

Breast Cancer

CORE SPC TEXT	AGREED UPDATED CORE SPC TEXT
<p>4.4 Special warnings and precautions for use <i>Epidemiological studies have reported an increased risk of having breast cancer diagnosed in women taking oestrogens or oestrogen-progestagen combinations for HRT for several years (see Section 4.8). This increased risk was found mostly for women with a lean or normal body build. Although obese women are at an increased risk of having breast cancer, HRT did not further increase this risk. This excess risk increases with duration of intake of HRT and seems to return to baseline in the course of about five years after stopping treatment. Women using oestrogen-progestagen combined HRT had a similar or possibly higher risk as compared with women who used oestrogens alone.</i></p> <p><i>Breast cancers diagnosed in current or recent users of HRT were less likely to have spread outside the breast than those found in non-users. Women whose breast cancers developed after HRT tended to have less aggressive tumour characteristics and possibly better survival compared with women with breast cancer who had not received HRT. The reported associations between long-term HRT exposure and an increased risk of breast cancer may be due to an earlier diagnosis, an actual effect of HRT or a combination of both.</i></p>	<p>Section 4.4 Inclusion of text to highlight that increased risks of breast cancer have been found in both observational studies and RCT data.</p> <p><u>Randomised controlled trials and</u> <i>epidemiological studies have reported an increased risk of having breast cancer diagnosed in women taking oestrogens or oestrogen-progestagen combinations for HRT for several years (see section 4.8). This increased risk was found mostly for women with a lean or normal body build. Although obese women are at an increased risk of having breast cancer, HRT did not further increase this risk. The excess risk increases with duration of intake of HRT and seems to return to baseline in the course of about five years after stopping treatment. Women using oestrogen-progestagen combined HRT had a similar or possibly higher risk as compared with women who used oestrogens alone.</i></p> <p><u>From epidemiological studies,</u> <i>breast cancers diagnosed in current or recent users of HRT were less likely to have spread outside the breast than those found in non-users. Women whose breast cancers developed after HRT tended to have less aggressive tumour characteristics and possibly better survival compared with women with breast cancer who had not received HRT. <u>The increased risk was found mostly for women with a lean or normal body build. Although obese women are at an increased risk of having breast cancer, HRT did not further increase this risk.</u></i></p> <p><i>The reported associations between long-term HRT exposure and an increased risk of breast cancer may be due to an earlier diagnosis, an actual effect of HRT or a combination of both.</i></p>

4.8 Undesirable effects

**The risk of breast cancer increases with the number of years of HRT usage. According to data from epidemiological studies – 51 epidemiological studies performed during 1970s to the early 1990s and reported in a re-analysis, and from more recent studies – the best estimate of the risk is that for women not using HRT, in total about 45 women in every 1000 women are expected to have breast cancer diagnosed over the period from ages 50 to 70 years. It is estimated that, among those with current or recent use of HRT, the total number of additional cases during the corresponding period will be between 1 and 3 (best estimate = 2) extra cases per 1000 for those using HRT for 5 years, between 3 and 9 (best estimate = 6) extra cases per 1000 for using HRT for 10 years between 5 and 20 (best estimate = 12) per 1000 treated women for those using HRT for 15 years (see section 4.4).*

Section 4.8

Inclusion of statement regarding similar excess risk in relation to age at menopause / starting HRT

*... between 5 and 20 (best estimate = 12) per 1000 treated women for those using HRT for 15 years (see section 4.4). **The number of additional cases of breast cancer is broadly similar for women who start HRT is irrespective of age at start of HRT use (only between the ages of 45 and 65).***

Endometrial Cancer

CORE SPC TEXT	MRFG PROPOSALS
<p>4.4 Special warnings and precautions for use <i>The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. To reduce, but not eliminate this risk, it is therefore essential to combine the oestrogen therapy with a progestagen for at least 12 days per cycle in non-hysterectomised women</i></p> <p>4.8 Undesirable effects <i>The table is to be followed by very rare ADRs, –(usually class-effects), common to all HRT products and specific texts generated by the PhVWP or other relevant groups. Oestrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer.</i></p>	No changes to the current warnings are needed

Ovarian Cancer

CORE SPC TEXT	MRFG PROPOSALS
<i>4.4 Special warnings and precautions for use</i>	New warning needed for <i>all</i> products to warn of increased risk with oestrogen-only products. For all HRT products: <u>“Long-term (at least 5 to 10 years) use of oestrogen-only HRT products in hysterectomised women has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRT confers a different risk than oestrogen-only products.”</u>

