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

Summary of the review for the Expert Committee

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1-Objectives
The main objectives of this presentation reviewing the application for inclusion of two combination injectable contraceptives to the EML are:
1-To establish the need of new contraceptives in the EML
2-To define based on the best available evidence its effectiveness/risk ratio and in the case that this ratio is adequate its cost/effectiveness

2-For listing should be selected only one of the proposed compounds
Here there are two compounds that belong to the same pharmacological group:
   a-depot-medroxyprogesterone 25 mg plus estradiol cypionate 5mg (DMPA/E2C)
   b-Norethisterone enanthate 50 mg plus estradiol valerate 5m (NET-EN/E2V

SUMMARY OF AVAILABLE EVIDENCE OF COMPARATIVE EFFECTIVENESS AND SAFETY

1. There are numerous studies assessing contraceptive efficacy, return to fertility, changes in bleeding pattern, aspects of compliance, acceptability, reasons for discontinuation and minor adverse effects.
2. The efficacy of CICs is very high and similar to progestin-only and oral combined contraceptives.
3. Since the point of view of the convenience, CICs being once-a-month injectables assure compliance more than OCs pills.
4. With regard to bleeding pattern alterations and subsequent amenorrhea, as an important cause of discontinuation, CICs have a better profile.
5. There are no long-term follow–up assessment of MPA/E2C and NET-EN/E2V users or information regarding non-contraceptive benefits of CICs.
6. There are no long term follow–up evaluation of cardiovascular risk and breast and gynecological cancer risk in CICs users.
7. There is no reason to show data of costs of treatment with CICs under consideration because their benefit/risk ratio is not thoroughly known yet.
RECOMMENDATIONS

Combined Injectable Contraceptives applied for inclusion in the EML:

- Represents a formulation for contraception with demonstrated efficacy as contraceptive,
- Permits to return to fertility earlier than progestagen-only contraceptive
- Presents a profile of mild adverse effects
- Fails to have long time trials assuring its safety for important clinical endpoints.
- Its better convenience because its easy way to be used (once each month) is counteracted by the need of a monthly assistance to a health center for the injection.

In our opinion we should wait for randomized controlled trials of long term use of these preparations, assessing the association between CICs use and cardiovascular diseases (stroke, MIA, thromboembolism), BDM and breast and gynecological cancer before considering include them into the EML
Application for inclusion of combination injectable contraceptives in the
WHO List of Essential Medicines

Review for the Expert Committee

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**Objectives**
The main objective of this presentation is to review the application for inclusion of two combination injectable contraceptives to the EML

**1- Summary of the proposal for inclusion**

In is stated that both, medroxyprogesterone acetate 25 mg plus estradiol cypionate 5mg (DMPA/E$_2$C) and the combination of norethisterone enanthate 50 mg plus estradiol valerate 5mg (NET-EN/ E$_2$V) have been in use for several years in developing countries.

The main benefits mentioned were that are highly effective (0-0.2% pregnancy rate at one year of use$^{(n)}$), reversible ,discrete ,convenient (do not have to be taken daily), with rapid return to fertility. At the same time are more likely to provide a normal bleeding pattern compared to progestin-only injectables.

In relation to its safety profile it is mentioned temporary changes in menstrual pattern, abdominal pain, acne, headache, breast tenderness/pain, decreased libido, depression, nausea and weight gain.

Both compound are registered in more than thirty countries, manly in Latin America and China.

**2- Name of the focal point in WHO submitting application and name of the organization supporting it.**
The application was submitted by Dr. Catherine d’Arcangues, coordinator of the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research, Family and Community Health Cluster (WHO/RHR).

The application was originally made by the Geneva Foundation for Medical Education and Research, WHO Collaborating Center in Education and Research in Human Reproduction

**3- International Nonproprietary Name (generic name)**

The proposal includes the brand names of both proposed preparations in addition to the International Nonproprietary Names and keeps using the brand names in all the presentation. This is something unusual to this Committee and it would be preferred to be avoided.

**4- Information supporting public health relevance**
Sixteen million women worldwide are estimated to be using injectable steroids for contraception and approximately 1.5-2 million women currently use once-a-month combined injectables, mainly in Latin America, Indonesia and China.

5- Treatment details
There is a description of treatment details included in the proposal for inclusion.

