured as the occurrences of pregnancy while using the method, was similar for progestin-only contraceptives and combined injectable contraceptives. 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 (4).

The return to fertility after method discontinuation was faster for ex-DMPA + E₂C-users, with a median time to conception of 5.5 months, when compared to ex-DMPA-users, who had a median time to conception of 8.5 months (9, 10).

- **Summary of available estimates of comparative effectiveness**
  1. Combined injectable contraceptives are as highly effective as both sterilization (11) and progestin-only injectable contraceptives at preventing pregnancy.
  2. Combination injectable contraceptives allow regular cyclic withdrawal bleeding and have a lower occurrence of amenorrhea than progestin-only injectable contraceptives.
  3. Intention to continue with the method was greater in the group using combined injectables compared to progestin-only preparations in the Cochrane review, although frequency of visits may be a factor in continuation rates that may vary based on locality.
  4. 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) (9, 10).
9. Summary of comparative evidence on safety:

- **Estimate of total patient exposure to date to combination injectable contraceptives**
  
  An estimated 1.2 million women currently use the DMPA+ E₂C combination injectable contraceptive, mainly in Latin America, Indonesia and Thailand (4). DMPA + E₂C is registered in 20 countries (Latin American countries, Indonesia, Hong Kong and Thailand) (10) and is available in both public and private sectors.

- **Description of adverse effects/reactions**
  
  The most frequent side effects are changes in bleeding patterns: between 0.1% and 2% users experience amenorrhea and 14.6% to 39.6% experience irregular bleeding during the first year of use (12). Nevertheless, a stabilization of the cycle usually appears after some months of use. Other side effects reported by a small percentage of women can be: weight gain, headache and dizziness (13). There have been case reports of the following side effects: abdominal pain, acne, alopecia, asthenia, breast tenderness, decreased libido, depression, enlarged abdomen, nausea, nervousness and vulvovaginal disorder (13).

- **Identification of variation in safety due to health systems and patient factors**
  
  For a safe use of the DMPA+ E₂C combination injectable contraceptive, technical quality of care must be available. This includes trained personnel to evaluate a woman’s health and administer injections, asepsis maintenance and sufficient supplies of contraceptives, needles and syringes.

  The DMPA+ E₂C combination injectable should not be used under the following conditions: while breastfeeding and less than 6 months postpartum or postpartum less than 21 days and not breastfeeding; age >35 years old and smoking more than 15 cigarettes per day; multiple risk factors for arterial cardiovascular disease; hypertension; history of or current deep venous thrombosis; history of or current pulmonary embolism; major surgery with prolonged immobilization; known thrombogenic mutations; history of or current ischemic heart disease; complicated valvular heart disease; stroke or history of cerebrovascular accident; certain hyperlipidemias; migraine and age >35 years or migraine with aura at any age; history of or current breast cancer; diabetes complicated by nephropathy, retinopathy, or neuropathy; active viral hepatitis; severe, decompensated liver cirrhosis; and liver tumors (2).
Summary of comparative safety against comparators

The estrogen component of DMPA + E₂C is naturally-occurring and therefore is physiologic and less potent than the synthetic estrogens of combined oral contraceptives (COCs). Comparative pharmacokinetic/pharmacodynamic clinical studies of DMPA+ E₂C illustrate that following administration of the contraceptive, the estradiol levels reach only low peak levels, within the follicular range, and allow an endogenous estradiol peak (not followed by a progesterone rise) in 41-49 days after administration (14).

Compared to progestin-only injectable contraceptives, combined injectables lead to fewer progestin-related side-effects. Given that the relative dosing is lower, and that the progestin is combined with estrogen, the DMPA+ E₂C combination injectable contraceptive has less effects on bone mineral density (15).

Studies conducted by the UNDP/UNFPA/World Bank/WHO Special Programme of Research, Development and Research Training in Human Reproduction and others have addressed the issues of known effects of hormonal contraceptives, namely: haemostasis and coagulation, lipid metabolism, liver function, glucose tolerance and bone metabolism. In a 9-month study of COC and DMPA + E₂C users (16), those using the oral formulation were found to have an increase in serum levels of fibrinogen, factor VII, factor X and antithrombin, whereas those on DMPA + E₂C had no changes in these haemostatic factors. DMPA + E₂C users had slightly decreased levels of protein C, and slightly increased plasminogen and fibrinogen levels. Overall, this suggests that DMPA + E₂C may be less likely to cause hypercoagulable states than oral preparations; however, whether this will translate to the development of fewer thromboembolic occurrences has yet to be demonstrated in epidemiologic studies.

