

## **HORMONE REPLACEMENT THERAPY (HRT): LATEST SAFETY UPDATE (updated 7 August 2003)**

The Medicines and Healthcare products Regulatory Agency (MHRA) and the Committee on Safety of Medicines (CSM) has prepared a summary of what is currently known about the risks and benefits of HRT.

### **LATEST CSM ADVICE ON HRT SAFETY**

- For short-term use of HRT for the relief of menopausal symptoms, the benefits outweigh the risks in most women.
- For longer-term use of HRT, you should be aware of the increased incidence of some adverse effects of HRT (see below).
- If you have concerns about your HRT treatment, you should make a routine appointment to discuss this information with your doctor.
- You can find more information about HRT and its associated risks and benefits by clicking on the following headings:
  - **What is HRT?**
  - **What are the benefits of HRT?**
  - **What are the risks of HRT?**
  - **Summary table of the risks and benefits of using HRT**
  - **What medical check-ups do I need if I'm using HRT?**
  - **What types of HRT have been studied?**
- There are other more minor side effects of HRT that are not discussed here. You are advised to always read the Patient Information Leaflet that is supplied with your medicine. If you are concerned about any new symptoms that you feel may be related to your HRT you should speak to your doctor, pharmacist or practice nurse.

## **WHAT IS HRT?**

When you reach the menopause, your levels of the hormones oestrogen and progestogen naturally fall. This fall in hormone levels causes your menstrual cycle to become irregular and your periods eventually to stop. This may also cause some of the unpleasant symptoms of the menopause, such as hot flushes and vaginal dryness. Hormone replacement therapy, also known as HRT, provides low doses of these hormones to replace those that your body no longer produces. There are two main types of HRT – oestrogen-only HRT and combined HRT that contains both oestrogen and progestogen. Tibolone (Livial<sup>®</sup>) is a different type of HRT product that combines oestrogenic and progestogenic activity.

**Oestrogen-only** replacement products are now available as:

- tablets
- implants
- patches
- vaginal rings
- gels and
- a nasal spray.

In **combined HRT** products, the oestrogen and progestogen may be taken in the same tablet or patch or they may be taken separately. The progestogen may be taken every day (continuous combined HRT) or for 12-14 days of each monthly treatment cycle (sequential combined HRT).

**Tibolone** is given as a daily tablet without any added progestogen.

## **WHAT ARE THE BENEFITS OF HRT?**

HRT is effective in relieving the symptoms of the menopause. These symptoms may include:

- hot flushes
- night sweats
- vaginal dryness and discomfort
- difficulty sleeping
- depression
- mood swings
- tiredness
- poor concentration

In most cases, using HRT for a short period of time is enough to relieve these symptoms, although they may recur for a short time after stopping HRT.

Some HRT products can also be taken for a longer time to help prevent osteoporosis (thinning of the bones) and so reduce the risk of hip fractures.

Some studies have shown that HRT reduces the number of cases of colon cancer (see '**Summary table of the risks and benefits of using HRT**').

It was previously thought that HRT was beneficial in the prevention of heart disease, but evidence now shows this is not the case (see '**The risks of HRT**').