6 - Listing is requested as two individual medicines
Two active principles that belong to the same pharmacological and therapeutic group are applying for inclusion: a combination of a progestagen plus an estrogen formulated as once-a–month injectable. So, in the case that the proposal for inclusion would be accepted, we should choose only one of them as a representative of the therapeutic group.

General Comments

1. Relevance of the health problem
The problem of unintended pregnancy continued to be a major public health issue in developed and developing countries. Each year about half of pregnancies in the United States are unintended. Twenty three percent of all pregnancies are terminated by elective abortion in US

Each year through the world, approximately 210 million women become pregnant and some 130 million of them go on to deliver live-born infants. As many as 80 million pregnancies are unplanned. Some of these are carried to term, while others end in spontaneous or induced abortion. Estimates indicate that 46 million pregnancies are voluntarily terminated each year – 27 million legally and 19 million outside the legal system. In the latter case the abortions are often performed by unskilled providers or under unhygienic conditions or both.

The estimated unsafe abortion ratios and rates are highest for the region of Latin America and the Caribbean, where almost four million unsafe abortions are estimates to take place each year. The ratios and rates of unsafe abortions for South America are particularly high (for example: incidence ratio 32 to 100 live births for all Latin America and the Caribbean, compares with 39 for South America). This means that for every ten live births in South America it is estimated that there are four unsafe abortions.

The unsafe abortions mortality ratio of 30 to 100,000 live births for Latin America and the Caribbean - approximately 3,700 deaths - corresponds to about one in six maternal deaths in the region. Because of low fertility, the relative risk of death is highest in South America. An analysis of data on unsafe abortion by age in LA and the Caribbean, women aged 20-29 years account for more than half of all unsafe abortions, with almost 70% of unsafe abortions being carried out on women below 30.
### Table of Unsafe Abortion (*)

<table>
<thead>
<tr>
<th></th>
<th>World</th>
<th>Developed Countries</th>
<th>Developing countries</th>
<th>Latin America and the Caribbean</th>
<th>South America</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsafe abortions to 100 live births</td>
<td>14</td>
<td>4</td>
<td>15</td>
<td>32</td>
<td>39</td>
</tr>
<tr>
<td>Unsafe abortions per 1,000 women aged 15-44</td>
<td>14</td>
<td>2</td>
<td>16</td>
<td>29</td>
<td>34</td>
</tr>
<tr>
<td>% of all maternal deaths</td>
<td>13</td>
<td>14</td>
<td>13</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Unsafe abortion deaths to 100,000 live births</td>
<td>50</td>
<td>3</td>
<td>60</td>
<td>30</td>
<td>40</td>
</tr>
</tbody>
</table>


### 2- Background

In the United States, oral contraceptives (OCs) are the most commonly used method of reversible contraception but only 22% of reproductive-aged women use OCs and discontinuation rates are report to be between 32% to 50% in the first year of use. Although adverse events are a prominent cause for OCs discontinuation, the need for a daily pill ingestion is an important factor in the high rate of OC discontinuation and misuse.

Long acting progestational options such as depo-medroxyprogesterone acetate (DMPA) under consideration for deletion for this Committee, offer as a positive feature its high contraceptive efficacy rate and convenience for compliance, taking into account its administration once each three months. Their main disadvantages are frequent and unpredictable irregularities in the bleeding patterns, including episodes of amenorrhea, decrease in bone density and some detrimental effects on metabolism.

There is a need of a method that could combine the convenience of long term contraception with the best possible benefit/risk ratio. Factors that could improve a contraceptive method’s acceptability include high efficacy, minimal side effects, convenience, reversibility, non-contraceptive benefits and accessibility.

We already have in the EML two injectable contraceptives: norethisterone enanthate 200mg (NET-EN) in the main List and depo-medroxyprogesterone acetate 150 mg (DMPA) in the complementary List. Their long duration of action becomes a disadvantage for women who experience side effects, since its action can not be reversed rapidly. Furthermore, nine to ten months after the last injection are needed to return to fertility, which is a longer time than other contraceptives methods. NET-EN share above disadvantages with a duration of action of 60 days.

