



**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**GUIDELINE ON CLINICAL INVESTIGATION OF STEROID CONTRACEPTIVES
IN WOMEN**

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This guideline replaces the NfG on Clinical Investigation of Steroid Contraceptives in Women CPMP/EWP/519/98

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1. GENERAL

The EU-guideline on the clinical investigation of oral contraceptives was last issued in 2000. The CHMP has felt a need to update this guideline in the light of scientific advance and the issuing of other guidelines on specific related topics.

This guideline concerns contraceptives, intended for use by women containing substances with sex steroid action as active substance(s). It is not only applicable for short-acting oral contraceptives containing a gestagen or a combination of gestagen and estrogen, but also for long-acting steroid contraceptives (e.g. implants, injectables, transdermal systems, intravaginal and medicated hormone releasing intrauterine devices (IUDs)). Emergency contraceptives are not addressed here.

Contraceptives are generally used by healthy individuals for prophylactic/preventive purposes. They therefore need to have a very low risk in order to have a favourable risk/benefit balance. They need to have a well-defined contraceptive efficacy and a well-founded description of risks and adverse events to enable the woman and the prescriber to make the best individual choice of contraceptive method.

This document should be read in conjunction with the Directive 2001/83/EEC, as amended, and all other relevant guidelines outlined in current and future EU and ICH guidelines especially those on:

- Fixed Combination Medicinal Products
- The Investigation of Drug Interactions
- Good Clinical Practice: Consolidated Guideline (ICH topic E6)
- Dose response information to support drug registration (ICH topic E4)
- Clinical Safety Data Management (ICH topic E2A and E2B)
- Statistical Principles for Clinical Trials (ICH topic E9)

This Note for Guidance is intended to assist applicants during the development of hormonal contraceptive products. It is only guidance; any deviation from guidelines should be explained and discussed in the Clinical Overview.

2. CLINICAL-PHARMACOLOGICAL STUDIES

2.1 Hormonal activity

The nature and hormonal activity of the steroid(s) and its (their) principal metabolites should be described. Such information may come from receptor binding studies, studies of individual metabolites in animals (and/or man) and studies of indicators of hormonal activity, such as SHBG (sex hormone binding globulin).

Receptor binding studies may give indications on actions other than the estrogenic and gestagenic actions aimed at. Indicators, such as SHBG, may give information on the balance between estrogenic and gestagenic/androgenic effects in women.

2.2 Pharmacological action

The pharmacological action or actions, by which the contraceptive effect is attained, should be known. For sex steroids, such actions include the effect on ovarian function, endometrial mucosa and cervical secretion.

2.2.1 Ovarian function

The effects on ovarian function in women with normal ovulatory function should be described. Methods to be used include plasma concentrations of ovarian steroids and gonadotrophins and ultrasound of ovaries. At least two cycles should be studied in each woman.

These studies will give information on the extent to which ovarian function is suppressed by the steroids used. Ultrasound investigation will supplement the interpretation of plasma steroid determinations. It is important that sampling is so frequent that possible LH (luteinising hormone) peaks or ovulations are not missed and the duration of the luteal phase or estrogen peaks can be registered.

For an entirely new contraceptive steroid or combination of steroids, comparative studies using a method with similar mechanism of action and dosage form should be made.

Comparative pharmacodynamic data should also be provided in case of a dose reduction of an available product.

Comparative pharmacodynamic data may be useful for the selection of comparator, and in the dimensioning of clinical studies (see Efficacy section).

For long-acting contraceptives (e.g. implants) this kind of data should be provided at intervals for the entire period of intended use.

The time to onset of action, in relation to start of treatment and dose of steroids and the time to return of normal ovarian function after discontinuation of treatment should be studied in a sufficient number of patients. This information is especially necessary for certain long-acting methods such as injectables but also for advice on the need for complementary protection at the initiation of treatment and in case of temporary lack of compliance.

The time to return of fertility should be followed for up to a year in all patients discontinuing treatment for wish of pregnancy.

2.2.2 Other pharmacological effects on the reproductive system

Other pharmacological effects on the reproductive system and process, including endometrial effects and effects on cervical mucus should be described, especially when ovulation inhibition is not regularly attained. The study of such effects has explanatory value, but rarely can give information that motivates a reduction in the size of clinical trials.

2.2.3 Effects on other endocrine systems

The effects on other endocrine systems (hypothalamic-pituitary, adrenal, thyroid) in woman should be described.

This may not be necessary in case of minor modification of dose and/or dosing regimen of a well-known steroid or steroid combination, provided the effects are well documented.

2.2.4 Metabolic effects

The effects on haemostatic variables, plasma lipids and carbohydrate metabolism should be studied with modern, state of the art methods (see also Safety section). Studies should include relevant comparator(s).

For products not containing an estrogen and suppressing estrogen secretion from the ovaries, the effect on bone mineral density and/or bone metabolism should be studied with validated methods.

2.2.5 Dose finding, pharmacokinetics and interactions

For guidance on dose finding, pharmacokinetics and interactions reference is made to other relevant guidelines.