## WHAT ARE THE RISKS OF HRT?

- As well as benefits, HRT has some risks which you need to consider when you're deciding whether to start HRT or to carry on taking it.
- As with all medicines, the use of HRT is associated with some side-effects. While many number of women have no side effects, nausea, breast tenderness, weight gain and fluid retention occur fairly commonly.
- Long-term use of HRT may increase the risk of getting some potentially more serious but much rarer conditions (see below). Key information about each of these risks is given below and the figures are summarised in a **table**. If you would like more detailed information about each of the conditions described below, click on the bold headings.
- It is important to remember that all these conditions can occur without using HRT and that a woman's risk of getting any of these conditions depends on her own health, her lifestyle and her family medical history. To help put these risks into perspective, the extra number of cases of each of these conditions associated with HRT is typically smaller than the health risks associated with smoking or being very overweight.
- For some of these risks, studies have allowed us to estimate the number of extra cases that will occur in a five or ten year period as a result of using HRT.
  - **Heart disease** – studies have shown that some products (that contain **conjugated oestrogens and MPA**) [link to 'types of HRT studied'] do not prevent heart disease and may make the chance of getting heart disease more likely in the first year of taking them. For other types of HRT, the picture is still unclear, but there is nothing to suggest that their effect on the heart will be any different. HRT does not prevent heart disease and should not be used to protect against heart disease.  
*You should stop HRT and seek urgent medical attention* if you experience episodes of chest pain, possibly related to exercise, with or without sweating, breathlessness or dizziness.
  - **Stroke** – Research suggests that HRT increases the risk of having a stroke. Taking average women in their 50s who do not use HRT, 3 in a thousand are expected to have a stroke in any five year period. For women of the same age who use HRT for 5 years, the expected number of strokes will be 4 in a thousand. The risk of stroke increases as a woman gets older so taking women in their 60s who do not use HRT 11 in a thousand will be expected to have strokes in any five year period. This compares with 15 in a thousand women of the same age who use HRT for 5 years.  
*You should stop HRT and seek urgent medical attention* if you experience unusual migraine-type headaches or unusual faints or limb weakness.
  - **Blood clots (venous thromboembolism, VTE)** – the risk of harmful blood clots in the veins is increased by taking HRT, especially in the first year. Taking average women in their 50s who do not use HRT, 3 in a thousand would get blood clots over five years. In women of the same age who use HRT for 5 years, that figure would be 7 in a thousand. The risk of VTE increases with age and so 8 in a thousand women in their 60s who do not use HRT could get clots over five years. This compares with 17 in a thousand women in their 60s who use HRT for 5 years.  
*You should stop HRT and seek urgent medical attention* if you experience a red, swollen or painful leg or sharp pains in your chest with breathlessness or feeling faint.

- **Breast cancer** - using oestrogen-only HRT slightly increases the chance of breast cancer. For combined (oestrogen plus progestogen) HRT the risk is higher than for oestrogen-only therapy. Tibolone (Livial<sup>®</sup>, a different type of HRT product) also increases the risk of breast cancer but not as much for combined HRT. In all cases, the risk of breast cancer begins to decline when HRT is stopped and by 5 years reaches the same level as in women who have never taken HRT.
- Taking women aged 50 who do not use HRT, about 32 in every thousand will be diagnosed with breast cancer by the time they reach the age of 65 years. For women who start oestrogen-only HRT at age 50 and take it for five years, the total number of cases would be between 33 and 34 in every thousand (ie an extra 1-2 cases). If they take it for ten years, there would be 37 in a thousand (ie an extra 5 cases).
- By comparison, for women who start combined HRT at age 50 the number of cases of breast cancer that would be diagnosed by the time they reach 65 would be 38 in a thousand after 5 years use (ie an extra 6 cases) and 51 in a thousand after 10 years use (ie an extra 19 cases). The numbers have not been calculated for tibolone but are thought to lie somewhere between those for oestrogen-only and combined HRT.
- It is important that you note any changes in your breasts and, if you are 50 or over, to attend for breast screening (for further information see [www.cancerscreening.nhs.uk/breastscreen/breastawareness.html](http://www.cancerscreening.nhs.uk/breastscreen/breastawareness.html)). *You should make an appointment to see your doctor* if you notice any changes to your breasts including skin changes, nipple changes or lumps.
- **Endometrial cancer (cancer of the lining of the uterus)** – taking *oestrogen-only* HRT for a long time increases the risk of cancer in the uterus lining (endometrium). For women who have not had their uterus removed by hysterectomy their doctor can prescribe a progestogen as well as an oestrogen to reduce this risk. *You should make an appointment to see your doctor* if you notice any abnormal vaginal bleeding which continues or starts some months after starting HRT, this may include heavy bleeding, irregular bleeding or bleeding regularly after sex.
- **Ovarian cancer** – using *oestrogen-only* HRT for more than 5 years may slightly increase the risk of this rare cancer. The effect of long-term combined HRT on the ovaries is not yet known. *You should make an appointment to see your doctor* if you experience abdominal swelling and discomfort, weight loss and/or abnormal vaginal bleeding, possibly associated with an abdominal lump.

