### Synopsis

<table>
<thead>
<tr>
<th>Title</th>
<th>Hormone replacement therapy (HRT) at menopause</th>
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<tr>
<td>Publication date</td>
<td>May 2004</td>
</tr>
<tr>
<td>Type of document</td>
<td>Guidelines</td>
</tr>
<tr>
<td>Requested by</td>
<td>Chief Executive of the French National Health Service</td>
</tr>
<tr>
<td>Produced by</td>
<td>ANAES – French National Agency for Accreditation and Evaluation in Healthcare (Guidelines Department)</td>
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| Objectives | - Provide guidance on HRT during the menopause and on the provision of information for women and health professionals.  
- Draw conclusions and produce guidelines for health professionals.  
- Draft key messages for women. |
| Method | Public hearing (May 11, 2004) |
| Literature search | Jan 2000 – May 2004 |
| Project management | Project leader: Dr. Frédéric de Bels (Department head: Dr. Patrice Dosquet)  
Literature search: Marie Georget, Maud Lefèvre, Julie Mokhbi (Department head: Rabia Bazi) |
| Collaborations and participants | Steering Committee  
Public Hearing Committee (Chair: Dr Annick Alperovitch, epidemiologist, Paris)  
Speakers  
Moderators (For participants, see Annex 1) |
| Related documents | Full report (in French)  
Available on ANAES website (www.anaes.fr) |
| Other ANAES publications on the topic | Osteoporosis in postmenopausal women and after corticosteroid therapy: diagnostic methods and indications, ANAES, 2001 |
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### Annex 1 – Participants

### Annex 2 – Estimating the number of women concerned by HRT-related risks
I. Introduction

I.1 Objective

The aims of this status report were:
- to provide general guidelines on HRT during the menopause and on the provision of information for women and health professionals
- to draw conclusions and produce practice guidelines for health professionals
- to draft key messages for women.

I.2 Context

The report was produced at the request of the Chief Executive of the French National Health Service. The work was planned and coordinated by the French National Agency for Accreditation and Evaluation in Health (ANAES) and the French Agency for Health Product Safety (AFSSAPS), with the assistance of the French Medical Research Institute (INSERM). It was financed by ANAES and AFSSAPS.

II. Method

II.1 Public hearing procedure

This status report was produced following a public hearing held on 27 April 2004 at the Xavier-Bichat Faculty of Medicine, Paris.

- The Steering Committee was made up of representatives from ANAES, AFSSAPS and INSERM, and the chair of the Public Hearing Committee.

- The Public Hearing Committee consisted of 21 members: 9 health professionals from different disciplines and 5 epidemiologists (with no declared major conflicts of interest), 6 members of the public concerned by the topic, and 1 ANAES representative responsible for the application of the ANAES method of guideline production (see Annex 1).

The Public Hearing Committee met twice to define the topic and draft questions to be sent to each of 21 speakers before their presentation. The day of the public hearing (27 April 2004) consisted in the 21 presentations followed by question and answer sessions with the Committee and the general public. The Committee then met for three days in closed session to produce a status report based on the information presented at the hearing and a literature search carried out by ANAES.

The Committee worked in 4 subgroups addressing: (i) menopausal symptoms, (ii) effects on bone, (iii) cardiovascular effects and (iv) risk of cancer. All 4 subgroups helped produce a report on benefits and risks. As this report was not ready by the end of the 3-day session, it was reworked by the Committee chair and the ANAES project manager, and the final version was submitted to the other Committee members for approval. It was approved on 11 May 2004.
II.2 Literature search

- A systematic search for articles in French or English on each aspect of the topic was performed by interrogating medical and scientific databases over appropriate search periods.
- All relevant websites (government agencies, professional societies, etc.) were explored.
- Documents not identified through the usual information channels (i.e. the grey literature) were sought by all available methods.
- Legislative and regulatory texts that might be related to the topic were consulted.
- References cited in the retrieved articles were examined to identify further relevant articles.
- Committee members and speakers contributed articles from their own reference sources.

The committee also used information from:
- presentations by experts attending an INSERM liaison meeting (26 March 2004, Necker Hospital, Paris);
- presentations at our public hearing; some speakers provided a list of the references supporting their presentation;
- the results of a survey carried out by SOFRES at ANAES’ request in a sample of 1000 women, concerning their perception and concerns with regard to HRT.

II.3 Level of evidence and grading of guidelines

The studies selected were allocated a level of scientific evidence using checklists. Whenever possible, the guidelines proposed by the Committee were based on this literature review. They were graded from A to C depending on the level of evidence of the supporting studies (Table 1). If no grading is given, the proposed guidelines were based on agreement among professionals.