3. EFFICACY

3.1 Study size requirements and pregnancy reporting

For a new contraceptive method (e.g. new steroid/s, lowered steroid dose, new administration form), non-comparative studies are accepted but a sufficient number of cycles should be studied to obtain the desired precision of the estimate of contraceptive efficacy.

The key studies, carried out in a sufficiently representative population, should normally be at least large enough to give the overall Pearl Index (number of pregnancies per 100 woman years) with a two-sided 95% confidence interval such that the difference between the upper limit of the confidence interval and the point estimate does not exceed 1 (pregnancies per 100 woman years).

Data for the calculation of the overall Pearl Index may emanate from more than one large study.

Pregnancy rates should be described by Pearl Index and life table analysis including all pregnancies during treatment. Pregnancies following premature discontinuation of study medication should also be included in the calculations, unless the date of conception determined by a valid method (e.g.

ultrasound, beta-HCG) is without doubt after the premature discontinuation. Pregnancies within three months following premature discontinuation of study medication should also be reported.

The separate calculation of the Pearl Index for method failure requires reliable methods for recording of compliance (e.g. electronic patient diaries) not to include non-compliers in the denominator.

For Pearl index calculations, 13/28-day cycles constitute one woman year. With non-cyclic methods one woman year equals one calendar year.

3.2 Reduced requirements in special circumstances

In case of minor modifications of existing products, a lower number of cycles may be required provided that:

- pharmacodynamic studies show at least an equivalent effect on ovarian function compared with the existing product
- the reference method has a well documented efficacy.

For minimum requirements see section 3.3 below.

3.3 Duration of studies

The duration of efficacy studies should be six months to one year or more. For any new contraceptive, at least 400 women should have completed one year of treatment.

For long-acting products (e.g. implants, medicated IUDs) the study duration should cover the claimed duration of effectiveness. For long-acting products, intended to be used for more than three years, the number of women completing the claimed duration of use should be at least 200.

3.4 Demography of women included in studies

The demography of the group of women included in studies should be carefully described, especially regarding factors thought to be relevant for the overall contraceptive efficacy of the method (e.g. weight, height, BMI, age, education, sexual relation/activity, parity, smoking, alcohol use, menstrual related symptoms, concomitant use of condoms to protect from sexually transmissible disease etc.). Where heterogeneity of fertility is likely (e.g. a study group containing a subgroup of breast feeding mothers or older women), separate estimates or specific studies of the Pearl Index should be presented for important subgroups.

3.5 Need for comparative efficacy studies

Studies including an active comparator are not generally requested for efficacy purposes. For a new product utilising a mechanism of action which may result in a relatively high pregnancy rate ($PI > 1$), comparative studies may be necessary. Pharmacodynamic data may serve as advisory information on the necessity for comparative studies. Generally this is a requirement for methods not consistently inhibiting ovulation.

4. SAFETY

4.1 Amount of safety information

For any new steroid contraceptive the minimum amount of safety information should come from studies including at least 400 women completing one year of treatment (see section 3.3).

4.2 Rare events

Clinical trials generally include too few women to provide information on rare risks, e.g. cancer, cardiovascular events, venous thromboembolism (VTE). Comparative pharmacodynamic data may indicate possible differences between products but there are no generally accepted surrogate end-points for the risk of cancer, cardiovascular events or VTE. Different products have, in observational studies, been associated with different VTE risks. Biological variables that may reflect different pharmacological effects, possibly related to VTE risk, should be investigated in the development of a new combined (oestrogen-progestogen) contraceptive product. Variables suggesting such different pharmacological effects may include prothrombin fragment 1+2, APC resistance (ETP-based, APTT-based), d-dimer, factor VII, factor VIII, factor II, antithrombin, protein S, protein C and SHBG. As

comparator, a product containing levonorgestrel + ethinylestradiol (150/30µg) or desogestrel + ethinylestradiol (150/30µg), where VTE risk has been established in observational studies, is appropriate. Such biomarker comparative studies should have a crossover design. The duration of study periods and timing of biomarker sampling should be selected so that carry-over effects are excluded. Moreover, a careful documentation of serious adverse events, e.g. cardiovascular events or VTE should be provided and related to the presence of established predisposing risk factors among the women included in the studies.

4.3 Other adverse events, need for comparative studies

Information on other adverse events, including vaginal bleeding events, should to a considerable extent come from studies including an active comparator. In addition to cycle control analyses with respect to bleeding and spotting, analyses of bleeding control during a reference period are advised, e.g. for periods of 90 days and in accordance with WHO recommendations.

The comparator should, whenever possible, be chosen among market leading products with a similar mechanism of action and schedule of use. When the dose of steroid in an existing product is reduced, comparison should also be made with the higher dosed product.

Comparative safety data provide important information for the user and the prescriber in the choice between different methods. A higher Pearl Index may under certain circumstances be acceptable if, e.g. tolerability is very high. Known differences in the spectrum of adverse reactions may also be useful if the first choice is not tolerated.

4.4 Follow up of pregnancies

All pregnancies occurring during a trial should be followed up for final outcome (mother and child). This will provide complementary information to preclinical studies in animals.