Several parenteral contraceptives, containing estrogen and progestogen were introduced 40 years ago but, only two of them remain currently in use in several countries of Latin America, Asia and Africa. The World Health Organization (WHO) supported the development of these two combination injectables already introduced.
in the pharmaceutical markets of developing countries\(^2\): Medroxyprogesterone acetate 25 mg plus estradiol cypionate 5 mg (MPA/E\(_2\)C) and Norethisterone enanthate 50 mg plus estradiol valerate 5 mg (NET-EN/E\(_2\)V).

Both progestin components of these preparations have been used for many years as progestin-only-contraceptives. Estradiol cypionate and estradiol valerate are two semisynthetic estrogens obtained as esters of the natural hormone estradiol. Addition of valerate and cypionate are responsible for the long action of these compounds that allow once-a-month administration.

Our goal is to review effectiveness and safety of two once-a-month injectable preparations that combine one progestagen with an estrogen.

### 3- Aims of the search

To assess the effectiveness and safety of medroxyprogesterone acetate 25 mg + estradiol cypionate 5 mg (MPA/E\(_2\)C) and Norethisterone enanthate 50 mg plus estradiol valerate 5 mg (NET-EN/E\(_2\)V) as once-a-month injectable contraceptives in order to decide on its inclusion to the WHO Essential List Medicines.

### 4- Methods

We identified randomized clinical trials, trials, reviews and a protocol of a systematic review\(^{(10)}\) from searches of the Cochrane Library, Medline (to December 2004) and reference list from identified articles.

### 5- Pharmacological Basis

#### 5.1. Mechanism of action and pharmacokinetics

The knowledge of the pharmacokinetics of these two compounds after each injection and also, after several cycles of administration is an important point, using hormonal depot i.m. injections. We should know maximum levels reached and the time course of the Dose/time curve. There are enough evidence about the increased risk of severe complications (cardiovascular, breast and gynecological cancer) with the use of other contraceptives and similar hormones in postmenopausal women. These data raise some concern about the dosage and long time of use of combined injectable contraceptives (CICs).

#### 5.1.1. Pharmacokinetics

What happens when we administer by i.m. combined injectable contraceptives (CICs), namely MPA.25mg/E\(_2\)C 5mg or NET-EN 50 mg/E\(_2\)V 5 mg?

- Aedo et all\(^{(11)}\) showed that, after MPA/E\(_2\)C injections, MPA levels increase slowly being to Cmax of 2,9 nmol/l, decreasing to 0,72 nmol/l 30 days after the last injection, and become undetectable 60 days after the final administration. It is also shown an accumulation of DMPA for up to 6 months declining then to baseline levels\(^{(12)}\)

- Women treated with NET-EN/E\(_2\)V showed a similar curve of absorption but shifted to the left than with MPA. C\(_{max}\) levels of norethisterone (10.1 nmol/l) are reached slightly earlier than with MPA. decreasing (to 1.7 nmol/l) 30 days after the last injection\(^{(11)}\)

- There is no accumulation of NET-EN over 6-12 months of treatment with NET-EN 50mg and estradiol valerate 5mg\(^{(13)}\)
Maximum levels of exogenous estradiol reached after MPA/E$_2$C or NET-EN/E$_2$V injection (890 pmol/l and 1570 pmol/l respectively) were obtained 3-4 days after injection. Such high levels were maintained for 7-11 days$^{(13)}$. After that time, there is a rapid fall to baseline levels. Similar peak estrogen levels occurs, physiologically, during 36 hours in the preovulatory surge of estradiol.

What happens when a progestin-only compound, depot medroxyprogesterone 150 mg or norethisterone enanthate (NET-EN 200 mg are administered by i.m. injection?

- MPA is absorbed slowly from a i.m. administration, reaching its maximum serum levels within the first three weeks (5-22 days) post-injection (15-26 nmol/l), decreasing (to less than 1.0 nmol/l) in the majority of women by 90-190 days post injection. This pattern allows its dosage schedule each three months$^{(14)}$.
- NET-EN levels increase rapidly, reaching peaks in most subjects within seven days. The half-life of absorption varied from 5.4 to 22.3 days and the half-life of elimination varied from 7.5 to 22.5 days, with significant correlation between these half-lives ($R=0.78$). In all subjects NET-EN was detectable in the circulation for a longer time after injection (mean values 43 days)$^{(15)}$.
- DMPA pharmacokinetics showed ethnic variability. Mexican women presented one order of magnitude lower serum DMPA levels than Thais women. Dosage should not be extrapolated from studies conducted in different populations$^{(14)}$.