<table>
<thead>
<tr>
<th>Level of scientific evidence provided by the literature (clinical trials)</th>
<th>Grading of guideline</th>
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<tbody>
<tr>
<td><strong>Level 1</strong></td>
<td>A</td>
</tr>
<tr>
<td>Randomised controlled trials of high power</td>
<td>Established scientific evidence</td>
</tr>
<tr>
<td>Meta-analyses of randomised controlled trials</td>
<td></td>
</tr>
<tr>
<td>Decision analyses based on properly conducted studies</td>
<td></td>
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<tr>
<td><strong>Level 2</strong></td>
<td>B</td>
</tr>
<tr>
<td>Randomised controlled trials of low power</td>
<td>Presumption of scientific foundation</td>
</tr>
<tr>
<td>Properly conducted non-randomised controlled trials</td>
<td></td>
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<tr>
<td>Cohort studies</td>
<td></td>
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<tr>
<td><strong>Level 3</strong></td>
<td>C</td>
</tr>
<tr>
<td>Case-control studies</td>
<td></td>
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<tr>
<td><strong>Level 4</strong></td>
<td>Low level of evidence</td>
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<tr>
<td>Comparative studies with major bias</td>
<td></td>
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<tr>
<td>Retrospective studies</td>
<td></td>
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<tr>
<td>Case series</td>
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III. General comments

III.1 Lack of French studies

In the last two years, results that bring into question the benefit-risk profile of HRT have been published for populations of American and English postmenopausal women. There is no reason to suppose that these results do not also apply to French women and to the products and administration routes they use. The Committee therefore included these studies in its analysis but drew attention to the lack of studies on the medium- and long-term effects of French products and of studies in French or European women. It urged the health authorities to act, if necessary by requesting studies from the pharmaceutical companies marketing these products.

Three points require study (depending on feasibility):
(i) whether a non-oral route of administration is safer, particularly with regard to cardiovascular risk;
(ii) whether certain types of progestin, e.g. progesterone itself, are safer with regard to breast cancer;
(iii) whether HRT offers long-term benefit in terms of preserving bone mass and reducing fracture incidence, compared with other treatments.

In addition, it is likely that some observational studies (e.g. the “E3N” and “3 Cités”) will generate reliable findings. The teams running these studies should be offered human and financial resources for more thorough analyses of the data collected (i.e. risk of cancer, fractures and cardiovascular events).

III.2 Numbers of HRT users

Information for estimating the size of the target population by indication is not easy to obtain. Nevertheless, the Committee was surprised that no-one had tackled this point. It urged the health authorities to request or sponsor clinical and economic studies to determine the public health benefit of different HRT regimens and their expected impact. The current AFSSAPS ad hoc “HRT Studies” group could contribute to this. Estimates of the impact of HRT on the incidence of cancers, cardiovascular effects and fractures are given in Table 2. (The method used to obtain these values is described in Annex 2).

III.3 Benefit-risk analysis

The Committee’s benefit-risk analysis, based on available information, broadly agreed with the assessments and recommendations made by the European Medicines Evaluation Agency (EMEA), AFSSAPS and the French Academy of Medicine. Its main conclusions and recommendations are given in Sections IV and V, but a few general remarks may be appropriate here.

• Menopausal symptoms

Menopausal symptoms cover a number of different symptoms, some of which have not been clearly shown to be related to the menopause. The notion of “severity” of symptoms found in the AFSSAPS recommendations is also ill defined. The Committee suggested that, in
practice, the indication “menopausal symptoms” should correspond to those symptoms that are causing - or perceived to be causing – fairly severe problems that prompt the woman to ask for and accept medical treatment. Before accepting, she should have been properly informed by her doctor and discussed the benefits and risks. Moreover, the concept of administering “the minimum effective dose, for the shortest time possible” should be adapted to treatment efficacy in controlling menopausal symptoms, side-effects (signs of hyperoestrogenism) and recurrence of symptoms during a treatment respite break.

Table 2. Potential or confirmed effects of HRT extrapolated to 3 500 000 women aged 50-60 on the hypothesis that 30% of women are exposed (of whom 80% on combined HRT, 20% on oestrogen alone)

<table>
<thead>
<tr>
<th></th>
<th>Anticipated cases without HRT N [95%CI]</th>
<th>Extra or prevented cases with HRT N [95%CI]</th>
<th>Attributable / preventable % [95%CI]</th>
</tr>
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<tbody>
<tr>
<td><strong>Cancers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Breast</td>
<td>9381 [8783;9897]</td>
<td>+ 540 [24;1138]</td>
<td>5.4 [0.2;11.5]</td>
</tr>
<tr>
<td>- Endometrial</td>
<td>821 [791;844]</td>
<td>+ 89 [66;119]</td>
<td>9.7 [7.2;13.0]</td>
</tr>
<tr>
<td>- Bowel</td>
<td>1986 [1858;2091]</td>
<td>- 186 [-58;-291]</td>
<td>9.4 [3.1;13.9]</td>
</tr>
<tr>
<td><strong>Cardiovascular effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Myocardial infarction**</td>
<td>2416 [2262;2555]</td>
<td>+ 139 [0;293]</td>
<td>5.4 [0;11.5]</td>
</tr>
<tr>
<td>- Stroke**</td>
<td>2901 [2634;3151]</td>
<td>+ 284 [34;551]</td>
<td>8.9 [1.1;17.3]</td>
</tr>
<tr>
<td>- Venous thrombo-embolism***</td>
<td>5566 [4283;6288]</td>
<td>+ 1593 [871;2336]</td>
<td>22.3 [12.2;32.6]</td>
</tr>
<tr>
<td><strong>Effects on fractures</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hip§</td>
<td>1255 [1143;1345]</td>
<td>- 129 [-219;-17]</td>
<td>10.3 [1.5;16.3]</td>
</tr>
<tr>
<td>- Vertebral</td>
<td>3763 [3442;4022]</td>
<td>- 402 [-661;-81]</td>
<td>10.7 [2.3;16.4]</td>
</tr>
<tr>
<td>- Wrist §</td>
<td>16808 [16069;17498]</td>
<td>- 1462 [-2152;-723]</td>
<td>8.7 [4.5;12.3]</td>
</tr>
</tbody>
</table>

* Estimates taken from French cancer registries. ** Estimates taken from the MONICA study. *** Estimates taken from WHI studies. § Extrapolated from WHI data on total populations; difference not significant for age range 50-60 years. The risks given are those for all women in WHI.

