



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

**GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR
HORMONE REPLACEMENT THERAPY OF OESTROGEN DEFICIENCY SYMPTOMS IN
POSTMENOPAUSAL WOMEN**

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This guideline replaces Points to Consider on Clinical Investigation of Medicinal Products for the Treatment of Hormone Replacement Therapy (CPMP/EWP/021/97).

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TABLE OF CONTENTS

EXECUTIVE SUMMARY	3
1. INTRODUCTION (BACKGROUND)	3
2. SCOPE.....	3
3. MAIN GUIDELINE TEXT	4
REFERENCES (SCIENTIFIC AND / OR LEGAL)	9

EXECUTIVE SUMMARY

Guidelines have been developed to provide advice on selected areas relevant to the development of medicinal products in specific therapeutic fields. This document related to Hormone Replacement Therapy (HRT) will be revised in accordance with the scientific advances made in this area. The current version is a revision of the Points to consider document on hormone replacement therapy in postmenopausal women (adopted by CHMP in November 1997)

1. INTRODUCTION (background)

Hormone Replacement Therapy (HRT) in postmenopausal women is generally defined as treatment with oestrogen or a combination of oestrogen plus progestogen.

The addition of a progestogen to the oestrogen regimen is aimed at preventing the increase in endometrial cancer risk associated with oestrogen therapy in women with uterus.

Two indications are currently proposed for most products:

- hormone replacement therapy for oestrogen deficiency symptoms in postmenopausal women,

prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.

This document only focuses on the first indication.

In women with severe oestrogen deficiency symptoms, HRT of any type is effective for symptom relief.

However, there is evidence for an increased risk of breast and endometrial cancer that increases with increasing duration of HRT with all types of oestrogens; this risk may be enhanced for breast cancer and is reduced for endometrial cancer when a progestogen of any type is added.

Additionally, HRT is associated with an increased risk of venous thromboembolism and stroke. Recent placebo-controlled data contradicted previously published epidemiological studies suggesting benefits of HRT on coronary heart disease. An increased risk of acute myocardial infarction in women taking combined HRT was shown, at least during the first year of use.

In view of this risk profile, for the initiation and the continuation of treatment, the minimum effective dose for the shortest duration should be used. And in all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk (core SmPC for HRT).

2. SCOPE

The aim of this position paper is to provide recommendations on specific issues for the development of a medicinal product containing as active substance:

- an oestrogen alone;
- an oestrogen in combination with a progestogen;
- a progestogen to be given with an oestrogen;

in the treatment of oestrogen deficiency symptoms in post-menopausal woman.

For the time being, there is very limited experience with other hormonal treatments for oestrogen deficiency symptoms in postmenopausal women. Therefore, the development of such kind of products will be out of scope of this document.

The population of perimenopausal women is also out of scope of this document. The perimenopausal period is not well defined for regulatory purposes; this transitional period is marked by irregularity of menstrual cycles and of variable “climacteric” symptoms, for a variable duration of time. In addition, oestrogen therapy is not usually recommended during perimenopause as cyclic endogenous oestrogen production has not yet ceased. Moreover, practices to treat perimenopausal symptoms vary from one country to another and from one physician to another. Therefore, specific guidance on hormone replacement therapy for the population of perimenopausal women can not be given for the time being.

3. MAIN GUIDELINE TEXT

A) GENERAL ISSUES

The validated standards across EU are largely different from country to country including progestogens added to oestrogen replacement therapy, mode of treatment (continuous or sequential), dose of oestrogen, route of administration (oral, transdermal). Companies are therefore advised to check the validity of their references (see chapter B, Pharmacokinetic studies) before conducting their kinetic and/or clinical development.

B) PHARMACOKINETIC STUDIES

For all applications, pharmacokinetic data are required as discussed in the CHMP note for guidance 'Pharmacokinetic studies in man'.

For abridged applications where bioequivalence with a reference product is claimed, pharmacokinetic data should be provided as follows:

- for oral medicinal products, the note for guidance on the 'Investigation of bioavailability and bioequivalence' (CPMP/EWP/QWP/1401/98) will apply.
- for transdermal pharmaceutical forms, bioequivalence should be determined at steady state. Each type of transdermal pharmaceutical form is recommended to be compared with a similar, approved system (e.g., matrix vs matrix).

The following criteria should be fulfilled on the basis of two-sided 90% confidence intervals (CI) for the ratio of means (test/reference).