5.1.2. Mechanism of Action

- MPA/E$_2$C and NET-EN/E$_2$V prevent pregnancy primarily by inhibiting ovulation and decreasing FSH and LH levels$^{(11)}$. Besides, they cause thickening of cervical mucus, blocking sperm entry to the uterine cavity.
- Addition of estrogen to a progestin-only preparation, improves bleeding patterns for users. An important issue was to find the best estrogen/progestin ratio, taking into account that it will affect ovulation inhibition$^{(14)}$.
- The biphasic nature of both estrogen and progestin profile during the cycle, with the second part of the injection cycle dominated by the progestogen, facilitates a regular bleeding pattern.
- Norethindrone enanthate (NET-EN) injectable act primarily by inhibiting ovulation, lowering the levels of follicle-stimulating hormone and luteinizing hormone.
- Both monthly injectables inhibit follicle maturation for some 30 days and ovulation and corpus luteum formation for some 60 days, giving a considerable margin of safety in terms of the expected duration of contraceptive protection$^{(11)}$.

Aedo´s and col. data from the Karolinska Institute and Hospital, Stockholm, Sweden are constantly referred in the literature. They treated 8 women with MPA/E$_2$C and other 7 volunteers with NET-EN. It is important to highlight that estrogens and progestogen are metabolized by liver enzymes. Their serum levels can change easily in response to several enzyme inhibitors and /or inducers. This is the basis of the wide variability shown in the pharmacokinetics patterns in different trials.
The main conclusions of the pharmacological data are:

1- There is a biphasic profile of both estrogen and progestin serum levels after the i.m. administration of combined injectable contraceptives (CICs).
2- Peak levels of estrogen are similar to physiologic ones but it last 7-11 days, instead of 36 hs as physiologically
3- The rapid decline after the peak explains the middle cycle bleeding which appears.
4- The dominance of progestin compound in the 2nd part of the cycle explains the presence of progestogen-like adverse effects.
5- Serum levels of estrogen and progestogen are the basis of its monthly administration and of its time to return to fertility after discontinuation of the treatment.

6. Effectiveness

6.1. Contraceptive efficacy

- Several clinical studies were carried out in developing countries to evaluate cycle control, side effects and contraceptive efficacy of combined injectable contraceptives MPA/E₂C and NET-EN/E₂V, demonstrating variability in the results with both contraceptives. The overall pregnancy rate at one year was between 0.0 to 0.5 per 100 women-years.\(^{(16-21)}\)

- The contraceptive efficacy of these compounds is similar to that of progestin-only contraceptives and to low-dose triphasic oral contraceptives\(^{(18)}\)

There is no doubt about the high contraceptive efficacy of CICs (> 99%) similar to that of DMPA and NET-EN

6.2. Discontinuation rate

- Major reasons for discontinuation of injectable contraceptives use are menstrual irregularities and adverse effects. Using MPA/E₂C approximately 35% of women discontinue because of menstrual problems at three months and 70% at 9 months. An equal number of users discontinue because personal reasons (inconvenience of having to return to the clinic for the injection on a monthly basis)

- Discontinuation of DMPA use are due to menstrual bleeding irregularity, weight gain, amenorrhea and small contraceptive failure (0.9 per 100 women-year)\(^{(25)}\). Low levels of compliance to OCs are due to the inconvenience of keeping the daily treatment, adverse effects and the concern about adverse health risks associated with use of these drugs\(^{(22)}\).
Discontinuation rate for bleeding problems was less than 5% and for amenorrhea oscillated between 0.55% to 1.11%. Chinese women appeared to tolerate slightly better NET-EN/E2V with regard to cycle control\(^{(16)}\).

In Chinese women, discontinuation rates at one year, were between 13.9% to 17.9% for NET-EN/E2V and 18.0% to 19.1% for MPA/E2C\(^{(33)}\).

Data on discontinuation rates of CICs and progestin-only contraceptives’ users show great variability.

