



## IRISH MEDICINES BOARD

### DRUG SAFETY NEWSLETTER

18th Edition

#### Availability of ADR Report Forms

Did you know that in addition to the standard “Yellow Cards” for notification of suspected ADR reports, a copy of the IMB’s ADR report form is also available from the IMB’s website ([www.imb.ie](http://www.imb.ie)) under the heading “Pharmacovigilance”. Pending availability of the secure network for transmission of electronic ADR data, downloaded forms should be completed and posted in an envelope marked:

“Freepost”,  
Pharmacovigilance Unit,  
Irish Medicines Board,  
Earlsfort Terrace,  
Dublin 2.

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#### **HORMONE REPLACEMENT THERAPY (HRT) RISK/BENEFIT UNFAVOURABLE FOR FIRST-LINE USE FOR PREVENTION OF OSTEOPOROSIS**

Further to previous articles, the IMB wishes to inform you of the latest advice on hormone replacement therapy (HRT). This advice is based on a review of the long-term risks and benefits of HRT in its licensed indications by the EU’s Committee for Proprietary Medicinal Products (CPMP) Expert Group on HRT. This review takes into consideration the latest findings from the Women’s Health Initiative (WHI) trial<sup>1</sup> and the Million Women Study<sup>2</sup> and has been adopted by the CPMP and endorsed by the European Heads of Agencies. The main 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 updated throughout Europe to reflect these recommendations and the data on which they are based as a matter of urgency.

#### **Background**

##### **Recent Safety Data**

The EU Pharmacovigilance Working Party and CPMP have kept the safety of HRT under careful review as new data have become available. Following termination of the combined (oestrogen plus progestogen) HRT arm of the WHI trial, important information on the long-term risks of HRT was included in the SPCs of HRTs that were approved by European procedures in December 2002. This included new information with respect to breast cancer, coronary heart disease, stroke and ovarian cancer.

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In August this year the findings of a large observational study, the Million Women Study, were reported in the Lancet. This study examined the effects of specific types of HRT and tibolone on the incidence of breast cancer in nearly a million postmenopausal women in the UK. This study confirms the previously described small increase in risk of breast cancer in association with **oestrogen-only** products (RR = 1.30 versus no-use) and indicates that the increased risk associated with use of **combined (oestrogen plus progestogen** – both continuous and sequential regimens) HRT is substantially higher (RR = 2.00 versus no-use). Tibolone also significantly increases the risk of breast cancer, but to a lesser extent than combined HRT (RR = 1.45 versus no-use). For all preparations this increase in risk is duration-dependent and begins to decline when HRT is stopped and by 5 years reaches the same level as in women who have never taken HRT. There is no evidence for a difference in risk of breast cancer between specific preparations or their route of administration within the classes of oestrogen-only therapy and any type of combined HRT.

The estimated number of extra cases of breast cancer occurring after 5 and 10 years of using combined HRT were almost identical in the Million Women Study and the WHI trial (see table).

**The effect of oestrogen-only and combined HRT on the cumulative incidence of breast and endometrial cancer (data taken from the Million Women Study<sup>2</sup>).**

|   | <b>No of additional cancers per 1000 women by age 65</b> |                                 |
|---|--|---------------------------------|
| <b>Duration of use of HRT (from age 50)</b> | <b>Breast*</b>   | <b>Endo-metrium<sup>s</sup></b> |
| <b>No HRT</b>                               | 32   | 5                               |
| <b>Oestrogen-only</b>                       |  |                                 |
| ≤5 years                                    | 1.5  | 4                               |
| 5-10 years                                  | 5  | 10                              |
| <b>Oestrogen progestogen</b>                |  |                                 |
| ≤5 years                                    | 6  | 0                               |
| 5-10 years                                  | 19   | <2 <sup>#</sup>                 |

#There may be a difference in the risk of endometrial cancer between sequential and continuous HRT

### **Latest European Review of the balance of risks and benefits of HRT**

The WHI, the Million Women Study and previous studies provide good evidence that use of **oestrogen-only HRT** increases the risk of breast cancer, endometrial cancer and possibly ovarian cancer in a duration-dependent manner. For **combined HRT**, the Million Women Study has shown that there is an increase in risk of breast cancer which is substantially higher than that for oestrogen-only products, although combined HRT is known to reduce and may avoid the risk of endometrial cancer that is associated with oestrogen-only HRT. 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.

### **What 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.

HRT may still be used to treat menopausal symptoms up to the age of 50 years in women who have experienced early menopause.

#### **Prevention of osteoporosis**

HRT should not be considered first-line therapy for the long-term prevention of osteoporosis in women who are at an increased risk of fractures. HRT remains an option for postmenopausal woman at high risk for fractures for those who are intolerant of other osteoporosis prevention therapies, for whom these are contraindicated. In such cases the individual benefit-risk balance should be carefully assessed.