Coronary Heart Disease

CORE SPC TEXT	MRFG PROPOSALS
<p>4.4 Special warnings and precautions for use For conjugated oestrogen products, the following warning should be included: <i>“One large prospective, randomised, placebo-controlled study with an average follow-up of 4.1 years observed an increase in cardiovascular morbidity and mortality in postmenopausal women with established CAD during the first year of treatment with conjugated oestrogens. The effects of long-term treatment with conjugated oestrogens on the incidence of cardiovascular morbidity and mortality in postmenopausal women suffering from CAD remain unclear. Physicians should carefully weigh the benefit against the increased risk in postmenopausal women with CAD.</i></p> <p>For other HRTs, the following warning should be included: <i>The effects of long-term treatment with HRT on the incidence of cardiovascular morbidity and mortality in postmenopausal women suffering from CAD remain unclear.</i></p>	<p>Warnings should be amended to reflect the possible increased risk of CHD events in <i>all</i> women in the first year of use.</p> <p>Existing text to be replaced with the following for <u>all</u> HRT products: <i>One large prospective, randomised, placebo-controlled study with an average follow up of 4.1 years observed an increase in cardiovascular morbidity and mortality in postmenopausal women with established CAD during the first year of treatment with conjugated oestrogens. The effects of long-term treatment with conjugated oestrogens on the incidence of cardiovascular morbidity and mortality in postmenopausal women suffering from CAD remain unclear. Physicians should carefully weigh the benefit against the increased risk in postmenopausal women with CAD.</i> <u><i>There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined conjugated oestrogens and MPA. Large clinical trials showed a possible increased risk of cardiovascular morbidity in the first year of use and no benefit thereafter. For other HRT products there are as yet no randomised controlled trials to date examining benefit in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.</i></u></p>

Stroke

CORE SPC TEXT	MRFG PROPOSALS
<p>4.4 Special warnings and precautions for use <u>Conditions which need supervision</u> <i>If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with X, in particular:</i></p> <ul style="list-style-type: none">- <i>A history of, or risk factors for, thromboembolic disorders (see below)</i>- <i>Hypertension</i>- <i>Diabetes mellitus with or without vascular involvement</i>- <i>Migraine or (severe) headache</i>- <i>Systemic lupus erythematosus.</i>	<p>A warning is needed for <i>all</i> HRT products to include quantification of absolute risk of stroke.</p> <p>For all HRT products, the following warning should be included:</p> <p><u>One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of stroke in healthy women during treatment with continuous combined conjugated oestrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1000 women aged 50 – 59 years and 11 per 1000 women aged 60 – 69 years. It is estimated that for women who use conjugated estrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per 1000 users aged 50-59 years and between 1 and 9 (best estimate = 4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.</u></p>

VTE

CORE SPC TEXT	MRFG PROPOSALS
<p>4.4 Special warnings and precautions for use <i>HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The studies found a two- to threefold higher risk for users compared with non-users, which for healthy women amounts to 1 to 2 additional cases of VTE in 10,000 patient years of treatment with HRT. The occurrence of such an event is more likely in the first year of HRT than later.</i></p>	<p>Existing warnings should be amended to reflect the higher absolute risk estimates now available from the WHI study (i.e. 18/10,000 or 1 to 2 additional cases of VTE in 1000 patient years of treatment with HRT):</p> <p><i>HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism.</i></p> <p><u>One randomised controlled trial and epidemiological</u> The studies <i>found a two- to threefold higher risk for users compared with non-users. , which for healthy women amounts to 1 to 2 additional cases of VTE in 10,000 patient years of treatment with HRT. <u>For non-users, it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged between 60-69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 year period wil be between 2 and 6 (best estimate = 4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate = 9) per 1000 women aged 60-69 years.</u> The occurrence of such an event is more likely in the first year of HRT use than later.</i></p>

Duration of Use

CORE SPC TEXT	MRFG PROPOSALS
<p>Section 4.4 Special Warnings and Precautions for use: Medical Examination/follow up A careful appraisal of the risks and benefits should be undertaken over time in women treated with hormone replacement therapy.</p>	<p>Section 4.2 Posology and Method of Administration: <i>For treatment of post-menopausal symptoms the lowest effective dose should be used.</i> <u>HRT should only be continued as long as the benefit in alleviation of severe symptoms outweighs the risks of HRT.</u></p>