**Summary table of risks and benefits associated with using HRT.**

These numbers are estimates - it is important to remember that not all risks will apply to everyone but will depend on their health, their lifestyle and their family medical history.

Condition	Age of woman (yr)	Number of cases/1000 non-HRT users	Extra number of cases in 1000 HRT users over the same period	
			5 years use	10 years use
<b>Cumulative cancer risk with time</b>				
Breast cancer	50-65	32	1.5 oestrogen-only 6 (combined HRT)	5 oestrogen-only 19 (combined HRT)
Endometrial cancer	50-64	5	4 (oestrogen-only) Data not available (combined HRT)	10 (oestrogen-only) <2 (combined HRT)
Ovarian cancer <sup>b</sup>	50-69	9	1 (oestrogen-only)	3 (oestrogen-only)
<b>Cardiovascular risks over 5 years</b>				
Stroke	50-59	3	1	Data not available
	60-69	11	4	
VTE	50-59	3	4	Data not available
	60-69	8	9	
<b>Benefits over 5 years</b>			<b>Reduced number of cases in 1000 HRT users over the same period</b>	
Colorectal cancer	50-59	3	1	2
	60-69	8	3	5-6
Fracture of neck of femur	50-59	1-2	0-1	1
	60-69	7-8	2-3	5

<sup>b</sup> The risks of ovarian cancer with combined HRT are unknown

## WHAT MEDICAL CHECK-UPS DO I NEED IF I'M USING HRT?

Before you start taking HRT, your doctor should ask about your own and your family's medical history.

Your doctor may decide to examine your breasts and/or your abdomen, and may do an internal examination — but only if these examinations are necessary for you, or if you have any special concerns.

Once you have started HRT, you should see your doctor for regular check-ups (at least once a year). At these check-ups, your doctor may discuss with you the benefits and risks of continuing to take HRT.

It is important that you are 'breast aware', whether you take HRT or not. You should know what is normal for you, know what to look and feel for, and to report any changes to your GP without delay. You are also encouraged to accept your invitations for breast screening from the age of 50.

Be sure to:

- **go for regular breast screening and cervical smear tests**
- **regularly check your breasts** for any changes such as dimpling of the skin, changes in the nipple, or any lumps you can see or feel (for further information go to [www.cancerscreening.nhs.uk/breastscreen/breastawareness.html](http://www.cancerscreening.nhs.uk/breastscreen/breastawareness.html)).

## **WHAT TYPES OF HRT HAVE BEEN STUDIED?**

Much of the evidence about the long-term risks of combined HRT relates to one product used in the United States - a continuous combined tablet that contains conjugated oestrogens (0.625mg) plus the progestogen medroxyprogesterone acetate (MPA, 2.5mg). This is similar to the UK products Premique (0.625mg conjugated oestrogens plus 5mg MPA) and Premique cycle (0.625mg conjugated oestrogens plus 10mg MPA).

Less is known about the long-term risks with other types of combined HRT, largely because many of them have not been available for long enough. While we can't therefore say for sure whether the long-term risks that have been identified also apply to other combined HRT regimens, there is currently little evidence to suggest that there is a difference in the risks with different combined HRT products.

Similarly, while some studies looking at the effects of oestrogen-only HRT have used specific types of oestrogens, there is little evidence to suggest that there is a difference in the risks with different oestrogen-only products.