- **High risk of fracture**

The indication “high risk of fracture” should be more closely defined. Risk is usually established from bone mineral density (BMD) measurements (T score < - 2.5) (sometimes combined with markers of bone remodelling), clinical risk factors (including a first fracture) and risk factors for falls. The indications for bone densitometry defined by ANAES only partially overlap with the risk factors for fracture defined by AFSSAPS. These elements should therefore all be combined when estimating risk of fracture. The role of BMD and intervention thresholds are specified in Section V (see Guideline 9).

Pending the availability of epidemiological or economic studies establishing the impact of fracture risk on public health, the Committee suggested that:
- bone densitometry should not be routine when deciding to prescribe HRT to a postmenopausal woman with no risk factors for fracture or indication for bone densitometry (ANAES, 2001). In women between the ages of 50 and 60, both the

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1 Guidelines to be produced on drug therapy for postmenopausal osteoporosis
incidence of fractures and the risk of fractures at 10 years are low, particularly for hip fractures (the risk of hip fracture at 10 years for women aged 60 is 2.3%);
- a control bone densitometry was not recommended in compliant postmenopausal women receiving an effective HRT dose (ANAES, 2001).

- **Choice of drug to prevent osteoporosis and risk of fracture**

  In December 2003, AFSSAPS performed a public health safety assessment of first and second choice drugs for preventing osteoporosis and risk of fracture in a woman with a high risk of fracture but no menopausal symptoms. At the time, two prevention strategies were compared:
  - HRT, which has been shown to prevent fractures in women aged between 50 and 60 but which has side-effects that contraindicate its use solely to prevent osteoporosis or risk of fracture;
  - drugs, notably biphosphonates and raloxifene, which have been shown to prevent fractures only in elderly women with osteoporosis (T score < -2.5) and with no major side-effects over 5-10 year study periods.

  HRT was deemed to be a second-line therapy. Since this comparison, no further evidence on benefit and risk has become available. The Committee therefore decided to qualify and endorse the AFSSAPS and EMEA guidelines currently in force on drug choice. However, it noted that the alternative therapies to HRT are not reimbursed by health insurance bodies if the woman has not had any fractures, and that it would be appropriate to consider introducing such reimbursement.

**III.4 Surveillance**

The monitoring of HRT-related risk of cancer or cardiovascular disease should be seen as part of the broader issue of monitoring these risks at the individual and population levels. An HRT observatory could be established to satisfy the need for such surveillance.

When HRT is prescribed or renewed, no examination is required other than the usual cardiovascular check-up (including history-taking to verify the absence of cardiovascular events such as transient ischaemic attacks (TIAs), angina, etc.) and breast palpation. Women should be encouraged to take part regularly in breast screening programmes, particularly at the start of treatment.

Between 5 and 25% of women on combined HRT have increased breast density. This increase may be independent of HRT. An increase in density can make it difficult to interpret the mammograms of these women. Ways to increase diagnostic sensitivity are needed (adding an ultrasound examination, shorter interval between 2 mammograms, etc.) but none have been assessed so far. It would be useful to carry out an economic study to compare these options to the current screening system.

**III.5 Provision of information**

In accordance with the law of 4 March 2002 on patients’ rights and the quality of the healthcare system, women who consult their doctor about HRT have the right to be given information about their state of health, the proposed treatment, its benefits, its consequences, and the normally foreseeable common and serious risks. This right means

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2 Article L 1111-2 subparagraph 1 of the Public Health Code
that doctors must provide women with this information\(^3\). The fact that the woman herself takes the decision concerning her own health, after discussion with the doctor\(^4\), does not mean that responsibility is transferred from the doctor to the patient. Similarly, the fact that the woman has been informed about potential risks does not mean that the doctor is absolved of all responsibility.

All women taking HRT or who have taken HRT must be informed of any new risks that have been identified\(^5\).

To ensure that the woman’s right can be exercised, health professionals must be kept informed of any new data and of acceptable strategies for managing HRT at the menopause. However, the knowledge that health professionals must have and how they can acquire this knowledge must be distinguished from the ways and means of informing women directly concerned by HRT.

- **Information for health professionals**
  This is the information (conclusions from published data and guidelines) contained in this document. The Committee considered that these guidelines should be distributed as widely as possible. AFSSAPS has already sent a letter to all practitioners involved. In addition, the following could be considered:
  - a letter sent out by the Council of the *Ordre des médecins* (the French Medical Association), backed up by continuing education;
  - standards for HRT drafted by professional associations;
  - an information campaign aimed at health professionals, implemented by the *Fonds de promotion de l’information médicale et médico-économique* (FOPIM);
  - the updating of all monographs in the Vidal\(^6\) (the French physicians’ desk reference) to include information about risks (the monographs vary considerably; some of them do not even mention the first risks to be discovered);
  - possibly capitalising on pharmaceutical companies’ representatives’ visits to health professionals.

  The information for prescribers should stress the need to communicate objective information, if this has not already been done:
  - not just to women who are starting HRT, are currently using HRT or who have discontinued HRT and would like to go back to it,
  - but also to women who have stopped using HRT within the last 5 years and who are still being monitored.