6.3 Return to ovulation and fertility

- Data on return to fertility after withdrawing MPA/E2C and NET-EN/E2V use presents a wide variability, possible due to individual differences in the metabolism of the different contraceptives.
- In the majority of studies, 70% of women who received MPA/E2C or NET-EN/E2V for three months, ovulated in the second month post-treatment\(^{(23-24)}\). Similar results were obtained after 2 years of treatment with both preparations\(^{(25)}\). The percentage of CICs users who return to fertility at one year is high (80 – 90%)\(^{(26)}\).
- It is important to highlight that after using NET-EN/E2V for 2-3 years\(^{(13)}\) there is no long term inhibition of the pituitary-ovarian axis.
- The return of ovulation following discontinuation of injectable DMPA is variable but it generally occurs later than using CICs\(^{(27)}\).

Data on return on fertility of Injectable contraceptives’ users show great variability.

In general terms, CICs return to fertility faster than progestin-only compounds.

7- Safety

There are numerous studies assessing minor adverse effects and aspects related to improve compliance and acceptability of CIC’s users. Long term safety information and data on hard clinical endpoints like stroke, myocardial infarction, cancer risks are not yet available.
7.1 Adverse effects
MPA/E2C and NETE-EN/E2V have been extensively used in developing countries, and several large trials have gathered information about their principal adverse effects: changes in the bleeding pattern, headache, nausea, dizziness, weight gain, minimal changes in glucose metabolism\(^{(16, 22)}\). They conclude that the side effects of DMPA, mainly amenorrhea and vaginal bleeding irregularities it induces, makes it less acceptable than DMPA – E\(_2\)C\(^{(21-22)}\).

For DMPA’s users, side effects were given as the most common reasons for stopping with menstrual disturbance and weight gain being cited most often\(^{(28)}\).

7.2. Vaginal bleeding patterns

- The main side effect that women experience using injectable contraceptives is an alteration of their regular menstrual pattern. This profile is seen more frequently with progestin-only contraceptives, specially with DMPA. It induces unpredictable pattern with episodes of prolonged and heavy bleeding, specially during the first months of use. These episodes are followed for long periods of amenorrhea, more frequent with continued use.

- On the other hand, MPA/E\(_2\)C offers more predictability in bleeding patterns compared to progestin-only users\(^{(29)}\). Frequent or prolonged menstrual bleeding were most likely to occur during the initial three cycles with the preparations under consideration. After 6 months of use, 70% - 80% of the CIC’s users reported acceptable bleeding patterns meanwhile only 50% of DMPA users does\(^{(30-33)}\).

- Approximately 50% of women using DMPA for 1 year report amenorrhea, more frequent which DMPA than with NET-EN. Menstrual changes are the most frequent causes of discontinuation of injectables.

- Fewer than 3% of women using MPA/E2C are amenorrheic at the end of the first year compared with 50% in DMPA users\(^{(23)}\). NET-EN users are in between.

- Combined Injectable contraceptives give a vaginal bleeding pattern more regular than progestin-only contraceptives
- DMPA users present more amenorrhea than NET-EN users

7.3 Effects on coagulation and fibrinolysis

- Several randomized controlled multicenter studies, mainly in developing countries, were undertaken to monitor the effects on hemostasis of these two once-a-month injectable contraceptive preparations: NET-EN/E\(_2\)V and MPA/E\(_2\)C in comparison with a well-known oral contraceptive (OC) norethisterone 1 mg and ethinyl-estradiol 35 \(\mu\)g.

- In most of the studies it was demonstrated a significant increase in activated partial thromboplastin time among NET-EN/E\(_2\)V users, no change among MPA/E2C users and a significant decrease among OC users.
• OC use led to increases in plasma levels of fibrinogen, factor VII, factor X, plasminogen, protein C and decreases in plasma levels of t-PAI and antithrombin III profile with a trend to thromboembolic diseases.
• Use of combined injectables induced no change (MPA/E₂C) or decreases (NET-EN/E₂V) in plasma levels of fibrinogen, factor VII, factor X and antithrombin III and protein C
• Overall, the combined injectable preparations may be more beneficial than the oral preparations in not enhancing a hypercoagulable state because of the reduced synthesis of fibrinogen, factors VII and X (-14%); however, decreases in antithrombin III (-20%) and protein C, which are potent coagulation inhibitors, may raise some concern. Whether these changes can lead to modifications in the risk of arterial or venous disease can only be ascertained by conducting epidemiological studies.