Regarding the risk of breast cancer, one large study in the UK looked at all types of HRT, including oestrogen-only, combined (oestrogen plus progestogen) HRT and tibolone (Livial<sup>®</sup> - a different type of HRT product). This study showed that within 'oestrogen-only' products the risk of breast cancer was not changed by the type of oestrogen or whether it was given as a tablet, patch or implant etc. Similarly, within 'combined HRT' products the risk was not changed by the type of progestogen or the number of days it was taken per cycle.

## **HRT AND CORONARY HEART DISEASE**

### **What is coronary heart disease?**

Coronary heart disease (CHD) occurs when the flow of blood to the heart is restricted. This may be caused by the build up of fatty deposits (known as atherosclerosis) or by the presence of a blood clot (thrombosis). This can result in angina – a chest pain that spreads to the left arm, neck, jaw or shoulder blade – and in severe cases can result in a heart attack.

### **Does HRT protect against heart disease?**

No. While some studies have shown that HRT has a favourable effect on fat levels in the blood (serum lipids), recent results from 2 large studies indicate that HRT does not prevent heart disease. Also, the women in these studies, who used combined HRT tablets containing **conjugated oestrogens and MPA**, may have been slightly more likely to have heart disease in the first year of use. There is currently no good evidence to suggest that other HRT products have a different effect on the heart from the product used in these studies. HRT should not be used to prevent heart disease.

### **Am I at risk of getting heart disease?**

You may be more likely to suffer from heart disease if it runs in your family, if you have high levels of cholesterol, if you smoke, or if you have high blood pressure or diabetes. The risk of heart disease also increases with age.

**HRT is not recommended for women with current or recent cardiovascular disease.** If you have had angina or a heart attack in the past you should see your doctor to discuss the possible benefits and risks of HRT for you.

### **Stop taking HRT and seek urgent medical attention if you experience:**

Episodes of chest pain, possibly related to exercise, with or without sweating, breathlessness or dizziness.

## HRT AND STROKE

### What causes a stroke?

A stroke occurs when the blood supply to the brain is restricted. In most cases this restriction is caused by the presence of a blood clot in one of the arteries that carries blood to the brain or by leakage of blood from a split artery. Strokes may also be caused by a gradual build up of fatty deposits (atherosclerosis) in blood vessels (similar to heart disease).

### What effect does HRT have on the risk of having a stroke?

Recent findings suggest that HRT slightly increases the risk of having a stroke. For women in their 50s who do not take HRT, the most recent estimates indicate that about 3 in a thousand will have a stroke in any five-year period. This compares with about 4 in a thousand women of the same age who use HRT for five years. The risk of having a stroke increases with age, so for women in their 60s who do not use HRT, about 11 in a thousand will have a stroke over a five-year period compared to about 15 in a thousand women who use HRT for five years. The number of extra strokes caused by HRT is:

Age (years)	Extra cases of stroke occurring over 5 years per 1000 women using HRT
50 – 59	1
60 – 69	4

### What other factors increase the chances of having a stroke?

Other factors that also increase this risk include having high blood pressure, smoking, excessive drinking or having an irregular heart beat (atrial fibrillation).

**HRT is not recommended for women with current or recent heart disease.** If you have previously had a stroke, angina or a heart attack you should see your doctor to discuss the possible benefits and risks of HRT for you.

### Stop taking HRT and seek urgent medical attention if you:

- Start getting unusual migraine-type headaches or unusual faints or temporary weakness in your arms or legs (as these may be an early warning sign of stroke).

## HRT AND BLOOD CLOTS (VENOUS THROMBOEMBOLISM)

### What is venous thromboembolism (VTE)?

Blood clotting stops you from bleeding when injured. However, harmful blood clots can sometimes form in the veins (typically in the calf), causing a red, swollen and often painful leg. This is called venous thrombosis (sometimes called deep vein thrombosis or DVT). On *rare* occasions a clot may move in the veins from the place where it is formed. If a clot travels and lodges in the lungs it may create an obstruction. This is a pulmonary embolism (PE) and may cause breathlessness, sharp pains in the chest and/or collapse or fainting. The term ‘venous thromboembolism’ covers both deep vein thrombosis and pulmonary embolism.