- **Information for women at the menopause**
  The Committee drafted 12 key messages for women (see Section VI).

  - For women receiving or about to receive HRT, it is a question of updating their knowledge and assessing benefits and risks with them. No special strategy is required as the information is given during the consultation when the prescription is initiated or renewed.

  - For women who have stopped taking HRT, it involves:
    - asking about their concerns about HRT

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\(^3\) Article L 1111-2 subparagraph 2 of the Public Health Code  
\(^4\) Article L 1111-4 of the Public Health Code  
informing them about the benefits they have gained from HRT and the risks they have incurred
- answering their questions
- warning them if they have stopped taking HRT within the last 5 years that the increased risk of breast cancer may persist for some time
- warning them of the risks related to the use of soy derivatives and phytoestrogens more generally.

In view of the media coverage and risk level, the Committee did not think it useful to make an active attempt to contact women who had received HRT in the past. However, it thought it advisable to give information about HRT to women taking part in breast cancer screening programmes, in addition to providing the doctor with information.

The Committee suggested using the following information channels: the women’s press and the general press; radio and television; women’s groups; healthcare and social welfare centres; mother and child care centres; posters in the waiting rooms of practitioners and of hospitals; distribution of a leaflet giving the key messages by either practitioners or pharmacists; access to validated information on a website (to be developed) or via a helpline (to be established); and, finally, a publicity campaign aimed at the general public, run by the Institut national de prévention et d’éducation pour la santé (INPES).

• **Measuring the impact of information provision**

It would be useful to assess the impact of these recommendations on the information given to women, on their perceptions of HRT and any changes in that perception, and on any resultant changes in management. This could be done by carrying out surveys in representative samples of women and practitioners (all specialties). It would also be useful to carry out a large-scale survey of practitioners’ opinions and outstanding concerns.

### III.6 Phytoestrogens

The Committee pointed out that soy derivatives, and phytoestrogens more generally, may have oestrogenic properties. This means that although they may be effective against hot flushes, they may have the same side-effects as oestrogens. These products are currently being assessed by AFSSA (the French Food Safety Agency) and AFSSAPS, and have not yet received a marketing authorisation. Their risks have not been assessed or tested, and their use does not satisfy the requirements of safe use of medicines.

The Committee called for greater vigilance with regard to advertising for these products which have been presented as medicines at scientific congress exhibits and in the women’s press. They would like manufacturers’ attention to be drawn to their responsibilities and to the risks incurred by users. These risks underlie one of the key messages aimed at women.

### III.7 Looking ahead

The Committee considered that the time available for thought, review of the literature and report writing was inadequate for such a broad subject. It was unable to give as much attention as it would have liked to all points. It would also have liked to include radiologists and pharmaco-epidemiologists among its members. Although these specialties were represented among the speakers at the public hearing, they were not represented on the Committee.
In addition, a large amount of data is likely to become available during the next few months:
- data on the oestrogen-only arms of the Women’s Health Initiative (WHI) study
- publication of additional analyses within the E3N study
- results from the “HRT study group” set up by AFSSAPS (the aim is to establish the benefits and risks of HRT by applying the available results to the French population and to French products and their mode of use)
- possible economic data
- ongoing assessment of phytoestrogens by AFSSAPS and AFSSA.

The new data are unlikely to lead to any radical changes in the guidelines. However, the Committee wished to reconvene in about a year to produce updated guidelines that incorporate the newly available data. The guidelines would be produced using ANAES’ method and with input from the agencies concerned.

IV. Conclusions of the critical review of the literature

IV.1 The indication for HRT: Control of menopausal symptoms

The indication for HRT is control of menopausal symptoms such as hot flushes, night sweats and vaginal atrophy (level of evidence 1). HRT improves quality of life with regard to these menopausal symptoms but has not been shown to do so if these symptoms are not present. Results on whether HRT has a positive or negative effect on urinary incontinence are inconclusive (level of evidence 2).

IV.2 Efficacy of HRT in preventing bone loss and fractures: epidemiology

In menopausal women between the ages of 50 and 60 years, the incidence of fractures and the risk of fracture at 10 years are low (approximately 5 wrist fractures, 12 vertebral fractures and 0.5 hip fractures per 1 000 women per year and an approximately 2.3% risk of hip fracture at 10 years for women aged 60).

In practice, the risk of fracture is defined from BMD (T score < -2.5) (at times combined with markers of bone remodelling), clinical risk factors (including occurrence of first fracture) and risk factors for falling. No long-term longitudinal data predict risk of fracture in women between 50 and 60 on the basis of these factors or scores combining them; predictive values of <20% have been obtained in older populations at higher risk of fracture. In younger women, the indications for bone densitometry established in 2001 by ANAES and the risk factors for fracture used by AFSSAPS should therefore be combined to estimate risk of fracture.

- BMD

HRT, as well as biphosphonates, raloxifene and tibolone, prevent postmenopausal bone loss as measured by bone densitometry. With HRT, the increase in bone mineral density (level of evidence 1) is

6 Guidelines soon to be published on drug therapy for postmenopausal osteoporosis
evidence 1) is particularly marked in the first year, then tends towards a plateau. It is dose dependent and has been observed with all treatment regimens.

After discontinuation of HRT, bone loss accelerates and markers of bone remodelling increase (level of evidence 2). Whether any gain in BMD persists more than 5 years after treatment is a moot point. Protection against fracture would seem to persist for less than 5 years (level of evidence 2).