7.4 Metabolic effects
7.4.1. Lipid profile
• DMPA 25mg/E₂C 5mg and NET-EN 50mg/E₂V 5mg. Both preparations produce a decrease in HDL-C (10%), apolipoprotein-A1 (9%) and triglycerides (15%) at 3 months of use, keeping its low values at one year. With DMPA/E₂C changes were smaller.
• The effects of DMPA/E₂C and NET-EN (NET-EN) (200 mg) on lipid profile, give a similar decrease, statistically significant, of total cholesterol, high density, low density and very low density lipoprotein cholesterol and triglyceride levels at 12 months
• Comparing DMPA/E₂C vs combined triphasic oral, in spite of the fact that MPA/ E₂C users had a decrease in total cholesterol, total triglycerides, LDL-C, HDL – C and apo A-I y apo A-2, there is a maintenance of the total C/ HDL-C ratio. Further investigations are needed designing protocols with dietary restrictions (alcoholic beverages were included in several earlier trials).
CICs and Bone Mineral density

• There are few studies assessing the effects of combined injectable contraceptives on bone mineral density (BMD). This is a sensitive issue taking into account that there is data showing an association between DMPA use and significant decrease in BMD\(^{39-42}\).

7.5. CICs and Breast and Gynecological Cancer Risk

7.5.1. There is considerable information on the relation between combined oral contraceptives and the risk of neoplasia. However, close analogies with combined injectables contraceptives cannot be drawn. There are several trials assessing the association between DMPA and breast cancer, showing an increase of risk in special subgroups of women. Most of the trials are of small size. There is an urgent need of epidemiological studies to get a conclusion\(^{43-48}\).

7.5.2. A few reflections on these issues

What doses of estrogens are receiving long time users of contraceptives?

THERAPEUTIC EQUIVALENCE

CEE * 0.625 mg/d = ethynil estradiol 5-10 µg/d ** = estradiol valerate 5mg/month = estradiol cypionate 5 mg/month ***

* CEE Conjugated equine estrogen(HRT); ** (mostly used as OCs in dosage between 35 to 50 µg /d) ; *** proposed for CICs to this Committe\(^{49-50}\)
Women exposed to contraceptives during a long period of their lives, receive higher dosage of estrogen than those of HRT.

Epidemiological studies are needed to define the association between combined injectable contraceptives and breast and gynecological cancer.

7.6. Analysis of Comparative Effectiveness. (taken from the application for inclusion of CICs in the WHO EML). Table 1

Comparative effectiveness between Combined Injectable Contraceptives with its correspondent progestin-only component (10 trials)\(^{(51)}\)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>MPA/E(_2) C* vs. DMPA*</th>
<th>NET-EN / E(_2) V* vs NET-EN*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>After 1st follow-up RR (95% C.I.)</td>
<td>After one year follow-up RR (95% C.I.)</td>
</tr>
<tr>
<td>More regular bleeding pattern</td>
<td>3.2 (2.4 – 4.2)</td>
<td>2.8 (2.2 – 3.6)</td>
</tr>
<tr>
<td>Less amenorrhea</td>
<td>0.3 (0.12 – 0.65)</td>
<td>0.08 (0.04 – 0.15)</td>
</tr>
</tbody>
</table>

Comparison between NET-EN vs. NET-EN/E\(_2\)C

<table>
<thead>
<tr>
<th>Discontinuation for other than amenorrhea</th>
<th>For other medical reasons</th>
<th>2.2 (1.2 – 4.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>For personal reasons</td>
<td>1.8 (1.2 – 2.7)</td>
<td></td>
</tr>
</tbody>
</table>
Comparison between DMPA/E$_2$C vs DMPA

| More women intending continuing after study ends | 2.65 (1.78 – 3.94) |

Comparison between MPA/E$_2$C and NET-EN/E$_2$V

<table>
<thead>
<tr>
<th>Discontinuation rate (3 trials)</th>
<th>Variability</th>
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<tbody>
<tr>
<td>Amenorrhea (3 trials)</td>
<td>Similar number in both groups</td>
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<tr>
<td></td>
<td>0.7 (0.2 – 2.3) after 1$^{st}$ follow-up</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>DMPA-only</th>
<th>NET-EN only</th>
<th>CICs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy rate 1 year use</td>
<td>0 – 0.1%</td>
<td>0.4%</td>
<td>0.0 – 0.12 %</td>
</tr>
<tr>
<td>Return to fertility</td>
<td>5.5 months</td>
<td></td>
<td>5.5 month (MPA/E$_2$C)</td>
</tr>
</tbody>
</table>