#### **Healthy post menopausal women**

In healthy women without climacteric symptoms, the benefit-risk balance for HRT, with different kinds of oestrogens and progestogen combinations, is considered generally unfavourable.

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 routine appointment.

### **Sources Of Further Information**

A Q&A document is available from the IMB's website ([www.imb.ie](http://www.imb.ie)). For telephone enquiries, please call 01 -6764971.

Further information is also available on the EMEA website: [www.emea.eu.int](http://www.emea.eu.int) and the European Heads of Medicines Regulatory Agencies website (<http://heads.medagencies.org>).

#### **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)

### **Clarithromycin– Medication Error**

Following a recent report of inappropriate administration of a bolus injection of clarithromycin intravenously, the IMB wishes to remind healthcare professionals of the need to closely adhere to appropriate administration practice and of the importance of developing protocols and procedures to avoid such errors.

The current product information clearly indicates that the product should not be given as a bolus or an intramuscular injection and clearly outlines the necessary preparation for appropriate intravenous administration. In addition, the product packaging clearly indicates that the product is not for use for bolus administration.

### **Update on Adverse Drug Reaction Reporting**

The IMB monitors the safety of all authorised medicinal products available on the Irish market on an on-going basis. Part of this monitoring is carried out through review and evaluation of suspected adverse drug reactions (ADRs) and the IMB encourages all healthcare professionals to notify suspected ADRs observed during their practice. The IMB greatly appreciates the interest in reporting and acknowledges the enormous contribution of busy healthcare professionals to the continued surveillance of

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the safety of medicines through the voluntary reporting system. While the burdensome nature of form filling is recognised and acknowledged, the collection of ADR reports is essential to ensure continued, effective surveillance of the safety of licenced medicines

During 2002, the IMB received a total of 1,661 suspected adverse drug reaction (ADR) reports, occurring in Ireland in association with use of medicinal products. This figure represents a decrease in the number of reports received in 2001 (2,282). However, analysis of the 2001 figures show a significant number of reports received during the period arose as result of stimulated reporting following introduction of the meningitis C vaccines. When adjustment is made for these reports, the overall figure for 2002 represents a continued, steady increase in the volume of ADR reports received. This increase in ADR reporting is very much welcomed as a sign of increasing awareness of pharmacovigilance on the part of healthcare professionals and a response to initiatives taken by the IMB to stimulate reporting.

**The following table provides a breakdown of reports by source**

|                          |             |
|--------------------------|-------------|
| Pharmaceutical Companies | 30.6%       |
| General Practitioners    | 19.9%       |
| Clinical Trials          | 18.4%       |
| Community Care Doctor    | 14.0%       |
| Hospital Doctor          | 7.6%        |
| Community Pharmacists    | 5.4%        |
| Nurses                   | 2.3%        |
| Hospital Pharmacists     | 1.6%        |
| Dentists                 | <u>0.2%</u> |
| Total                    | 100%        |

The IMB's ADR database includes anonymised case details of approximately 31,000 suspected ADR reports provided by healthcare professionals and pharmaceutical companies in relation to reports of Irish ADRs, notified since 1968. This information is helpful not only to the IMB in its evaluation of the safety profile of medicinal products, but is also used for provision of anonymised summaries of information in response to enquiries.

Spontaneous reporting of suspected ADRs is an inexpensive and effective method for the lifetime surveillance of medicines following their introduction to the marketplace. While an individual's experience may be limited to one or two cases, when collated with additional reports from other sources may contribute considerably to the assessment of a potential safety hazard. Healthcare professionals are reminded that it is not necessary to determine a causal relationship between a drug and subsequent event, prior to reporting a suspected ADR.

**You are particularly reminded to report:**

- All suspected adverse reactions to new medicinal products (i.e. those available on the market for less than two years).
- Serious suspected reactions to established medicines. A serious reaction is defined as one which is fatal, life threatening, results in persistent or significant disability/incapacity, results in or prolongs hospitalisation. This definition also includes congenital abnormalities or birth defects and serious adverse clinical consequences.
- Any suspected increase in the frequency of minor reactions.
- Any suspected teratogenic effects.
- Any suspected reactions associated with the use of vaccines.

The IMB is always keen to help, encourage and establish ADR monitoring and reporting practices. Any centres or practices wishing to develop their reporting systems should contact the Pharmacovigilance Unit of the IMB (telephone 01-6764971, fax 01-6762517, e-mail [imbpharmacovigilance@imb.ie](mailto:imbpharmacovigilance@imb.ie)).

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