- **Prevention of risk of fracture**
  - In the primary prevention of risk of fracture (vertebrae, wrist, hip), HRT is the only treatment which has been shown to be effective in postmenopausal women (level of evidence 1). However, in women aged between 50 and 60 who have a low incidence of fractures, a protective action of HRT has only been established for vertebral fractures (level of evidence 1). It persists for less than 5 years after HRT has been discontinued (level of evidence 2). No studies have shown that bisphosphonates or raloxifene are effective in primary prevention of fractures in postmenopausal women not selected for risk of osteoporosis or fracture.
  - In women with osteopenia alone, no studies have demonstrated that HRT prevents risk of fracture.
  - In confirmed osteoporosis, defined by densitometric criteria, with or without fracture, a fracture prevention rate of about 30-50% over 3 years of treatment has been recorded with bisphosphonates or raloxifene (level of evidence 1). No sufficiently well-designed studies were found on the efficacy of HRT in confirmed osteoporosis with or without fractures (a single old study with a level of evidence 4).

### IV.3 Cancer risk with HRT

- **Increased risk of breast cancer**

  There is an increased risk of breast cancer in women using combined HRT (level of evidence 1). This risk increases with duration of use (level of evidence 2) and is well established for treatments lasting more than 5 years. It is not possible to determine a treatment duration that carries no increased risk. The risk returns to a level similar to that of non-users during the 5 years after HRT discontinuation. Persistence of risk is governed by duration of use (level of evidence 2).

  Study results are inconclusive on whether oestrogen-only HRT increases the risk of breast cancer (level of evidence 1).

  Absence of hormone treatment does not mean that there is no risk of breast cancer (level of evidence 1). Risk increases with age.

  No difference in breast cancer risk has been shown in relation to route of administration (oral, parenteral) (level of evidence 2) or regimen (sequential or continuous) (level of evidence 2).

  The increased risk of breast cancer for combined HRT could vary according to type of progestin, but this needs to be confirmed (level of evidence 4). There is no proof that 17-β oestradiol (used in France) and equine oestrogens have different effects (level of evidence 2).

  In the WHI study, the increase in risk with combined HRT was associated with more advanced stage breast cancers in users than in non-users under similar surveillance (level of evidence 1). On the other hand, in observational studies, cancers in HRT users are often
less extensive with regard to size, lymph node invasion and, more globally, stage (level of evidence 2) partly maybe because better follow-up in HRT users compared to non-users leads to diagnosis of early stage rather than advanced cancers.

The WHI study did not find any significant difference in the biological and histoprognostic factors of breast tumours in HRT users and non-users. However, observational studies have indicated more favourable features in HRT users, notably a lower frequency of grade III tumours (level of evidence 2). Some studies also suggest that cancers in HRT users could be hormone dependent (level of evidence 3).

Combined HRT increases breast density in 5-25% of women (level of evidence 1). This may reduce the diagnostic sensitivity of mammography and delay diagnosis. Ultrasonography or a shorter interval between mammograms might be considered. There are no economic studies.

HRT is contraindicated in women with a personal history of breast cancer (level of evidence 1). In women with a family history of genetic susceptibility to breast cancer, there is a lack of data. According to currently available data, HRT must be discontinued if the patient develops in situ breast cancer or invasive cancer.

No interaction has been found between HRT and either the earlier use of a progestin at the onset of menopause or the use of oral contraception, with regard to breast cancer occurrence.

- **Increased risk of endometrial cancer for oestrogen-only HRT**
  Oestrogen-only HRT increases the risk of endometrial cancer (level of evidence 1). Adding a progestin decreases the risk for sequential treatment and cancels the risk for continuous treatment (level of evidence 1).

  Absence of hormone therapy does not mean that there is no risk of endometrial cancer (level of evidence 1). Risk increases with age.

- **Ovarian cancer**
  Available studies lack power and are inconclusive on whether there is any increased risk of ovarian cancer associated with HRT. There are no data that contraindicate HRT after treatment of ovarian cancer or of a borderline tumour.

- **Protective effect of combined HRT in colorectal cancer**
  Combined HRT has a protective effect against colorectal cancer, which seems to be more marked for colon cancer than for rectal cancer (level of evidence 1). However, more advanced stage colon cancers have been detected in users (level of evidence 1). The protective effect of oestrogen-only HRT is a moot point (level of evidence 1).

### IV.4 Cardiovascular risk of HRT

- **Increased risk of coronary disease**
  HRT (combined or oestrogen-only) does not protect against coronary disease in women with or without a history of cardiovascular disease. On the contrary, there is an increased risk of coronary disease under combined HRT, apparently unrelated to treatment duration. In women with a low risk of cardiovascular disease, this increase does not justify not prescribing or discontinuing HRT, if the anticipated benefits of treatment are high.
• **Increased risk of stroke**
HRT (combined or oestrogen-only) does not protect against the risk of stroke. It even increases this risk, independently of treatment duration. In women with a low risk of stroke, this increase does not justify not prescribing or discontinuing HRT, if a benefit is anticipated from treatment.

• **Increased risk of venous thromboembolism (VTE)**
There is an increased risk of VTE under combined HRT. This increase has not been observed for transdermal oestrogen (level of evidence 3) but further studies are required.
- In women at low risk of VTE, the increase in risk of VTE from HRT does not justify not prescribing or discontinuing HRT, if the anticipated benefits of treatment are high.
- In women at high risk of VTE, the increase in risk is a reason for not prescribing or discontinuing HRT, while the risk factors persist.