A similar one-year longitudinal study (17) of lipid metabolism demonstrated very minor changes in lipid profiles, with less than a 10% change from baseline (for all parameters) for DMPA + E₂C users. This is in contrast to an historic control, users of progestin-only injectables, whose change in serum lipids is noted in multiple studies to be 10-40% from baseline. Such small variations in lipid metabolism for users of DMPA + E₂C are unlikely to modify cardiovascular risk.

The parental administration of CICs eliminates the first-pass effect of the hormones on the liver. To investigate its effects on both glucose metabolism and liver function (18), the same study parameters were applied to women over a one-year time frame. 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.

A recent, cross-sectional descriptive study (15) compared the affects of two types of injectable contraception, DMPA+ E₂C and NET-EN + E₂V, on the bone mineral density of women using the method in comparison to a control group using non-hormonal contraception. Ninety-seven women were included in each group. The measured bone mineral density after at least one year of CIC use did not differ significantly from that of a demographically similar control group (midshaft ulna 0.457 for DMPA+ E₂C users and 0.465 in copper-IUD users), nor did the duration of CIC use influence the BMD values.

Epidemiological data on the long-term effects of combined injectables is limited. The WHO Expert Working Group for Contraceptive Use concluded that the evidence available for the safe use of combined oral contraceptives applies to combined injectables in most cases (2). Therefore, the safety of combined injectables is considered to be similar to combined oral contraceptives; however, given the metabolic studies noted above and the fact that the parenteral administration avoids first-pass hepatic metabolism, its restriction for use in women with medical problems is more relaxed than those for COC use. Nevertheless, for severe disease, the guidelines recommend the same category of use as for combined oral contraceptives (2).

10. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group

- **Range of costs of the proposed medicine**
  
  The costs for Cyclofem use are between USD 15 to USD 42 per year. Public sector cost is 10.2 USD per year. Those costs are for the injections only; costs of the health care services, medical fees etc. vary largely per region and are not included in this application.

- **Comparative cost-effectiveness presented as range of cost per routine outcome**
  
  Public sector cost for DMPA (progestin-only) injections is USD 3.5 per year.

11. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

The DMPA+ E₂C combination injectable contraception is available throughout Latin America, and in Indonesia, Hong Kong and Thailand. It is registered in 20 countries and is available in both public and private sectors.

International and British Pharmacopoeia: not available

13. Proposed (new/updated) text for the WHO Model Formulary

Medroxyprogesterone acetate (DMPA) plus estradiol-cypionate (E₂C): Cyclofem, Cyclofemina, or Novafem

**Uses:** Monthly combined injectable contraception

**Contraindications:** while breastfeeding and less than 6 months postpartum or postpartum less than 21 days and not breastfeeding; age >35 years old and smoking more than 15 cigarettes per day; multiple risk factors for arterial cardiovascular disease; hypertension; history of or current deep venous thrombosis; history of or current pulmonary embolism; major surgery with prolonged immobilization; known thrombogenic mutations; history of or current ischemic heart disease; complicated valvular heart disease; stroke or history of cerebrovascular accident; certain hyperlipidemias; migraine and age >35 years or migraine with aura at any age; history of or current breast cancer; diabetes complicated by nephropathy, retinopathy, or neuropathy; active viral hepatitis; severe, decompensated liver cirrhosis; and liver tumors (2).

**Precautions:** hyperlipidaemias; liver dysfunction; fluid retention; use with anticonvulsants (2,11).

The WHO Medical Eligibility Criteria for Contraceptive Use (2) sees no restriction on use of DMPA+E₂C in women with depression, however, the Physician's Desk Reference recommends use with precaution in women with emotional disorders (13).

**Dosage:** Medroxyprogesterone acetate (DMPA) 25 mg and estradiol cypionate (E₂C) 5 mg;
One injection IM every 28-30 days.

**Side effects:** menstrual changes during the first months of use; less common side effects of weight gain, headache and dizziness.
References


3. UN Population Division of Contraceptive Use in 2005. 


13. PDR Drug information for Lunelle Monthly (Pharmacia & Upjohn) http://www.drugs.com/PDR/Lunelle_Monthly_Injection.html#C05