AUC, C_{max} : CI lies entirely within the range 80-125%

These criteria would ensure that the concentration-time profile of the test falls within the concentration range of the reference.

Bioequivalence data are not needed for all strengths provided that the applicant demonstrates dose-proportionality for the test within the applied dose-range.

The daily dose stated for a transdermal system should be based on pharmacokinetic bioequivalence data. Hence, correction for 'amount released from patch' is not accepted.

C) CLINICAL STUDIES

1. Efficacy

Treatment of symptoms related to oestrogen deficiency

The term “climacteric symptoms” is frequently used for symptoms occurring in women before the actual menopause. However, this term may be inaccurate, since not all those symptoms are in fact caused by low oestrogen. Therefore, the most suitable expression is “oestrogen deficiency symptoms”. The most important oestrogen deficiency symptoms are vasomotor symptoms (hot flushes). The severity of hot flushes is defined clinically as follows:

- mild: sensation of heat without sweating
- moderate: sensation of heat with sweating, able to continue activity
- severe: sensation of heat with sweating, causing cessation of activity

Only moderate to severe and severe hot flushes are to be treated by HRT. The proposed primary endpoint for efficacy trials is the frequency of moderate to severe hot flushes. Enrolled subjects should have a defined minimum of hot flushes per day at baseline to justify a need for treatment (at least 5 moderate to severe hot flushes).

The Kupperman index could be accepted as a secondary endpoint to assess efficacy. Other scales, if fully validated, can also be used.

Placebo-controlled studies are considered sufficient to demonstrate efficacy of an oestrogenic product.

A duration of treatment of 3 months is generally recommended for symptom efficacy evaluation.

2. Safety

2.1. Endometrial safety

For a new combination of oestrogen/progestogen (e.g. new administration scheme or new strength) or a new progestogen in a fixed combination, endometrial data are required.

For a new medicinal product containing as active substance an oestrogen which would show an increase in bioavailability compared to a reference product (on the basis of pharmacokinetic data), endometrial safety data are required.

For a new medicinal product containing as active substance a progestogen, alone (aimed to be combined with an oestrogen in order to prevent endometrial hyperplasia) or in combination with an oestrogen, the need of endometrial data depends on the oestrogen exposure. Endometrial data are required in most situations except for a known progestogen, with the same administration route and the same progestogen dose as in known fixed combination with oestrogen, where data on endometrial safety can be extrapolated from the fixed combination if exposure to the oestrogen is similar or lower.

- In other situations, endometrial data are needed:
 - Known progestogen, same route of administration,
 - same dose of progestogen as in known fixed combination, but higher exposure to oestrogen;
 - lower dose of progestogen than in known fixed combination;
 - Known progestogen, different route of administration;
 - New progestogen.

Evaluation for endometrial hyperplasia during Hormone Replacement Therapy:

2.1.1. Endometrial biopsy is the gold standard method

Assessment of endometrial biopsies should be made according to predefined and generally accepted microscopic criteria (see 2.1.2.5. Methodological requirements).

A biopsy should be conducted at baseline, at the end of the study and/or at the end of treatment if it is stopped before the end of study (provided that it is longer than 3 months). Among women withdrawn from the study, only those treated for longer than 3 months should have “end of treatment” biopsy. For sequentially combined treatment, it is recommended that biopsies be obtained at a pre-specified time in the treatment cycle-(at least 10 days after the start of the progestogen-administration). In case of a continuous combined treatment, a biopsy may be performed at any time during the cycle.

The endometrial tissue obtained by endometrial biopsy at screening, during the conduct of the study, and at the end-of-study should be processed in the same manner by a central laboratory.

All included subjects should have an evaluable screening endometrial biopsy. For the purpose of the study, an evaluable biopsy is defined as “endometrial tissue sufficient for diagnosis”. Nevertheless, biopsies with insufficient tissue for diagnosis and endometrial thickness < 5 mm on ultrasonography can be categorised as “atrophic endometrium” (see 2.1.2.5).

Patients with histologically proven endometrial hyperplasia or cancer should be excluded from enrolment.

Patients with uterine polyps are also recommended to be excluded from enrolment

2.1.2. Uterine ultrasound cannot replace biopsy

Transvaginal ultrasonography, does not appear to be sufficiently standardised. Therefore, endometrial thickness measured by transvaginal ultrasound is not recommended to replace the biopsy for the evaluation of endometrial hyperplasia.