• **Absence of protection against decline in cognitive function and dementia**
HRT does not have any protective effect against decline in cognitive function or dementia (level of evidence 1). It even increases the risk of dementia in women over 65 years (level of evidence 1).

### IV.5 Benefit-risk ratios

The Committee established the benefit/risk ratios shown in Table 3 (see Annex 2).

<table>
<thead>
<tr>
<th>Without HRT</th>
<th>With HRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N [95%CI]</td>
<td>N [95%CI]</td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td></td>
</tr>
<tr>
<td>- Breast</td>
<td>268 [251;283] + 64 [3;136] 0</td>
</tr>
<tr>
<td>- Endometrial</td>
<td>23 [23;24] 0 + 42 [31;57]</td>
</tr>
<tr>
<td>- Colon</td>
<td>57 [53;60] - 22 [-35; -7] 0</td>
</tr>
<tr>
<td><strong>Cardiovascular effects</strong></td>
<td></td>
</tr>
<tr>
<td>- Myocardial infarction**</td>
<td>69 [65;73] + 17 [0;35] 0</td>
</tr>
<tr>
<td>- Stroke**</td>
<td>83 [75;90] + 26 [2;51] + 52 [9;58]</td>
</tr>
<tr>
<td>- Venous thromboembolism***</td>
<td>159 [138;180] +177 [104;251]</td>
</tr>
<tr>
<td><strong>Effects on fractures</strong>*</td>
<td></td>
</tr>
<tr>
<td>- Hip ¶</td>
<td>36 [33;38] - 12 [-20; -1] - 14 [-23; -3]</td>
</tr>
<tr>
<td>- Wrist ¶</td>
<td>480 [459;500] -139 [-205; -69] -139 [-205; -69]</td>
</tr>
</tbody>
</table>

* Not justified if hysterectomy is being considered * Estimates based on French cancer registries. ** Estimates based on the MONICA study; *** Estimates based on WHI studies. ¶Extrapolation from complete WHI data, non-significant for the age range 50-60 years. The risks given are those corresponding to all women in the WHI study.
V. The Committee's guidelines for health professionals

1. In a woman with menopausal symptoms that are causing problems or perceived by her to be doing so, HRT is recommended as first choice of treatment, irrespective of her osteoporosis status (grade A). Menopausal problems are the main indication for HRT in women who ask for it. However, HRT should be prescribed only after the woman has been given and accepted objective information on benefits and risks.

2. The demonstrated or suspected increased level of risk of breast, endometrial or ovarian cancer does not by itself invalidate the indication for HRT in women with menopausal symptoms that justify its prescription (grade A). A personal history of breast cancer is a contraindication to HRT (grade A).

3. In the event of hysterectomy, oestrogen-only HRT should be prescribed rather than combined HRT (grade A). Combined HRT would expose a woman to an increased risk of breast cancer without any anticipated benefit against endometrial cancer. Moreover, the potential protective action against colorectal cancer, demonstrated for combined HRT only, would be lost.

4. In the event of cardiovascular risk factors:
   - HRT should not be prescribed to women with a history of myocardial infarction or coronary disease, stroke, or venous thromboembolism (grade A).
   - In a woman with a high level of cardiovascular risk\(^7\), HRT should not be prescribed or should be discontinued while the risk persists (grade B).
   - A moderate single cardiovascular risk factor (hypertension, hypercholesterolaemia, smoking, overweight) is not a major and permanent contraindication to HRT according to the current state-of-the-art. The requirement to manage cardiovascular risk factors effectively is the same in women taking HRT as for the general population.
   - In women with a low risk of cardiovascular disease or stroke, the increased risk does not justify not prescribing or discontinuing HRT if other benefits might be anticipated.
   - Cardiovascular risk should be closely monitored during HRT as in all persons over 50, i.e. by seeking traditional risk factors (blood pressure, total and HDL-cholesterol, blood glucose, smoking), asking about antihypertensive, lipid-lowering and/or antidiabetic treatment, and enquiring about any history of cardiovascular disease.

5. The dose of oestrogen required to treat menopausal symptoms varies among women. Treatment should be adjusted according to observed efficacy against symptoms and according to any signs of hyperoestrogenism that may be related to HRT. If the menopausal symptoms persist, the dose should be gradually increased. If signs of hyperoestrogenism appear, it should be decreased or a combination drug with a slightly different spectrum should be used (agreement among professionals). Treatment should be stopped if a contraindication arises.

6. It is necessary to check each year whether HRT needs to be continued (agreement among professionals in the absence of studies or consensus):
   - either by gradually reducing the dose of oestrogen
   - or by suspending treatment for a few weeks.

\(^7\) A woman is at high risk of cardiovascular disease if she has:
   - peripheral arterial disease of the carotid arteries, the aorta and/or the lower limbs;
   - severe hypertension, severe hypercholesterolaemia or diabetes;
   - multiple risk factors, leading to a high cumulated risk of coronary complications at 10 years (calculated using the European risk score).
If the problems recur and the patient wishes to continue HRT, it may be resumed. As a guide, observational data show that the mean duration of HRT is for 2 or 3 years and that approximately 1 in 4 women who stopped taking it after the publication of studies describing HRT-related risks resumed treatment.

The Committee noted that local treatment may improve genital symptoms such as vaginal atrophy, which is likely to reappear or be exacerbated when HRT is discontinued.