### How serious is VTE?

In most cases blood clots are successfully treated with anticoagulants (drugs that stop blood from clotting) or other drugs that break clots down. Very occasionally a blood clot can cause serious problems, such as pulmonary embolism, and in rare cases may be fatal.

### What are the chances of getting a blood clot?

Studies have shown that women who use HRT are more likely to develop VTE than women of similar age who do not use HRT, especially in the first year of HRT use. In all women the chance of developing VTE increases with age.

For women in their 50s who do not use HRT, the most recent estimates indicate that about 3 in a thousand will have a VTE over a five-year period. This compares to about 7 in a thousand women of the same age who use HRT for 5 years. For women in their 60s who do not use HRT, about 8 in a thousand will have a VTE over a 5-year period compared with about 17 in a thousand women who use HRT for 5 years. The extra number of cases of VTE caused by HRT is:

Age (years)	Extra cases of VTE occurring over 5 years per 1000 women using HRT
50 – 59	4
60 – 69	9

### Other factors that may increase the risk of DVT

Some women have a higher risk of developing blood clots because they, or someone in their family, has already had a DVT, because they are severely overweight, have cancer or heart disease. If you have any of these conditions or if you are currently being treated with anti-coagulant (blood-thinning) medicines (eg. warfarin) you should ask your doctor whether you should take HRT. You should also tell your doctor if you or your close relatives have a history of blood clots or have had several miscarriages, as your blood may have an increased tendency to clot.

### DVT and surgery

The risk of DVT may *temporarily* be increased if you are off your feet for a long time. This may happen if you suffer major injuries to your body or if you undergo major surgery. If you are going to have an operation it is important that you let your doctor or surgeon know beforehand that you are on HRT. He or she might advise you to stop taking HRT 4-6 weeks before surgery to reduce your chances of getting DVT. You should be able to start HRT again once you are fully mobile.

### Stop taking HRT and seek urgent medical attention if you experience:

- A red, swollen or painful leg or
- Sharp pains in your chest with breathlessness or faintness.

## HRT AND BREAST CANCER

### Breast cancer and HRT use

An increase in the risk of breast cancer becomes apparent within 1-2 years of starting any type of HRT. The longer HRT is used, the higher the risk of breast cancer. However, in all cases, the risk of breast cancer begins to decline when HRT is stopped and by 5 years reaches the same level as in women who have never taken HRT.

### Oestrogen-only HRT

Women using oestrogen-only HRT have a small increase in the risk of breast cancer. Among women aged 50 who do not use HRT, approximately 32 in every 1000 will develop breast cancer by the age of 65. For women who start oestrogen-only HRT at age 50 and who use it for five years this number will increase to about 33-34 per 1000 women (ie an extra 1-2 cases). For women who take oestrogen-only HRT for 10 years this number increases to about 37 per 1000 women (ie an extra 5 cases).

### Combined HRT

Women using combined HRT have a higher risk of developing breast cancer than women using oestrogen-only HRT. Among women aged 50 who do not use HRT, approximately 32 in every 1000 will develop breast cancer by the age of 65. For women who start combined HRT at age 50 and who use it for five years this number will increase to about 38 per 1000 women (ie an extra 6 cases). For women who take combined HRT for 10 years this number increases to about 51 per 1000 women (ie an extra 19 cases).

The extra number of breast cancers caused by HRT is:

Type of HRT	Extra breast cancers between the ages 50 to 65 per 1000 women using HRT	
	5 years of use	10 years of use
Oestrogen-only	1-2	5
Combined (oestrogen plus progestogen)	6	19

### Tibolone

Tibolone (Livial<sup>®</sup>, a different type of HRT product) also increases the risk of breast cancer but the risk is not as high as for combined HRT. The number of extra cases of breast cancers associated with use of tibolone has not been calculated but is thought to lie somewhere between those for oestrogen-only and combined HRT.