* DMPA= 25 mg; E$_2$C 5mg; NET-EN = 50 mg; E$_2$V= 5 mg; DMPA 150 mg; NET-EN 200mg

Commentary on the results of Table 1:

- It was shown that both CICs under consideration produce more regular bleeding pattern and less amenorrhea than their progestin-only counterparts.
- NET-EN/E2V demonstrated a lower discontinuation rate than NET-EN.
- There are not shown results about DMPA/E2C.
- More DMPA/E2C users, intended continuing after study ends.
- When comparing MPA/E2C with NET-EN/E2V, the discontinuation rate showed variability (no differences in amenorrhea was observed)
- In regard to the pregnancy rate at one year, no differences were shown between CICs and both progestin-only preparations.
- 5.5 months is the time to return to fertility shown for CICs and DMPA
- It should be enphasized that there are no assessments of hard clinical outcomes such as risk of stroke, MIA, thrombembolic diseases, breast and gynecological cancer, bone mineral density, etc. In association with the use of the contraceptives under discussion.
- In conclusion: there is information about efficacy of both preparations, but evidence on safety is lacking.
7.7 Summary of available evidence of comparative effectiveness and safety

1. There are numerous studies assessing contraceptive efficacy, return to fertility, changes in bleeding pattern, aspects of compliance, acceptability, reasons for discontinuation and minor adverse effects.

2. The efficacy of CICs is very high and similar to progestin-only and oral combined contraceptives.

3. Since the point of view of the convenience, CICs being once-a-month injectables assure compliance more than OCs pills.

4. With regard to bleeding pattern alterations and subsequent amenorrhea, as an important cause of discontinuation, CICs have a better profile.

5. There are no long-term follow–up assessment of MPA/E_2C and NET-EN/E_2V users or information regarding non-contraceptive benefits of CICs.

6. There are no long term follow–up evaluation of cardiovascular risk and breast and gynecological cancer risk in CICs users.

7. There is no reason to show data of costs of treatment with CICs under consideration because their benefit/risk ratio is not thoroughly known yet
RECOMMENDATION

Combined Injectable Contraceptives applied for inclusion in the EML:

- Represent two preparations for contraception with demonstrated efficacy as contraceptive
- Permit to return to fertility earlier than progestagen-only contraceptive
- Present a profile of mild adverse effects
- Fail to have long time trials assuring its safety for important clinical endpoints.

They are convenient because its easy way to be used (once each month), but this is counteracted by the need of a monthly assistance to a health center for the injection.

In our opinion we should wait for randomized controlled trials of long term use of these preparations, assessing the association between CICs use and cardiovascular diseases (stroke, MIA, thromboembolism), changes in BMD and breast and gynecological cancer before considering its inclusion.


18. Kaunitz AM, Garceau RJ, Cromie MA. Comparative safety, efficacy, and cycle control of Lunelle monthly contraceptive injection (medroxyprogesterone acetate and estradiol cypionate injectable suspension) and Ortho-Novum 7/7/7 oral contraceptive (norethindrone/ethinyl estradiol triphasic). Lunelle Study Group. *Contraception*. 1999; 60 (4): 179-87


37. Canto de Cetina T, Ordoñez Luna M, Cetina Canto JA and Bassol S. Menstrual pattern and lipid profiles during use of medroxyprogesterone acetate and estradiol cypionate and NET – EN (200 mg) as contraceptive injections. *Contraception 2004; 69: 115-119*


41. Clark MK, Sowers MR, Nichols S et al.; Bone mineral density changes over two years in first time users of depot medroxyprogesterone acetate *Fertility and Sterility 2004; 82: 1580-1586*


51. Results of a Cochrane systematic review (in press) taken from the application for inclusion of MPA/E\textsubscript{2}C and NET-EN/ E\textsubscript{2} C. 2005