Application for inclusion of
Combination injectable contraceptives
in the WHO List of Essential Medicines

1. Summary statement of the proposal for inclusion, change or deletion
Monthly combined injectable contraceptives, such as the combination of medroxyprogesterone acetate (DMPA) 25 mg plus estradiol cypionate (E\textsubscript{2} C) 5 mg (Cyclofem\textsuperscript{®}, Lunelle\textsuperscript{®}) and the combination of norethisterone enanthate (NET-EN) 50 mg plus estradiol valerate (E\textsubscript{2}V) 5 mg (Mesigyna\textsuperscript{®}) have been in use for several years. Combined injectable contraceptives are highly effective (with 0 to 0.2% pregnancy rate at one year of use)\textsuperscript{(1)}, reversible, discrete and do not have to be taken daily or just before sexual intercourse. They also offer a rapid return to fertility and are more likely to provide a normal bleeding pattern compared to progestin-only injectables. Complications are rare and the most common side effect is usually temporary- changes in menstrual pattern. Other less common side effects include abdominal pain, acne, headache, breast tenderness/pain, decreased libido, depression, nausea and weight gain. Injectable contraceptives are registered in more than thirty countries, mainly in Latin America and China.

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 (E₂ C): Cyclofem (or Lunelle or Cyclo-Provera or Feminena)
- Norethisterone enanthate (NET-EN) plus estradiol valerate (E₂V): Mesigyna (or Norigynon).

5. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Listing as two individual medicines

6. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

Sixteen million women worldwide are estimated to be using injectable steroids for contraception which includes injectable methods effective for 3, 2 or 1 month\(^2\).

Approximately 1.5-2 million women currently use once-a-month combined injectables, mainly in Latin America, Indonesia and China\(^2\).

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:**
  1. Medroxyprogesterone acetate (DMPA) 25 mg plus estradiol cypionate (E₂ C) 5 mg
  2. Norethisterone enanthate (NET-EN) 50 mg plus estradiol valerate (E₂V) 5 mg
- **Duration:** one dose of combination injectable contraceptive is effective during one month
- **Diagnostic:** used for reversible contraceptive use
- **Treatment facilities:** combination injectable contraceptives need to be 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. No special facilities 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 September 2003 were systematically searched. Reference lists of retrieved papers were also searched. Experts in the field were contacted to identify any ongoing or unpublished trials.

A not yet published Cochrane systematic review \(^{(3)}\) was identified. Studies selected for the 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 were: contraceptive efficacy, bleeding patterns, continuation, user preferences and side effects (reported medical or personal reasons). Concerning bleeding patterns, outcomes were reported for different reference periods. 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 review.

Outcomes:
1. Combined injectable contraceptives (DMPA 25 mg and E₂C 5 mg, NET-EN 50 mg and E₂V 5 mg) compared to their progestin-only counterparts (DMPA 150 mg or NET-EN 200 mg) led to:

- more regular bleeding pattern 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)
- less 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 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)
- more discontinuation due to other reasons than amenorrhea (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) with the combined method
- more women intending to continue with the method after the study ends in the group using the combined method (DMPA: one trial, RR 2.65, 95% CI 1.78-3.94).

2. NET-EN 50 mg and E₂V 5 mg compared to DMPA 25 mg and E₂C 5 mg:

- Trials reporting on discontinuation showed heterogeneity, with one trial conducted in China reporting less discontinuation in the group using NET-EN. However, life-table estimates of three trials showed no difference in discontinuation rates between the two groups.
- Amenorrhea occurred in a similar number of women in both 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

Reports from large cohort studies showed that effectiveness, measured as pregnancies, 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 (²).
For return to fertility, the median time to conception was reported to be 5.5 months for Cyclofem and DMPA \(^\text{(4)}\).

- **Summary of available estimates of comparative effectiveness**
  1. Combined injectable contraceptives show similar effectiveness compared to progestin-only injectable contraceptives.
  2. Combination injectable contraceptives lead to a more regular bleeding pattern and to less 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.
  4. Median time to conception may be longer with combined contraceptives than with IUD (4.5 months) and oral contraceptives (3 months) \(^\text{(4)}\).

9. **Summary of comparative evidence on safety:**

- **Estimate of total patient exposure to date to combination injectable contraceptives**
  Approximately 1.5-2 million women currently use once-a-month combined injectables, mainly in Latin America \(^\text{(2)}\), Indonesia and China. Cyclofem is registered in 22 countries (Latin American countries, Indonesia and Thailand) \(^\text{(5)}\) and is available in both public and private sector. Mesigyna is registered in 42 countries (Latin American and African countries, Turkey and China).