7. HRT should not be routinely prescribed at the onset of menopause solely to preserve bone mass or prevent fractures. The incidence of osteoporosis-related fractures is very low before the age of 60. Results for BMD changes after HRT discontinuation are inconsistent and no studies have shown that HRT is effective in the long term in preventing fractures (after withdrawal of HRT).

8. In postmenopausal women aged 50-60 years with no menopausal symptoms nor risk factors constituting an indication for bone densitometry nor risk factors for fracture:

- Bone densitometry is not indicated (ANAES, 2001) and should therefore not be ordered when deciding whether to prescribe HRT. As yet, no studies have assessed the benefit of routine radiological screening for osteoporosis at the time of the menopause.
- HRT should not be prescribed solely to preserve bone mass or prevent fractures because of the risk of cancer or cardiovascular disease (grade A). These risks are considered to be greater than the anticipated benefits.

9. In postmenopausal women with no menopausal symptoms but with risk factors justifying an indication for bone densitometry or risk factors for fracture, bone densitometry should be performed. Therapy to preserve bone mass or prevent fractures depends on the T score:

- If the T score is > -1, i.e. if BMD is normal, no treatment should be given. Preventive action in the form of lifestyle and dietary measures may be taken to avoid future calcium deficiency. Bone densitometry may be performed at a later date, in 5-10 years.

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8 Indications for bone densitometry (ANAES, 2001):
- radiological discovery of a vertebral fracture not caused by trauma or visible tumour (recommended);
- personal history of peripheral fracture without major trauma (excluding fractures of the skull, toes, fingers or cervical spine) (recommended);
- documented history of disease that could cause osteoporosis (prolonged hypogonadism, active untreated hyperthyroidism, hypercorticism and primary hyperparathyroidism) (recommended);
- history of a vertebral or hip fracture in the absence of major trauma in a first-degree relative;
- BMI < 19 kg/m²;
- menopause before age 40 irrespective of cause or iatrogenic menopause;
- history of prolonged corticosteroid therapy (> 3 months) at a corticosteroid dose of prednisone equivalent = 7.5 mg/ day;

9 Risk factors for fracture (apart from age) (AFSSAPS 2004, guidelines on drug therapy for postmenopausal osteoporosis):
- personal history of fracture;
- current or previous corticosteroid therapy;
- history of fracture of upper extremity of the femur in a first-degree relative;
- decreased visual acuity;
- inadequate body mass,
- neuromuscular or orthopaedic disorders;
- smoking;
- increase in markers of bone remodelling (after obtaining specialist’s opinion).
- If the T score is between -1 and -2.5, treatment may be given but is not essential. It depends on the severity of the osteopenia and on whether the risk factors for fracture are major. As first choice of treatment, AFSSAPS recommends biphosphonates or raloxifene as they are safer than HRT. However, if they are contraindicated or poorly tolerated, HRT is the preferred option. Other options are calcium and vitamin D supplementation prescribed, with physical exercise, as part of general lifestyle and dietary measures, in order to avoid calcium deficiency. Daily calcium intake should therefore be evaluated at the consultation.

- If the T score is < -2.5, biphosphonates and raloxifene are indicated as first choice of treatment (French Marketing Authorisation). HRT is indicated if the patient cannot tolerate these two drugs.

10. The Committee confirmed that control bone densitometry is not recommended in compliant postmenopausal women taking an effective HRT dose (ANAES, 2001).

11. No special monitoring is required when prescribing or renewing HRT apart from normal cardiovascular examination and breast palpation. Women should be encouraged to participate in breast screening programmes, particularly at the start of treatment. However, increased breast density may interfere with diagnosis and may require an appropriate monitoring strategy (complementary ultrasound, reduced interval between mammograms, etc.). These strategies need to be assessed.

12. In view of the incidence of breast cancer, women who are not taking HRT should also be encouraged to participate in breast screening programmes (grade B).

13. Patients should be given objective information about the anticipated benefits and risks of HRT during a personal consultation with their doctor. Provision of information is a patient’s right. Written information does not dispense with the need for appropriate oral information. It is not useful or recommended to ask the patient to sign a document to confirm that she has received and properly understood the information.

14. Postmenopausal women over 65 should be asked about previous HRT use. If they used HRT less than 5 years ago, they should be told that an increased risk of breast cancer will persist for some time. This is an opportunity to inform the patient of newly identified HRT-related risks (this is a right) if this has not already been done.

VI. Twelve key messages for women

1. The menopause is not an illness. However, HRT is medication with indications, contraindications and side effects. It should be prescribed for a limited period. On average, a period of 2-3 years is long enough (discuss it with your doctor).

2. HRT is by far the most effective treatment for some of the problems occurring at menopause such as hot flushes, vaginal atrophy and night sweats. However, it is not a panacea against ageing; you will be disappointed if you use HRT with this in mind. It does not protect against cognitive function deficit or the risk of dementia.

3. HRT is effective in preventing certain types of fracture at the menopause. However, fractures are uncommon before the age of 60 and other treatments may be offered. Discuss this with your doctor.
4. If you need or wish to take oestrogen-only HRT, current information suggests that this does not increase the risk of breast cancer but does increase the risk of cardiovascular disease and of endometrial cancer. Discuss it with your doctor.