However, ultrasonography can be helpful when insufficient tissue has been obtained by biopsy. The most frequent reasons for “insufficient tissue” are either endometrial atrophy or technical problems while performing the biopsy. Transvaginal ultrasonography may in those cases help to differentiate atrophic endometrium (thickness < 5 mm) from other causes.

In practice, patients with insufficient tissue obtained by biopsy and endometrial thickness < 5 mm may be included in the study and/or analysis of results; in patients with endometrial thickness ≥ 5 mm, the biopsy should be repeated or patient excluded from the study

In patients where no tissue has been obtained, the biopsy should be repeated.

Decisions to continue or conclude repeated attempts at endometrial sampling should be fully documented by the investigator.

Transvaginal ultrasonography cannot be used to distinguish atrophic endometrium from other causes of no tissue material.

2.1.3. A minimal duration of one year is necessary

For a new combination of oestrogen/progestogen, studies of at least 12 month duration are required. For long-acting products (e.g. medicated IUDs, implants) the duration should cover the claimed duration of effectiveness in the prevention of endometrial hyperplasia.

2.1.4. An assessment of vaginal bleeding in clinical HRT trials is mandatory

In case of persistent and/or recurrent bleeding/spotting during treatment, the endometrium should be investigated to identify cases of hyperplasia and cancer. These data should be summarised in the dossiers. The assessment should be done during the whole trial duration (12 months). Particular attention will be drawn to the findings during the first 3 months (months 0 – 3) and the last 3 months (months 10 – 12) (required in the core SmPC).

2.1.5. Methodological requirements

a) Assessment of endometrial biopsies

Biopsies should be assessed by two independent pathologists blinded to treatment and time of biopsy. In case of disagreement in the interpretation of results (e.g. on hyperplasia or carcinoma diagnosis) between the two pathologists, a third one, also blinded, should be called upon to make the final determination. This biopsy will be evaluated by the third pathologist together with other biopsies, with and without hyperplasia, for which there was no disagreement during the first evaluation.

Endometrial biopsy with a pipelle or another aspiration technique is required using standardised criteria of quality.

b) Classification of results

The endometrial biopsies should be classified, according to standardized criteria into the general classes of atrophic, proliferative, secretory, hyperplasia without atypia, hyperplasia with atypia, cancer and others.

Endometrial polyps, if present, should be fully histologically characterised (see 2.1.2.5 e)

c) Sample size

A new HRT should be comparable to, or better than, currently marketed HRTs with respect to endometrial safety. The decision on endometrial safety must be based on reliable data from a sufficient number of patients, treated for a sufficient time period.

For a new HRT, a reasonable requirement is that the incidence should be statistically less than 2% after one year of treatment, i.e. the upper limit of a two-sided 95% confidence interval of the observed frequency of endometrial events should not exceed 2%. Pooled data from several recently authorised oestrogen/progestin HRT combinations in Europe show that the incidence of hyperplasia or more serious adverse endometrial outcomes was approximately 0.26% during the first year of treatment. Under the assumption that the new combination does not increase the frequency of hyperplasia as compared to recently authorised combinations, a sample size of 300 patients treated for one year should provide more than 80% statistical power.

d) Pooling of the data

Endometrial safety data from different studies can be pooled if:

- the oestrogen and progestogen formulations are the same, AND
- the progestogen and oestrogen doses are the same, except for lower oestrogen doses (see also 2.1) AND
- the duration of treatment is the same, AND
- the treatment sequence is the same.

e) Results analysis

The analysis of biopsy results should be based on:

- evaluable endometrial biopsies at 1 year (see Section 2.1.1.1),
- biopsies with insufficient tissue for diagnosis and endometrial thickness < 5 mm, (considered as atrophic endometrium),
- biopsies with diagnosis of hyperplasia or carcinoma performed during the study, whatever the duration of treatment.

It is recommended not to include the following biopsies in the final analysis:

- biopsies with no tissue,
- biopsies with insufficient tissue for diagnosis and endometrial thickness ≥ 5 mm if a new biopsy has not been done,
- biopsies performed before minimal treatment duration (one year), except for biopsies showing hyperplasia or carcinoma.

The time and the reason of exclusion of patients from the final analysis should always be specified.

The number and the reason for biopsies not performed should be specified.

It is recommended to present the data in a table for each study and each treatment group (see Annex 1)

Additionally, endometrial polyps, if found during the study, should be fully histological characterized (see Annex 2).

