

From: Professor Gordon Duff, Chairman – Committee on Safety of Medicines

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## **FURTHER ADVICE ON SAFETY OF HRT : RISK: BENEFIT UNFAVOURABLE FOR FIRST-LINE USE IN PREVENTION OF OSTEOPOROSIS**

Dear Colleague

I last wrote to you in August 2003 at the time of publication of the Million Women Study, with the immediate implications for advice to women about hormone replacement therapy (HRT). This letter provides further advice and is based on the outcome of a more detailed review of recent studies with regard to long-term risks and benefits of HRT. This review has been adopted by the European Committee for Proprietary Medicinal Products (CPMP) and endorsed by the Regulatory Authorities throughout Europe, including the UK's Committee on Safety of Medicines (CSM) Expert Working Group on HRT. The conclusions of the review are:

- **The risk:benefit of HRT is favourable for treatment of menopausal symptoms. The minimum effective dose should be used for the shortest duration.**
- **The risk:benefit of HRT is unfavourable for the prevention of osteoporosis as first-line use.**
- **In healthy women without symptoms, the risk:benefit of HRT is generally unfavourable.**

Product information will be changed to reflect this new advice.

### **Background**

A review of the balance of risks and benefits of HRT in its licensed indications was initiated in response to growing concern about its safety following the recent publication of several important studies, most notably the Women's Health Initiative (WHI)<sup>1</sup> and the UK Million Women Study<sup>2</sup>. These and previous studies provide good evidence that use of HRT increases the risk of breast cancer, endometrial cancer and ovarian cancer in a duration-dependent manner. There is no evidence for a beneficial effect of HRT on cardiovascular disease – in fact HRT has been shown to increase the risk of myocardial infarction and VTE, especially in the first year of use, and to increase the risk of ischaemic stroke. The risk of most of these conditions increases with age, therefore increasing the overall risks the longer HRT is taken. HRT also has no beneficial effect on cognitive function and may increase the risk of dementia in the elderly. HRT has also been shown to have no beneficial effect on the quality of life of women who do not have menopausal symptoms.

The benefits of HRT include the effective relief of menopausal symptoms and the prevention of osteoporosis and fractures in the long-term. HRT has also been shown to reduce the risk of colorectal cancer.

Despite its effectiveness in preventing osteoporosis, the review concluded that for long-term use, the balance of risks and benefits is such that HRT should no longer be considered as a first-line therapy for preventing osteoporosis.

### **Which products does this affect?**

The conclusions of the review apply to **all** conventional oestrogen-only and combined (oestrogen plus progestogen) HRT products that are authorised for the prevention of osteoporosis.

### **Advice for prescribers**

#### **Short-term treatment of menopausal symptoms**

The outcome of this review does not have any implications for women who are using HRT for the short-term treatment of menopausal symptoms, as the benefits are still considered to outweigh the risks for the majority of women. The lowest effective dose should be used for the shortest duration; each decision to start HRT should be made on an *individual* basis with a fully informed woman; and treatment should be reviewed at least annually in light of new knowledge and any changes in a woman's risk factors.

#### **Prevention of osteoporosis**

HRT should not be considered first-line therapy for the long-term prevention of osteoporosis in women who are over 50 years of age and at an increased risk of fractures. HRT remains an option for those who are intolerant of other osteoporosis prevention therapies, for whom these are contraindicated, or for whom there is evidence of a lack of response to other therapies. In such cases the individual risk:benefit balance should be carefully assessed.

This new advice does not necessitate any urgent changes but women currently receiving HRT as long-term prophylaxis should have their treatment reviewed at the next appointment.

### **Women with premature menopause**

HRT may be used in younger women who have experienced a premature menopause (due to ovarian failure, surgery or other causes) for treating their menopausal symptoms and for preventing osteoporosis until the age of 50 years. After this age, therapy for preventing osteoporosis should be reviewed and HRT considered a second-line choice.

### **Sources of Further Information**

An information sheet for women is attached and more detailed information about the safety of HRT is available on the MHRA website (<http://www.mhra.gov.uk>).

For telephone enquiries, please call the Medicines and Healthcare products Regulatory Agency 020 7273 0000 (and 020 7084 2000 from 8<sup>th</sup> December).

Information is also available on the website of the European Agency for the Evaluation of Medicinal Products ([www.emea.eu.int](http://www.emea.eu.int)) and the Heads of European Medicines Regulatory Agencies website (<http://heads.medagencies.org>).

Further information on the role of HRT in clinical practice is available on the website of the Royal College of Physicians ([www.rcpe.ac.uk/esd/consensus/hrt\\_03.html](http://www.rcpe.ac.uk/esd/consensus/hrt_03.html))

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#### References:

- 1 Risks and benefits of estrogen plus progestin in healthy postmenopausal women.

JAMA 2002; 288:321-333. [www.jama.com](http://www.jama.com)

2 Breast cancer and hormone replacement therapy in the Million Women Study. Lancet 2003;362:419.  
[www.thelancet.com](http://www.thelancet.com)