5. If you need or wish to take combined HRT (containing both oestrogen and progestin), you would avoid the increased risk of endometrial cancer and you might reduce the risk of colorectal cancer, but you would be exposed to an increased risk of breast cancer and cardiovascular disease. Discuss it with your doctor.

6. If you have had a hysterectomy, there is no benefit in taking combined HRT (oestrogen plus progestin); oestrogen alone is sufficient. Otherwise you might run a needless increased risk of breast cancer.

7. If you do not have any particular risk factors, experts feel that the increased risks do not preclude HRT treatment for menopausal symptoms such as hot flushes, vaginal atrophy or night sweats. Discuss this with your doctor.

8. Not taking HRT does not eliminate risk of cancer or cardiovascular disease. Breast or endometrial cancer and cardiovascular disease also develop in women who have never taken HRT.

9. If you stop taking HRT, the increased risk of cardiovascular disease will cease. The increased risk of breast cancer will have disappeared 5 years after you stop.

10. The best form of monitoring to avoid problems involves regular visits to your doctor (e.g. twice a year) for a gynaecological examination and attending breast screening every 2 years.

11. Soy derivatives and phytoestrogens in general can have an effect on hot flushes but can carry the same risks as oestrogens. Their reliability is not guaranteed and their safety has not been assessed. It is inadvisable to take them to treat symptoms until they have been granted a licence by the health authorities.

12. If you would like any further information, don’t hesitate to ask your doctor or contact the French National Health Authority (HAS) or AFSSAPS via their websites.
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Annex 2 – Estimating the number of women concerned by HRT-related risks

Calculating the benefits and risks of HRT is a major and complex issue. The Committee made a preliminary attempt using the studies available to them. However, their efforts need to be pursued, notably by the working group set up by AFSSAPS, using more sophisticated and lengthy epidemiological modelling. This would incorporate data they did not have at hand and results that should soon become available.

The following method was used to establish a preliminary benefit/risk analysis:

- The Committee included in their analysis only those potential benefits and risks that were supported by a level of evidence of 1 in the literature review and in the presentations at the public hearing, i.e.
  - benefits: decreased incidence of osteoporosis-related fractures (hip, vertebrae, wrist) and of colon cancer;
  - risks: increased incidence of breast and endometrial cancer, and of cardiovascular disease (myocardial infarction, stroke, venous thromboembolism). (The risk of dementia was not included because the disease is very rare before the age of 60.)

- The effect on menopausal symptoms - the main indication of HRT - cannot be measured in the same way as the above benefits and risks and was not included in the calculations. However, there are methods for combining all effects in a single analysis and these could be used in future.

- An important hypothesis in the calculations is that percentages of decrease or increase in risk due to HRT, estimated from the value for relative risk, are independent of the so-called baseline risk, i.e. the level of risk in the absence of HRT. As an example, supposing that HRT reduces by a third the proportion of fractures in a given age range, this reduction would apply irrespective of the baseline risk of fracture which is governed by factors such as weight, smoking, personal history of fracture, etc. This is equivalent to assuming that there is no interaction between HRT and the other risk factors. With a few exceptions (e.g. HRT, lipids and risk of coronary events), this hypothesis does not appear to contradict the data currently available.

- Incidence data for cancer and vascular disease (excluding VTE) in France were available from cancer registries, registries of cardiovascular disease (MONICA for coronary events, Dijon registry for stroke), etc. The data were for the general population, i.e. included women who were taking or who had taken HRT.

- The annual number of incident cases of a disease (n) in a population of size N is given by
  \[ n = N \left( p r + p o r o + r o \right) \]
  where
  - r is the risk of disease without HRT,
  - \( rr_{op} \) and \( rr_o \) are the relative risks associated with combined HRT and oestrogen-only HRT, respectively.
  - \( p \), \( p_{op} \) and \( p_o \) are the respective proportions of women not treated, treated with combined HRT and treated with oestrogen-only HRT (\( p + p_{op} + p_o = 1 \)).
When incidence data were not available for France (e.g. VTE), the Committee used the baseline incidence reported in international studies.

The Committee considered that the current indications for HRT target mostly women in the 50-60 age range as they would benefit most from a benefit-risk analysis. Results were extrapolated to all French women aged 50-60 years (3 500 000 women according to the last census); surveys estimate that at least 30% (1 150 000 women) are taking HRT.

Separate calculations were performed for combined HRT and oestrogen-only HRT. They were combined by assuming that 80% of women were taking combined HRT and only 20% were taking oestrogen-only HRT.

For each disease, the following indicators were calculated:
- annual number of cases per 100 000 women treated;
- annual number of cases per 100 000 women treated with HRT (combined and oestrogen-only in the proportion 80% / 20%);
- expected number of cases for all women aged 50-60 (approximately 3.5 million) assuming that 30% are treated;
- number of cases and the fraction that could be attributed to HRT.

The value of 30% of women treated was taken from survey results (SOFRES, and the French Association for the Study of the Menopause (AFEM)). This is probably a minimum value as it represents women being treated at the time of the survey.

The values used for relative risk were taken from WHI studies. The relative risk of breast cancer has only been established for more than 5 years of treatment but the risk values used correspond to 5.2 years of follow-up.

The results of the risk extrapolations are given in two tables:
- Table 2 gives risk estimates for the whole population of women aged 50-60 years and the proportion attributable to HRT.
- Table 3 uses incidence data per 100 000 women without HRT and the increases or decreases in incidence based on the hypothesis that these 100 000 women were treated with combined HRT or oestrogen-only HRT.