The incidence rate of endometrial hyperplasia should be calculated by taking into account the number of evaluable biopsies at 1 year.

$$\text{Incidence rate of hyperplasia / carcinoma (\%)} = \frac{\text{Number of hyperplasia / carcinoma}}{\text{Number of evaluable biopsies at 1 year}}$$

To conclude to an established endometrial safety, the upper limit of the two-sided 95% CI of the incidence of hyperplasia/carcinoma should be $\leq 2\%$.

2.2. Other safety issues

2.2.1. Biological parameters

Lipid, glucose homeostasis and hemostatic variables are of potential interest for new combination of oestrogen and progestogen products.

2.2.2. Venous thromboembolism

Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent in hormone replacement therapy users than in non-users (see core SmPC for HRT). Therefore, a careful monitoring of this kind of events is strongly recommended.

2.2.3. Bleeding control

For combined treatments, bleeding data should include in general bleeding and spotting, incidence of amenorrhagic cycles (total absence of bleeding or spotting) and percentage of women with withdrawal bleeding where appropriate. More specifically:

- For cyclic or sequential products:

Bleeding data should include percentage of women with regular withdrawal bleeding, the mean duration of these bleedings, and the time they start before/after the last pill of the progestogen phase. Data should also include percentage of women with breakthrough bleeding and/or spotting appearing during the first three months and during months 10 to 12 of treatment. The incidence of amenorrhoea (no bleeding or spotting) during the first year of treatment should also be specified.

- For continuous combined products:

Bleeding data should include the incidence of amenorrhoea (no bleeding or spotting) during months 10 to 12 of treatment, and the percentage of women with bleeding and/or spotting appearing during the first three months of treatment and during months 10 to 12 of treatment.

All data should come from comparative studies to make an evaluation possible.

The minimum duration of these studies should be at least 12 months, unless justified by the applicant.

2.2.4. Breast examination

Before initiating or reinstating HRT, a complete personal and family medical history should be taken, and a breast examination performed, including mammography. Mammography should be performed within a reasonable time frame before HRT to exclude malignancy. During treatment, periodic check-ups are recommended of a frequency and nature in accordance with nationally accepted screening practices, and adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse. (see core SmPC for HRT products)

2.2.5 Local Tolerance

Local tolerance of different oestrogen and progestogen formulations (patches, gels, intravaginal rings, intranasal solutions) should always be assessed.

The following is recommended to be assessed:

For patches and gels: skin tolerability (irritation, sensitisation, phototoxicity), and adhesivity of patches;

For intravaginal rings: vaginal tolerability;

For intranasal treatments: local tolerance.

REFERENCES (SCIENTIFIC AND / OR LEGAL)

1. Women's Health Initiative

Writing group for the Women's Health Initiative investigators. Risks and benefits of oestrogen plus progestin in healthy post menopausal women. JAMA 2002 ; 288 : 321-333

Influence of Oestrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women (WHI) -Chlebowski RT et al, JAMA 2003, 289 (24) : 3243-3253

Effects of Oestrogen Plus Progestin on Gynecologic Cancers and Associated Diagnostic Procedures -Anderson G.L et al, JAMA 2003, 290 (13) : 1739 – 1748

2. Million Women Study

Breast Cancer and Hormone-Replacement Therapy in the Million Women Study (MWS) - Lancet 2003, 362 (419-427)

3. Core SPC on HRT products

MRFG web site: www.medagencies.org

4. FDA guidance for industry: oestrogen and oestrogen/progestin drug products to treat vasomotor symptoms and vulvar and vaginal atrophy symptoms – recommendations for clinical evaluation. January 2003.

ANNEX 1:

Presentation of endometrial biopsy results for each study and each treatment group:

	Baseline	End of treatment
Number of randomised subjects		
Number of biopsies not done reasons		
Number of biopsies done		
Excluded biopsies: No tissue Tissue insufficient for diagnosis, thickness ≥ 5 mm Performed before 12 cycles with no hyperplasia or carcinoma		
Evaluable biopsies: Atrophic and/or inactive endometrium Tissue insufficient for diagnosis, thickness < 5 mm Proliferative endometrium Secretory/progestational endometrium Menstrual type endometrium Hyperplasia without atypia Hyperplasia with atypia Carcinoma		
Number of evaluable biopsies		

ANNEX 2:

If there are any polyps, please specify the type or types as follows:

- Functional
- Atrophic
- Hyperplastic without atypia
- Hyperplastic with atypia
- Carcinomatous