### Effect of age at menopause

The risk of breast cancer increases for each year older a woman is when she has her menopause, but it falls after menopause. Women who have early menopause (before the age of 50) naturally have a lower risk of breast cancer. The effect of using HRT after the menopause on the risk of breast cancer is similar to delaying the age of menopause.

### What other factors may affect the chances of developing breast cancer?

A number of factors, including family history influence the risk of developing breast cancer. If your mother, sister, aunt or grandmother had breast cancer your risk of developing breast cancer is increased.

HRT is not recommended for women who have breast cancer or have had it in the past.

### What can I do to be breast aware?

You should :

- know what is normal for you
- know what to look and feel for
- regularly check your breasts for any changes such as dimpling of the skin, changes in the nipple, or any lumps you can see or feel
- report any changes to your GP without delay
- accept your invitations for breast screening after the age of 50

For further information go to [www](#).

## **HRT AND CANCER OF THE UTERUS LINING (ENDOMETRIUM)**

It has been known for some time that taking oestrogens alone for a long time increases the risk of abnormal growth of the uterus lining (the endometrium) and other endometrial disease, including endometrial cancer. However, taking a progestogen as well, for part or all of the monthly treatment cycle, lowers this added risk.

### **If you still have your uterus**

Your doctor may prescribe 'combined' HRT. This consists of an oestrogen together with a progestogen and lowers your risk of endometrial cancer compared to taking oestrogen-only HRT. Oestrogens and progestogens can be taken as two separate products or as a single combined product. The progestogen component can either be taken every day or for between 12 and 14 days of the monthly treatment cycle.

### **If you have had your uterus removed (hysterectomy)**

Your doctor will probably recommend that you take oestrogen-only HRT as you are no longer at risk of getting endometrial cancer. You are unlikely to need to take added progestogen.

### **If you have had your uterus removed because of endometriosis**

Any endometrium left behind after your hysterectomy may be at risk. If you remind your doctor that you had endometriosis he or she may advise that you add a progestogen to your oestrogen, to protect any patches of endometrium that may have been left behind.

### **Abnormal bleeding while taking HRT**

It is fairly common for some women to experience breakthrough bleeding or spotting during the first few months of taking HRT. This may also happen if you forget to take your HRT or when you take certain other medicines at the same time. However, if you have any breakthrough bleeding or spotting that continues for longer than the first few months, or starts after you have been taking HRT for some time, or continues even though you have stopped taking HRT, you should tell your doctor.

### **See your doctor if you experience:**

- Any abnormal vaginal bleeding some months after starting HRT, including heavy bleeding, irregular bleeding or bleeding regularly after sex.

## **HRT AND OVARIAN CANCER**

### **The effect of HRT on women with ovaries**

Limited evidence suggests that women who use oestrogen-only HRT for 5 years or longer may have a slightly higher risk of developing this rare but serious cancer. This additional risk is very small, especially when HRT is used for a short time, but increases with length of use.

At the moment most combined oestrogen/progestogen HRT products have not been used for long enough to know if they increase the risk of ovarian cancer in the same way.

### **How do I know if I have ovarian cancer?**

Ovarian cancer may be discovered through a routine gynaecological examination but there are often no obvious symptoms in the early stages making it difficult to diagnose. The symptoms of ovarian cancer may include general abdominal swelling and discomfort, unexplained weight loss or gain and/or a noticeable abdominal lump. The presence of any or all of these symptoms does not necessarily mean that you have ovarian cancer. More commonly, abdominal lumps are due to non-cancerous ovarian cysts.

### **See your doctor if you experience:**

Abdominal swelling and discomfort, weight loss and/or abnormal vaginal bleeding, possibly associated with an abdominal lump.