- **Description of adverse effects/reactions**
  The most frequent side effects are changes in bleeding patterns: between 0.1% and 2% for amenorrhea and 14.6% to 39.6% for irregular bleeding during the first year of use \(^\text{(7)}\). Nevertheless, a stabilization of the menstrual 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 \(^\text{(8)}\).
• **Identification of variation in safety due to health systems and patient factors**

For a safe use of combination injectable contraceptives, technical quality of care has to be provided. It includes trained personnel to check the women’s health and administer injections, asepsis maintenance and sufficient supplies in contraceptives and in needles and syringes.

Cyclofem and Mesigyna should not be used under the following conditions: during breastfeeding less than 6 months postpartum if not breastfeeding, postpartum less than 21 days; women >35 years smoking more than 15 cigarettes per day; multiple risk factors for arterial cardiovascular disease; hypertension; history/current deep venous thrombosis; history/current pulmonary embolism; major surgery with prolonged immobilization; known thrombogenic mutations; history/current ischemic heart disease; complicated valvular heart disease; stroke/ history of cerebro-vascular accident; certain hyperlipidemias; migraine for women >35 years and/or with aura; breast cancer; diabetes complicated by nephropathy or retinopathy or neuropathy; viral hepatitis; severe liver cirrhosis; liver tumors (6).

• **Summary of comparative safety against comparators**

The safety of the progestins in Cyclofem and Mesigyna is well established. Compared to progestin-only injectable contraceptives, combined injectables lead to the same progestin-related side-effects. Estrogens included in Cyclofem and Mesigyna are natural and may therefore be beneficial with regard to lipid metabolism and cardiovascular functions. The level of estrogens with combined injections is similar to normal levels in the first half of the menstrual cycle. Therefore, estrogen-related side effects should be minimal (7).

There are few epidemiological data on the long-term effects of combined injectables, and the WHO Expert Working Group concluded that the evidence available for combined oral contraceptives applies to combined injectables in most cases (6). Therefore, safety level of combined injectables are situated between combined oral contraceptive and progestogen-only pills categories. Nevertheless, for severe pathologies, safety information recommends to use the same classification of conditions as for combined oral contraceptives (6).
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 11.20 to USD 30 per year. Public sector cost is 7.8 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 therefore not included here.

- **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)

Combination injectable contraception is available mainly in Latin America, Indonesia and China. Cyclofem is registered in 22 countries and is available in both public and private sector and Mesigyna is registered in 35 countries.


  British Pharmacopoeia: requested
  International Pharmacopoeia: requested
  United States Pharmacopoeia: requested

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

  Medroxyprogesterone acetate (DMPA) plus estradiol cypionate (E₂ C): Cyclofem or Lunelle
  Norethisterone enanthate (NET-EN) plus estradiol valerate (E₂ V): Mesigyna or Norigynon

**Uses**: Monthly combined injectable contraceptives
**Contraindications:** during breastfeeding less than 6 months postpartum; if not breastfeeding, postpartum less than 21 days; women >35 years smoking more than 15 cigarettes per day; multiple risk factors for arterial cardiovascular disease; hypertension; history/current deep venous thrombosis; history/current pulmonary embolism; major surgery with prolonged immobilization; known thrombogenic mutations; history/current ischemic heart disease; complicated valvular heart disease; stroke/ history of cerebro-vascular accident; certain hyperlipidemias; migraine for women >35 years and/or with aura; breast cancer; diabetes complicated by nephropathy or retinopathy or neuropathy; viral hepatitis; severe liver cirrhosis; liver tumors [6].

**Precautions:** hyperlipidaemias; liver dysfunction; fluid retention; emotional disorders; anticonvulsants use [8]; diabetes mellitus; tendency towards diabetes mellitus; varicose veins; a history of phlebitis; otosclerosis; multiple sclerosis; epilepsy; porphyria; tetany; chorea minor [9].

**Dosage:** Medroxyprogesterone acetate (DMPA) 25 mg and estradiol cypionate (E₂C) 5 mg; Norethisterone enanthate (NET-EN) 50 mg and estradiol valerate (E₂V) 5 mg. One injection every 28-30 days.

**Side effects:** menstrual changes during the first months of use; weight gain; headache; acne; breast tenderness; rare side effects: decreased libido; abdominal pain; depression; nausea.

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**Reference**


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